**Chapter 589** ◆ Diabetes Mellitus **2761**

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| **Table 589-1** | Etiologic Classifications of Diabetes Mellitus | |
| 1. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)    1. Immune mediated    2. Idiopathic 2. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)    1. Typical    2. Atypical 3. Genetic defects of β-cell function    1. MODY (maturity-onset diabetes of the young) syndromes       1. MODY 1 chromosome 20, HNF4α       2. MODY 2 chromosome 7, glucokinase       3. MODY 3 chromosome 12, HNF1α, TCF-1       4. MODY 4 chromosome 13, IPF-1       5. MODY 5 chromosome 17, HNF1β, TCF-2       6. MODY 6 chromosome 2q32, neuro-D1/β2    2. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, diabetes mellitus, deafness)    3. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin— chromosome 4p       1. Wolfram locus 2—chromosome 4q22-24       2. Wolfram mitochondrial    4. Thiamine responsive megaloblastic anemia and diabetes 4. Drug or chemical induced    1. Antirejection—cyclosporine, sirolimus    2. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)    3. L-Asparaginase    4. β-Adrenergic blockers    5. Vacor (rodenticide)    6. Phenytoin (Dilantin)    7. α-Interferon    8. Diazoxide    9. Nicotinic acid    10. Pentamidine 5. Diseases of exocrine pancreas    1. Cystic fibrosis–related diabetes    2. Trauma—pancreatectomy    3. Pancreatitis—ionizing radiation    4. Others | | VI. Infections   1. Congenital rubella 2. Cytomegalovirus 3. Hemolytic-uremic syndrome   VII. Variants of type 2 diabetes   1. Genetic defects of insulin action    1. Rabson-Mendenhall syndrome    2. Leprechaunism    3. Lipoatrophic diabetes syndromes    4. Type A insulin resistance—acanthosis 2. Acquired defects of insulin action    1. Endocrine tumors—rare in childhood 3. Pheochromocytoma 4. Cushing 5. Others    1. Antiinsulin receptor antibodies 6. Genetic syndromes with diabetes and insulin resistance/insulin deficiency    1. Prader-Willi syndrome, chromosome 15    2. Down syndrome, chromosome 21    3. Turner syndrome    4. Klinefelter syndrome    5. Others       1. Bardet-Biedel       2. Alström       3. Werner    6. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)    7. Celiac disease    8. Autoimmune polyendocrinopathy 7. Gestational diabetes 8. Neonatal diabetes    1. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1β, others    2. Permanent—agenesis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others |

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| **Table 588-3** | Ambiguous Genitalia: Steps in Establishing the Diagnosis | | | | | |
| **21-OH DEFICIENCY** | | | **GONADAL DYSGENESIS WITH Y CHROMOSOME** | **OVOTESTICULAR DSD** | **PARTIAL ANDROGEN INSENSITIVITY** | **BLOCK IN TESTOSTERONE SYNTHESIS** |
| CLINICAL FEATURE | |  |  |  |  |  |
| ± | + | + |
| Palpable gonad(s) | | – | ± |
| Uterus present\* | | + | + | Usually | – |
| – |
| Increased skin | | ± | – | – | – | – |
| pigmentation | |  |  |  |  |  |
| Sick baby | | ± | – | – | – | ± |
| Dysmorphic features | | – | ± | – | – | – |
| DIAGNOSTIC CONSIDERATIONS  Serum 17-OHP Elevated  Electrolytes Possibly abnormal  Karyotype 46,XX  Testosterone NA response to hCG  Gonadal biopsy NA Other testing | | | Normal Normal  45,X/46,XY or others Positive  Dysgenetic gonad | Normal Normal 46,XX  Normal or reduced Ovotestis | Normal Normal 46,XY  Positive response  Normal testis with  ± Leydig cell hyperplasia Genital skin fibroblast  culture  For AR assay  Or DNA screening for AR mutations in blood cells | Normal  Possibly abnormal 46,XY  Reduced or absent Normal testis Measure  Testosterone Precursors |

\*As determined by ultrasound or rectal examination.

AR, androgen receptor; DSD, disorders of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.

*Adapted from Donohoue PA, Saenger PH: Ambiguous genitalia. In Finberg L, Kleinman RE, editors:* Saunders manual of pediatric practice*, Philadelphia, 2002, WB Saunders, p. 874.*

**2766 Part XXVI** ◆ The Endocrine System

(Precipitating event)



**Genetic**

**predisposition**

**Overt**

**immunological abnormalities**

**Progressive**

**loss of insulin release**

6. Increasing glucose

excursions as individual approaches symptomatic onset

**Normal insulin**

**release**

**Overt**

**diabetes**

7. Some patients produce

low concentrations of

C-peptide long after onset

**Glucose**

**normal**

**C-peptide No C-peptide**

**present**

8. β-cell mass not always zero in long-standing

disease

4. Although overall loss of β

cells is potentially linear, it

could show a relapsing or remitting pattern

3. Beyond precipitating, environment might influence entire natural history

5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes

1. Precipitating events might occur in utero

2. Genetic predisposition probably the key driver or linkage to immune abnormalities

Age (yr)

β-cell mass

**Figure 589-3** The natural history of type 1 diabetes—a 25 yr old concept revisited. A recreation of the model of type 1 diabetes, originally proposed in 1986, is shown in *black.* Additions and conjectures based on recent knowledge gains are shown in *green*. *(From Atkinson MA, Eisen- barth GS, Michels AW: Type 1 diabetes.* Lancet *383:69–78, 2014, Fig. 4, p. 73.)*

Exposure to unknown

environmental “triggers”? Chance?

Lack of exposure to “triggers”?

Chance?

Autoimmunity

No autoimmunity

Progressive β-cell loss

No apparent β-cell loss

Why?

Clinical diabetes

No diabetes

Clinical remission

(honeymoon period) Complications

Genetic susceptibility

\*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

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| **Table 589-3** | | Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue\* | |
|  | **HIGH PLASMA INSULIN (POSTPRANDIAL STATE)** | | **LOW PLASMA INSULIN (FASTED STATE)** |
| Liver | Glucose uptake Glycogen synthesis Absence of  gluconeogenesis Lipogenesis  Absence of ketogenesis | | Glucose production Glycogenolysis Gluconeogenesis  Absence of lipogenesis Ketogenesis |
| Muscle | Glucose uptake Glucose oxidation  Glycogen synthesis Protein synthesis | | Absence of glucose uptake Fatty acid and ketone  oxidation Glycogenolysis  Proteolysis and amino acid release |
| Adipose tissue | Glucose uptake Lipid synthesis  Triglyceride uptake | | Absence of glucose uptake Lipolysis and fatty acid release  Absence of triglyceride uptake |

###### **Figure 589-4** Schematic of the natural history of type 1 diabetes mellitus. Unknown triggers act upon a genetically susceptible host to trigger autoimmunity. Some proportion of those with autoimmunity develop progressive β-cell loss that eventually leads to clinical diabe- tes. This is followed by temporary clinical remission (honeymoon period) in most patients. Over time, insulin secretion is almost com- pletely lost and complications may develop in some patients (in direct proportion to the occurrence of hyperglycemia).

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| **Table 589-15** | Monitoring for Complications and Comorbidities | | |
| **CONDITION** | | **SCREENING TEST** | **COMMENT** |
| Hypertension | | Blood pressure |  |
| Fatty liver | | Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound |  |
| Polycystic ovary syndrome | | Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone |  |
| Microalbuminuria | | Urine albumin concentration and albumin : creatinine ratios |  |
| Dyslipidemia | | Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides) | Obtain at diagnosis and every 2 yr |
| Sleep apnea | | Sleep study to assess overnight oxygen saturation |  |

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| **Table 589-4** | Classification of Diabetic Ketoacidosis | | | | |
|  | | **NORMAL** | **MILD** | **MODERATE** | **SEVERE\*** |
| CO2 (mEq/L, venous)† | | 20-28 | 16-20 | 10-15 | <10 |
| pH (venous)† | | 7.35-7.45 | 7.25-7.35 | 7.15-7.25 | <7.15 |
| Clinical | | No change | Oriented, alert but fatigued | Kussmaul respirations; oriented but sleepy; arousable | Kussmaul or depressed respirations; sleepy to depressed sensorium to coma |

\*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.

†CO2 and pH measurement are method dependent; normal ranges may vary.

Insulin effect

Lispro/aspart

Regular

NPH/Lente

Ultralente

Glargine/detemir

8:00 12:00 4:00 8:00 12:00 4:00

Duration (hr)

|  |  |  |
| --- | --- | --- |
| **Table 589-5** | Starting Doses of Insulin (units/kg/day) | |
|  | **NO DIABETIC KETOACIDOSIS** | **DIABETIC KETOACIDOSIS** |
| Prepubertal | 0.25-0.50 | 0.75-1.0 |
| Pubertal | 0.50-0.75 | 1.0-1.2 |
| Postpubertal | 0.25-0.50 | 0.8-1.0 |

#### A

###### **Figure 589-6** Approximate insulin effect profiles. Meals are shown as rectangles below time axis. **A,** The following relative peak effect and duration units are used: lispro/aspart, peak 20 for 4 hr; regular, peak

Insulin effect

15 for 7 hr; neutral protamine Hagedorn/Lente, peak 12 for 12 hr; Ultralente, peak 9 for 18 hr; glargine, peak 5 for 24 hr. Although Lente and Ultralente are no longer manufactured, they are shown to give historical comparison to newer insulin analogs. ▲, Injection time. **B,** Two Ultralente injections given at breakfast and supper. Note overlap of profiles. **C,** Composite curve showing approximate cumula- tive insulin effect for the 2 Ultralente injections. This composite view is much more useful to the patient, parents, and medical personnel because it shows important combined effects of multiple insulin injections with variable absorption characteristics and overlapping durations.

#### B

C

Insulin effect

8:00 12:00 4:00 8:00 12:00 4:00

Unmerged Ultralente independent profile

Composite Ultralente profile

8:00 12:00 4:00 8:00 12:00 4:00

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| **Table 589-6** | Diabetic Ketoacidosis Treatment Protocol | | |
| **TIME** | | **THERAPY** | **COMMENTS** |
| 1st hr | | 10-20 mL/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 units/kg/hr | Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema |
| 2nd hr until DKA resolution | | 0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar >250 mg/dL  (14 mmol/L) | IV rate  85 mL/kg  maintenance  bolus  23 hr  If K <3 mEq/L, give 0.5-1.0 mEq/kg as oral K solution *or* increase IV K to 80 mEq/L |
| Variable | | Oral intake with subcutaneous insulin | No emesis; CO2 ≥16 mEq/L; normal electrolytes |
| Note that the initial IV bolus is considered part of the total fluid allowed in the 1st 24 hr and is subtracted before calculating the IV rate. | | | |
| Maintenance (24 hr) = 100 mL/kg (for the first 10 kg) + 50 mL/kg (for the second 10 kg) + 25 mL/kg (for all remaining kg) | | | |
| Sample calculation for a 30-kg child:  1st hr = 300 mL IV bolus 0.9% NaCl or LR  2nd and subsequent hr  (85 mL  30)  1750 mL  300 mL  175 mL  23 hr hr  (0.45% NaCl with 20 mEq/L Kphos and 20 mEq/L KAc) | | | |

DKA, diabetic ketoacidosis; I/O, input and output (urine, emesis); K, potassium; KAc, potassium acetate; KPhos, potassium phosphate; LR, lactated Ringer solution; NaCl, sodium chloride; NPO, nothing by mouth.

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| **Table 589-7** | Calorie Needs for Children and Young Adults | |
| **AGE** | | **KCAL REQUIRED/KG BODY WEIGHT\*** |
| CHILDREN | |  |
| 0-12 mo | | 120 |
| 1-10 yr | | 100-75 |
| YOUNG WOMEN | |  |
| 11-15 yr | | 35 |
| ≥16 yr | | 30 |
| YOUNG MEN | |  |
| 11-15 yr | | 80-55 (65) |
| 16-20 yr | |  |
| Average activity | | 40 |
| Very physically active | | 50 |
| Sedentary | | 30 |

Numbers in parentheses are means.

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| **Table 589-8** | Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus |
| NUTRITION CARE PLAN  Promotes optimal compliance.  Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach. | |
| NUTRIENT RECOMMENDATIONS AND DISTRIBUTION | |
| **(%) OF RECOMMENDED DAILY**  **NUTRIENT CALORIES INTAKE** | |
| Carbohydrate Will vary High fiber, especially soluble  fiber; optimal amount unknown  Fiber >20 g/day  Protein 12-20  Fat <30  Saturated <10  Polyunsaturated 6-8  Monounsaturated Remainder of  fat allowance  Cholesterol 300 mg  Sodium Avoid excessive; limit to  3,000-4,000 mg if  hypertensive | |
| ADDITIONAL RECOMMENDATIONS  *Energy:* If using measured diet, reevaluate prescribed energy level at least every 3 mo.  *Protein:* High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.  *Alcohol:* Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.  *Snacks:* Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).  *Alternative sweeteners:* Use of a variety of sweeteners is suggested.  *Educational techniques:* No single technique is superior. Choice of educational method used should be based on patient needs.  Knowledge of variety of techniques is important. Follow-up education and support are required.  *Eating disorders:* Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.  *Exercise:* Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis. | |

\*Gradual decline in calories per unit weight as age increases.

*From* Nutrition guide for professionals: diabetes education and meal planning, *Alexandria, VA, and Chicago, IL, 1988, The American Diabetes Association and The American Dietetic Association.*

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| **Table 589-11** | Guidelines for Intravenous Insulin Coverage During Surgery | | |
| **BLOOD GLUCOSE**  **LEVEL (mg/dL)** | | **INSULIN INFUSION**  **(units/kg/hr)** | **BLOOD GLUCOSE MONITORING** |
| <120 | | 0.00 | 1 hr |
| 121-200 | | 0.03 | 2 hr |
| 200-300 | | 0.06 | 2 hr |
| 300-400 | | 0.08 | 1 hr\* |
| 400 | | 0.10 | 1 hr\* |

An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times maintenance rate.

\*Check urine ketones.

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| **Table 589-9** | Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A1c for Each Age Group | | | |
| **AGE GROUP (yr)** | | **TARGET PREMEAL BG RANGE**  **(mg/dL)** | **30-DAY AVERAGE BG RANGE**  **(mg/dL)** | **TARGET HbA1c (%)** |
| <5 | | 100-200 | 180-250 | 7.5-9.0 |
| 5-11 | | 80-150 | 150-200 | 6.5-8.0 |
| 12-15 | | 80-130 | 120-180 | 6.0-7.5 |
| 16-18 | | 70-120 | 100-150 | 5.5-7.0 |

In our laboratory, the nondiabetic reference range for HbA1c is 4.5-5.7% (95% confidence interval). BG, blood glucose; HbA1c, hemoglobin A1c.

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* Criteria\*

Overweight (body mass index >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

*Plus*

Any 2 of the following risk factors:

Family history of type 2 diabetes in 1st- or 2nd-degree relative Race/ethnicity (Native American, African-American, Hispanic,

Asian/Pacific Islander)

Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)

* Age of initiation: age 10 yr or at onset of puberty if puberty occurs at a younger age
* Frequency: every 2 yr
* Test: fasting plasma glucose preferred

Testing for Type 2 Diabetes in Children

**Table 589-13**

##### \*Clinical judgment should be used to test for diabetes in high- risk patients who do not meet these criteria.

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| **Table 589-10** | Guidelines | for | Sick | Day | Management | |
| **URINE KETONE STATUS** | | **GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN**  **Insulin Correction Doses**\* | | | | **COMMENT** |
| Negative or small† | | q2hr | | q2hr for glucose >250 mg/dL | | Check ketones every other void |
| Moderate to large‡ | | q1hr | | q1hr for glucose >250 mg/dL | | Check ketones each void; go to hospital if emesis occurs |

Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and Lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.

Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.

Call physician or nurse if blood glucose remains elevated after 3 extra doses; if blood glucose remains less than 70 mg/dL and child cannot take oral supplement; if dehydration occurs.

\*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.

†For home serum ketones <1.5 mmol/L per commercial kit.

‡For home serum ketones >1.5 mmol/L.

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| **Table 589-14** | Oral Hypoglycemic Agents | | | | | | |
| **DRUG** | | **MECHANISM OF ACTION** | **DURATION OF BIOLOGIC EFFECT (hr)** | **USUAL DAILY DOSE (mg)** | **DOSES/DAY** | **SIDE EFFECTS** | **CAUTION** |
| Biguanide  Metformin | | Insulin sensitizer |  | 1500-2500 | 2-3 | Gastrointestinal disturbance, lactic acidosis | Avoid in hepatic or renal impairment |
| Sulfonylureas | |  |  |  |  |  |  |
| 1st generation | |  |  |  |
| Acetohexamide | | 12-18 | 500-750 | 1 or divided |
| Chlorpropamide | | 27-72 | 250-500 | 1 |
| Tolbutamide | | 14-16 | 1000-2000 | 1 or divided |
| 2nd generation | |  |  |  |
| Glipizide | | 14-16 | 2.5-10 | 1 or divided |
|  | |  | XL: 5-10 | 1 |
| Glyburide | | 20-24+ | 2.5-10 | 1 or divided |
| Glimepiride | | 24+ | 2-4 | 1 |
| Glitinides | | Promote insulin secretion | ≤24 4 | 2-16  360 | 3  3 |  | Titrate carefully in renal or hepatic dysfunction |
| Repaglinide Nateglinide | |
| α-Glucosidase inhibitors  Acarbose Miglitol | | Slow hydrolysis and absorption of complex carbohydrates |  | 150-300  150-300 | 3 (with meals)  3 (with meals) | Transient gastrointestinal disturbances |  |
| Thiazolidinedione  Rosiglitazone Pioglitazone | | Peripheral insulin sensitizer |  | 4-8  15-45 | 1 or divided  1 | Upper respiratory tract infection, headache, edema, weight gain |  |
| Sitagliptin | | GLP-1 receptor agonist | 24 | 50-100 | 1 | Upper respiratory tract infection, sore throat, diarrhea | No data in children or adolescents |

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| **Table 589-16** | | Summary of MODY Types and Special Clinical Characteristics | | |
|  | **GENE MUTATED** | | **FUNCTION** | **SPECIAL FEATURE** |
| MODY1 | *HNF4α* | | Transcription factor | Decreased levels of triglycerides, apolipoproteins AII and CIII (5-10% of MODY), neonatal hypoglycemia, very sensitive to sulfonylureas |
| MODY2 | Glucokinase *(GCK)* | | Enzyme, glucose sensor | Hyperglycemia of early onset but mild and nonprogressive; common (30-70% MODY) |
| MODY3 | *HNF1α* | | Transcription factor | Decreased renal absorption of glucose and consequent glycosuria; common (30-70% of cases of MODY); very sensitive to sulfonylureas |
| MODY4 | *IPF-1* | | Necessary for pancreatic development | Homozygous mutation causes pancreatic agenesis |
| MODY5 | *HNF1β* | | Transcription factor | Renal malformations; associated with uterine abnormalities, hypospadias, joint laxity, and learning difficulties, pancreatic atrophy, pancreatic exocrine insufficiency; 5-10% of MODY |
| MODY6 | *NEUROD1* | | Differentiation factor in the development of pancreatic islets | Extremely rare |
| MODY7 | *KFL11* | | Zinc finger transcription factor | Early-onset type II diabetes mellitus |
| MODY8 | *CEL* | | Bile salt–dependent lipase | Hyperglycemia; fecal elastase deficiency; exocrine pancreatic atrophy |
| MODY9 | *PAX4* | | Transcription factor |  |
| MODY10 | *INS* | | Insulin gene | Usually associated with neonatal diabetes |
| MODY11 | *BLK* | | B-lymphocyte tyrosine kinase | Early-onset T1DM without autoantibodies |

MODY, maturity-onset diabetes of the young.

*From Nakhla M, Polychronakos C: Monogenic and other unusual causes of diabetes mellitus,* Pediatr Clin North Am *52:1637–1650, 2005.*

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| **Table 589-17** | Clinical and Biochemical Features Associated with Type 1 Diabetes, Type 2 Diabetes and the Common Subtypes of Maturity-Onset Diabetes of the Young | | | | |
| **FEATURES** | | **TYPE 1 DIABETES** | **TYPE 2 DIABETES** | **GCK-MODY** | **HNF1A/4A-MODY** |
| Typical age of diagnosis (yr) | | 10-30 | >25 | Present from birth; presents at any age | 15-45 |
| Diabetic ketoacidosis | | Common | Rare | Rare | Rare |
| Insulin dependent | | Yes | No | No | No |
| Parental history of diabetes | | <15% | >50% in young onset type 2 diabetes | If tested, 1 parent usually has impaired fasting glycemia (may not be previously known) | 60-90%\* |
| Obesity | | Uncommon | Common | Uncommon | Uncommon |
| Insulin resistance | | Uncommon | Common | Uncommon | Uncommon |
| Presence of β-cell antibodies | | >90% | Negative | Rare | Rare |
| C-peptide concentrations | | Undetectable/low | Normal/high | Normal | Normal |
| Optimal first-line treatment | | Insulin | Metformin | None | Sulfonylurea |

\*Family history is often part of the criteria for testing. Some reports cite a parental history of 60-70%.

GCK, glucokinase; HNF1A/4A, hepatocyte nuclear factor 1α/4α; MODY, maturity-onset diabetes of the young.

*From Thanabalasingham G, Owen KR: Diagnosis and management of maturity onset diabetes of the young (MODY),* BMJ *343:d6044, 2011, Table 2, p. 838.*

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| **Table 589-18** | Clinical and Biochemical Features of Inherited Lipodystrophies | | |
| **CONGENITAL GENERALIZED LIPODYSTROPHY**  **Subtype BSCL1 BSCL2** | | **FAMILIAL PARTIAL LIPODYSTROPHY** | |
| **FPLD2** | **FPLD3** |
| Defective gene *AGPAT2 BSCL2* | | *LMNA* | *PPARG* |
| Clinical onset Soon after birth Soon after birth | | Puberty | Usually puberty, but may present in younger children |
| Fat distribution Generalized absence Generalized absence | | Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost | Loss of limb and gluteal fat; preserved facial and trunk fat |
| Cutaneous features Acanthosis nigricans and Acanthosis nigricans and  skin tags; hirsutism skin tags; hirsutism common in women common in women | | Acanthosis nigricans and skin tags; hirsutism common in women | Acanthosis nigricans and skin tags; hirsutism common in women |
| Musculoskeletal Acromegaloid features Acromegaloid features  common common | | Frequent muscle hypertrophy; some have overlap features of muscular dystrophy | Nil specific |
| Nonalcoholic fatty Severe Severe liver disease | | Yes | Yes |
| Dyslipidemia Severe associated with Severe associated with  pancreatitis pancreatitis | | Yes, may be severe | Yes, may be severe |
| Insulin resistance Severe early onset Severe early onset | | Severe | Severe; early onset in some |
| Diabetes onset <20 yr <20 yr | | Variable; generally later in men than women | Variable; generally later in men than women |
| Hypertension Common Common | | Common | Very common |
| Other Mild mental retardation  possible | | | |

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| **Table 590-1** | Screening Scheme for Developmental Delay: Upper Range | | | |
| **AGE (mo)** | **GROSS MOTOR** | **FINE MOTOR** | **SOCIAL SKILLS** | **LANGUAGE** |
| 3 | Supports weight on forearms | Opens hands spontaneously | Smiles appropriately | Coos, laughs |
| 6 | Sits momentarily | Transfers objects | Shows likes and dislikes | Babbles |
| 9 | Pulls to stand | Pincer grasp | Plays pat-a-cake, peek-a-boo | Imitates sounds |
| 12 | Walks with 1 hand held | Releases an object on command | Comes when called | 1-2 meaningful words |
| 18 | Walks upstairs with assistance | Feeds from a spoon | Mimics actions of others | At least 6 words |
| 24 | Runs | Builds a tower of 6 blocks | Plays with others | 2-3–word sentences |

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| **Table 590-2** | Timing of Selected Primitive Reflexes | | |
| **REFLEX** | **ONSET** | **FULLY DEVELOPED** | **DURATION** |
| Palmar grasp | 28 wk gestation | 32 wk gestation | 2-3 mo postnatal |
| Rooting | 32 wk gestation | 36 wk gestation | Less prominent after 1 mo postnatal |
| Moro | 28-32 wk gestation | 37 wk gestation | 5-6 mo postnatal |
| Tonic neck | 35 wk gestation | 1 mo postnatal | 6-7 mo postnatal |
| Parachute | 7-8 mo postnatal | 10-11 mo postnatal | Remains throughout life |

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| **Table 590-2** | Timing of Selected Primitive Reflexes | | |
| **REFLEX** | **ONSET** | **FULLY DEVELOPED** | **DURATION** |
| Palmar grasp | 28 wk gestation | 32 wk gestation | 2-3 mo postnatal |
| Rooting | 32 wk gestation | 36 wk gestation | Less prominent after 1 mo postnatal |
| Moro | 28-32 wk gestation | 37 wk gestation | 5-6 mo postnatal |
| Tonic neck | 35 wk gestation | 1 mo postnatal | 6-7 mo postnatal |
| Parachute | 7-8 mo postnatal | 10-11 mo postnatal | Remains throughout life |

# The nervous System

**Chapter 590** ◆ Neurologic Evaluation **2801**

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| **Table 590-3** | Preferred Imaging Procedures in Neurologic Diseases | |
| ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK  CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions  Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images  If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA  Obtain an MRV if the infarct does not follow an arterial distribution CT or MRI can detect infarcts more than 24 hr old, although MRI is  generally preferred to avoid exposure to ionizing radiation | | HEADACHE  CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations as it does not involve ionizing radiation and provides a better view of the parenchyma) |
| HEAD TRAUMA  CT without contrast initially  MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities |
| INTRAPARENCHYMAL HEMORRHAGE  CT if <24 hr; MRI if >24 hr  MRI and MRA to assess for underlying vascular malformation, tumor, etc.  Catheter angiography if MRA is nondiagnostic | | EPILEPSY  MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected  PET  Interictal SPECT |
| ARTERIOVENOUS MALFORMATION  CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible  Catheter angiography if noninvasive imaging is nondiagnostic | | BRAIN TUMOR  MRI with and without gadolinium MRS  PET |
| CEREBRAL ANEURYSM  CT without contrast for acute subarachnoid hemorrhage MRA or CTA to identify the aneurysm  Catheter angiography may be necessary in some cases TCD to detect vasospasm | | MULTIPLE SCLEROSIS  MRI with and without gadolinium Obtain sagittal FLAIR images |
| MENINGITIS OR ENCEPHALITIS  CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination  MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis |
| HYPOXIC–ISCHEMIC BRAIN INJURY  Ultrasound in infants  If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI  In older children, CT if unstable; otherwise, MRI  MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes | |
| BRAIN ABSCESS  MRI with and without gadolinium  Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor  If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible |
| METABOLIC DISORDERS  MRI, particularly T2-weighted and FLAIR images  Diffusion-weighted images may be useful in distinguishing acute and chronic changes  MRS, SPECT, and PET may be useful in certain disorders | |
| MOVEMENT DISORDERS  MRI with and without gadolinium PET  DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes) |
| HYDROCEPHALUS  Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus MR with and without gadolinium for diagnosis of noncommunicating  hydrocephalus  Ultrasound (in infants) or CT to follow ventricular size in response to treatment | |

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography;

MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

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| **Table 591-5** | Commonly Used Clinical Genetic Classifications of Craniosynostoses |
| **DISORDER CAUSE** | |
| ISOLATED CRANIOSYNOSTOSIS  Morphologically described Unknown, uterine constraint, or  *FGFR3* mutation | |
| SYNDROMIC CRANIOSYNOSTOSIS  Antler-Bixler syndrome Unknown  Apert syndrome Usually 1 of 2 mutations in *FGFR2* Beare-Stevenson syndrome Mutation in *GFGR2* or *FGFR3* Baller-Gerold syndrome Mutation in *TWIST* heterogenous Carpenter syndrome Unknown  Craniofrontonasal dysplasia Unknown gene at *Xp22*  Crouzon syndrome Numerous different mutations at  *FGFR2*  Crouzonomesodermoskeletal Mutation in *FGFR3*  syndrome  Jackson-Weiss syndrome Mutation in *FGFR2*  Muenke syndrome Mutation in *FGFR3*  Pfeiffer syndrome Mutation in *FGFR1* or numerous mutation in *FGFR2*  Saethre-Chotzen syndrome Mutation in *TWIST*  Shprintzen-Goldberg Mutation in *FBEN1*  syndrome | |

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| **Table 591-1** | Cutaneous Lesions Associated with Occult Spinal Dysraphism |
| IMAGING INDICATED  Subcutaneous mass or lipoma Hairy patch  Dermal sinus  Atypical dimples (deep, >5 mm, >25 mm from anal verge) Vascular lesion, e.g., hemangioma or telangiectasia  Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages  Scar-like lesions | |
| IMAGING UNCERTAIN  Hyperpigmented patches Deviation of the gluteal fold | |
| IMAGING NOT REQUIRED  Simple dimples (<5 mm, <25 mm from anal verge) Coccygeal pits | |

*From Ridgway EB, Weiner HL: Skull deformities,* Pediatr Clin North Am

*51:359–387, 2004.*

**2810 Part XXVII** ◆ The Nervous System

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| **Table 591-2** Disorders Associated with Agenesis of | the | Corpus | Callosum\* |
| **DISORDER** | **SALIENT FEATURES** | | |
| WITH IDENTIFIED GENES† |  | | |
| Andermann syndrome *(KCC3)* | ACC, progressive neuropathy, and dementia | | |
| Donnai-Barrow syndrome *(LRP2)* | Diaphragmatic hernia, exomphalos, ACC, deafness | | |
| Frontonasal dysplasia *(ALX1)* | ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft | | |
| XLAG *(ARX)* | Lissencephaly, ACC, intractable epilepsy | | |
| Microcephaly *(TBR2)* | ACC, polymicrogyria | | |
| Microcephaly with simplified gyral pattern and ACC *(WDR62)* |  | | |
| Mowat-Wilson syndrome *(ZFHX1B)* | Hirschsprung disease, ACC | | |
| Pyridoxine-dependent epilepsy *(ALDH7A1)* | ACC, seizures, other brain malformations | | |
| Pyruvate dehydrogenase deficiency *(PDHA1, PDHB, PDHX)* | ACC with other brain changes | | |
| ACC with fatal lactic acidosis *(MRPS16)* | Complexes I and IV deficiency, ACC, brain malformations | | |
| HSAS/MASA syndromes *(L1CAM)* | Hydrocephalus, adducted thumbs, ACC, MR | | |
| ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED) |  | | |
| Acrocallosal syndrome | ACC, polydactyly, craniofacial changes, MR | | |
| Aicardi syndrome | ACC, chorioretinal lacunae, infantile spasms, MR | | |
| Chudley-McCullough syndrome | Hearing loss, hydrocephalus, ACC, colpocephaly | | |
| FG syndrome | MR, ACC, craniofacial changes, macrocephaly | | |
| Genitopatellar syndrome | Absent patellae, urogenital malformations, ACC | | |
| Temtamy syndrome | ACC, optic coloboma, craniofacial changes, MR | | |
| Toriello-Carey syndrome | ACC, craniofacial changes, cardiac defects, MR | | |
| Vici syndrome | ACC, albinism, recurrent infections, MR | | |
| ACC SEEN OCCASIONALLY (PARTIAL LIST)‡ |  | | |
| ACC with spastic paraparesis *(SPG11; SPG15)* | Progressive spasticity and neuropathy, thin corpus callosum | | |
| Craniofrontonasal syndrome | Coronal craniosynostosis, facial asymmetry, bifid nose | | |
| Fryns syndrome | CDH, pulmonary hypoplasia, craniofacial changes | | |
| Marden-Walker syndrome | Blepharophimosis, micrognathia, contractures, ACC | | |
| Meckel-Gruber syndrome | Encephalocele, polydactyly, polycystic kidneys | | |
| Nonketotic hyperglycinemia *(GLDC, GCST, GCSH)* | ACC, cerebral and cerebellar atrophy, myoclonus, progressive | | |
|  | encephalopathy | | |
| Microphthalmia with linear skin defects | Microphthalmia, linear skin markings, seizures | | |
| Opitz G syndrome | Pharyngeal cleft, craniofacial changes, ACC, MR | | |
| Orofaciodigital syndrome | Tongue hamartoma, microretrognathia, clinodactyly | | |
| Pyruvate decarboxylase deficiency | Lactic acidosis, seizures, severe MR and spasticity | | |
| Rubinstein-Taybi syndrome | Broad thumbs and great toes, MR, microcephaly | | |
| Septooptic dysplasia (de Morsier syndrome) | Hypoplasia of septum pellucidum and optic chiasm | | |
| Sotos syndrome | Physical overgrowth, MR, craniofacial changes | | |
| Warburg micro syndrome | Microcephaly, microphthalmia, microgenitalia, MR | | |
| Wolf-Hirschhorn syndrome | Microcephaly, seizures, cardiac defects, 4p− | | |

\*Reliable incidence data are unavailable for these very rare syndromes.

†Gene symbols in parentheses.

‡Many of these also may consistently have a thin of dysplastic corpus callosum, such as Sotos’ syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.

4p−, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.

*From Sherr EH, Hahn JS: Disorders of forebrain development. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman’s pediatric neurology*, 5th ed. Philadelphia, 2012, WB Saunders, Table 23-2.*

**Chapter 591** ◆ Congenital Anomalies of the Central Nervous System **2813**

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| **Table 591-3** Causes of Microcephaly |
| **CAUSES CHARACTERISTIC FINDINGS** |
| PRIMARY (GENETIC)  Familial (autosomal Incidence 1 in 40,000 live births  recessive) Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain, poorly differentiated and disorganized cytoarchitecture  Autosomal dominant Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears Normal linear growth, seizures readily controlled, and mild or borderline mental retardation  *Syndromes*  Down (trisomy 21) Incidence 1 in 800 live births  Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructure abnormalities of cerebral cortex  Edward (trisomy 18) Incidence 1 in 6,500 live births  Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons  Cri-du-chat (5 p-) Incidence 1 in 50,000 live births  Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry No specific neuropathology  Cornelia de Lange Prenatal and postnatal growth delay; synophrys; thin, downturning upper lip  Proximally placed thumb  Rubinstein-Taybi Beaked nose, downward slanting of palpebral fissures, epicanthic folds, short stature, broad thumbs and toes  Smith-Lemli-Opitz Ptosis, scaphocephaly, inner epicanthic folds, anteverted nostrils  Low birthweight, marked feeding problems |
| SECONDARY (NONGENETIC)  *Congenital Infections*  Cytomegalovirus Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures Central nervous system calcification and microgyria  Rubella Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness  Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations  Toxoplasmosis Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification  *Drugs*  Fetal alcohol Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart disease, feeding problems, neuroglial heterotopia, disorganization of neurons  Fetal hydantoin Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, anteverted nostrils  *Other Causes*  Radiation Microcephaly and mental retardation most severe with exposure before 15th wk of gestation Meningitis/encephalitis Cerebral infarcts, cystic cavitation, diffuse loss of neurons  Malnutrition Controversial cause of microcephaly  Metabolic Maternal diabetes mellitus and maternal hyperphenylalaninemia  Hyperthermia Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies Pathologic studies show neuronal heterotopias  Further studies show no abnormalities with maternal fever  Hypoxic–ischemic Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI encephalopathy |

**2820 Part XXVII** ◆ The Nervous System

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| **Table 591-6** | | Epidemiology and Clinical Characteristics of the Common Craniosynostoses | | |
| **TYPE** | **EPIDEMIOLOGY** | | **SKULL DEFORMITY** | **CLINICAL PRESENTATION** |
| Sagittal | Most common CSO affecting a single suture, 80% male | | Dolicocephaly or scaphocephaly (boat-shaped) | Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter |
| Coronal | 18% of CSO, more common in girls Associated with Apert syndrome  (with syndactyly) and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface) | | Unilateral: plagiocephaly Bilateral: brachycephaly,  acrocephaly | Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to harlequin sign on radiograph and outward rotation of orbit can result in amblyopia  Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis |
| Lambdoid | 10-20% of CSO, M : F ratio 4 : 1 | | Lambdoid/occipital plagiocephaly; right side affected in 70% of cases | Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior  Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears |
| Metopic | Association with 19p chromosome abnormality | | Trigonocephaly | Pointed forehead and midline ridge, hypotelorism |
| Multiple |  | | Oxycephaly | Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure |

CSO, craniosynostosis; OFC, occipital-frontal circumference.

*From Ridgway EB, Weiner HL: Skull deformities,* Pediatr Clin North Am *51:359–387, 2004.*

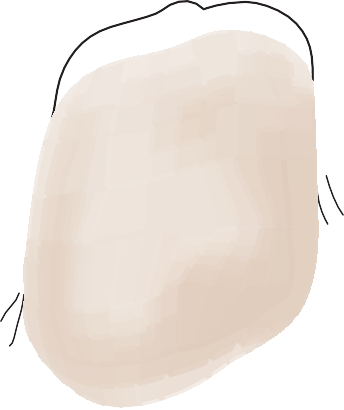
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| **Table 592-2** | Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly | | |
|  | | **DEFORMATIONAL** | **SYNOSTOTIC** |
| Birth history | | * Intrauterine compression * Firstborn child | * Typically no complications |
| Head shape at birth | | * Typically normal | * Can be irregular |
| Age first noticed shape irregularity | | * Usually in 1st few mo of life | * Can be at birth |
| How patient prefers to sleep | | * Same side, same position * Same even during naps | * Variable |
| Bald spot | | * Yes | * No |
| Motor development for age | | * If age atypical for deformational plagiocephaly, typically slow motor development for age * Torticollis present * History of limited activity or mobility | * Varies depending on presence of concomitant syndrome |
| Tummy time | | * Decreased | * Suggested time |
| Signs/symptoms of increasing intracranial pressure | | * No | * Possible |

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| **Table 592-3** | Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly | | |
|  | | **DEFORMATIONAL PLAGIOCEPHALY** | **CRANIOSYNOSTOSIS** |
| Causes | | External forces applied to the skull   * Prenatal: uterine compression, intrauterine constrained * Postnatal: congenital torticollis, sleeping position | Premature fusion of 1 or more cranial sutures |
| Common types | | * Lateral * Posterior | * Bilateral coronal * Sagittal * Metopic |
| Common distinguishing features | | * Normal round head shape at birth * Parallelogram shape to head * Ipsilateral ear anteriorly displaced * No palpable bony ridges | * Can have abnormal head shape at birth * Trapezoid shape to head * Ipsilateral ear posteriorly displaced * Palpable bony ridges |
| Management | | * Repositioning * Physical therapy * Helmet in some cases | * Surgery * Helmet in some cases |

*Adapted from Nield LS, Brunner MD, Kamat D: The infant with a misshapen head.* Clin Pediatr (Phila) *46:292–298, 2007, Tables 1 and 2.*

**Chapter 592** ◆ Deformational Plagiocephaly **2821**

###### Positional molding Unilateral lambdoid synostosis



Contralateral occipital

###### Flattening

Ipsilateral ear displaced anteriorly

###### Parietal bossing

###### Flattening

Ipsilateral ear displaced posteriorly

bossing

Ipsilateral

(variable)

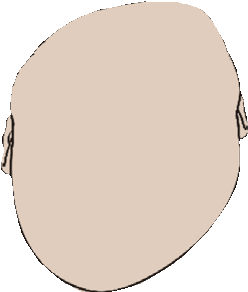
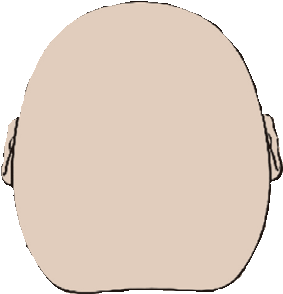
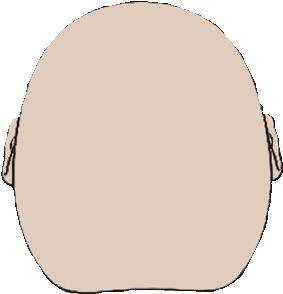
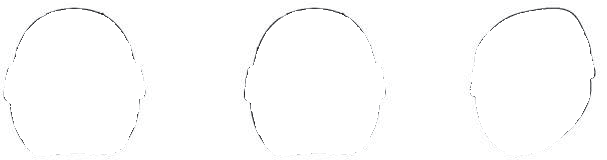
occipitomastoid



A B bossing

### **Figure 592-1** Differentiating physical find-ings between deformational plagiocephaly and craniosynostosis. Vertex views. **A,** Right-sided deformational plagiocephaly exhibit-ing a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape.

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Width

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| **Table 591-4** Causes of Hydrocephalus |
| COMMUNICATING  Achondroplasia Basilar impression  Benign enlargement of subarachnoid space Choroid plexus papilloma  Meningeal malignancy Meningitis Posthemorrhagic |
| NONCOMMUNICATING  Aqueductal stenosis Infectious\*  X-linked Mitochondrial Autosomal recessive Autosomal dominant *L1CAM* mutations Chiari malformation  Dandy-Walker malformation Klippel-Feil syndrome  Mass lesions Abscess Hematoma  Tumors and neurocutaneous disorders Vein of Galen malformation  Walker-Warburg syndrome |
| HYDRANENCEPHALY  Holoprosencephaly Massive hydrocephalus Porencephaly |

Length Transcranial

diagonal difference

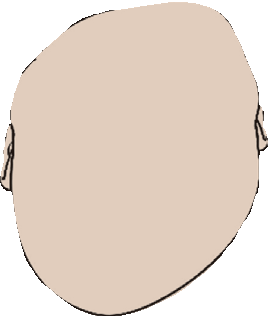
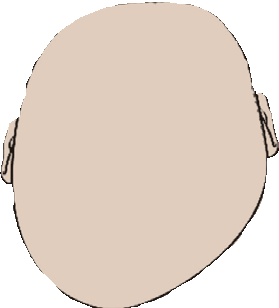
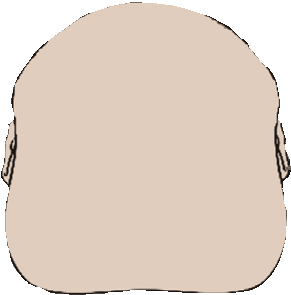
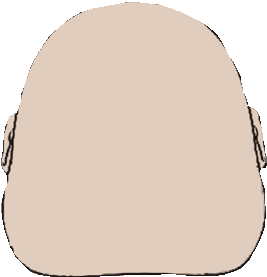
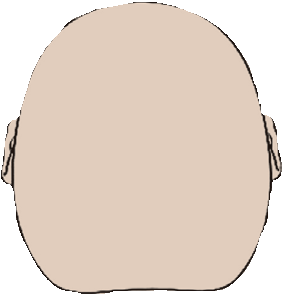
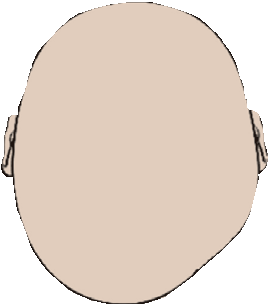
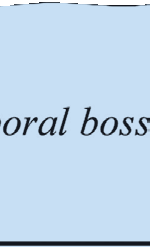
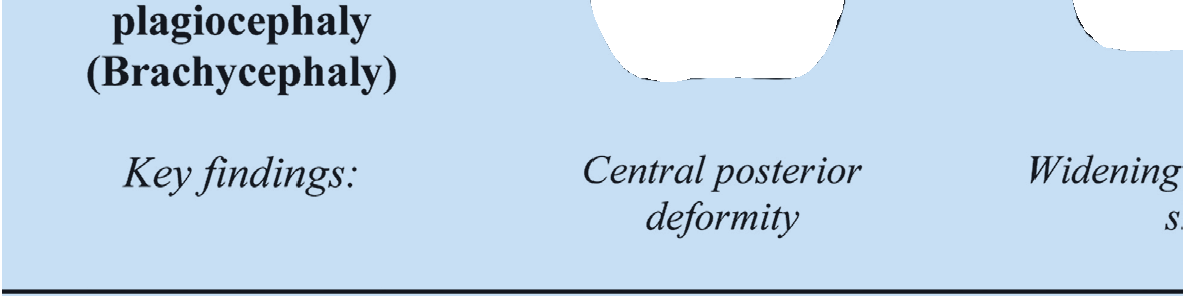
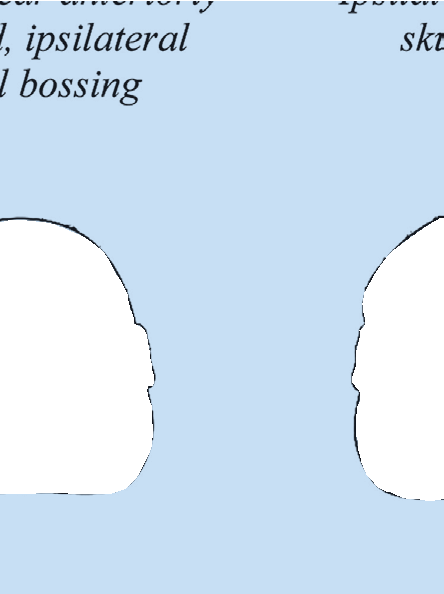
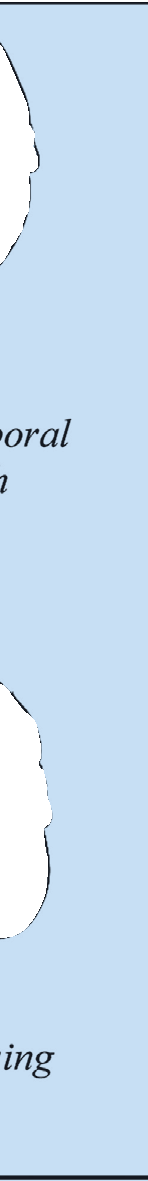
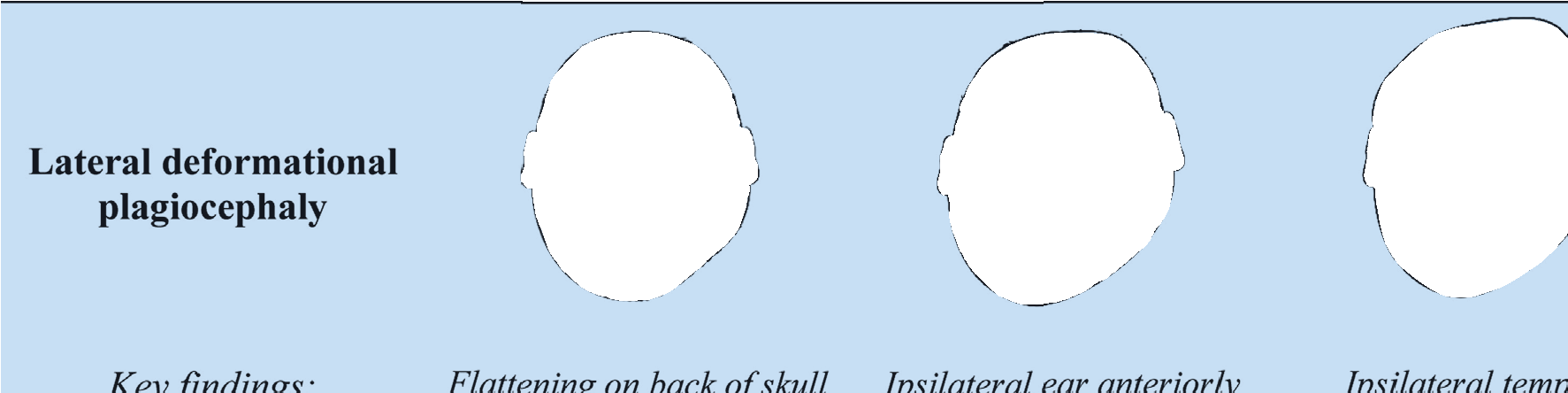
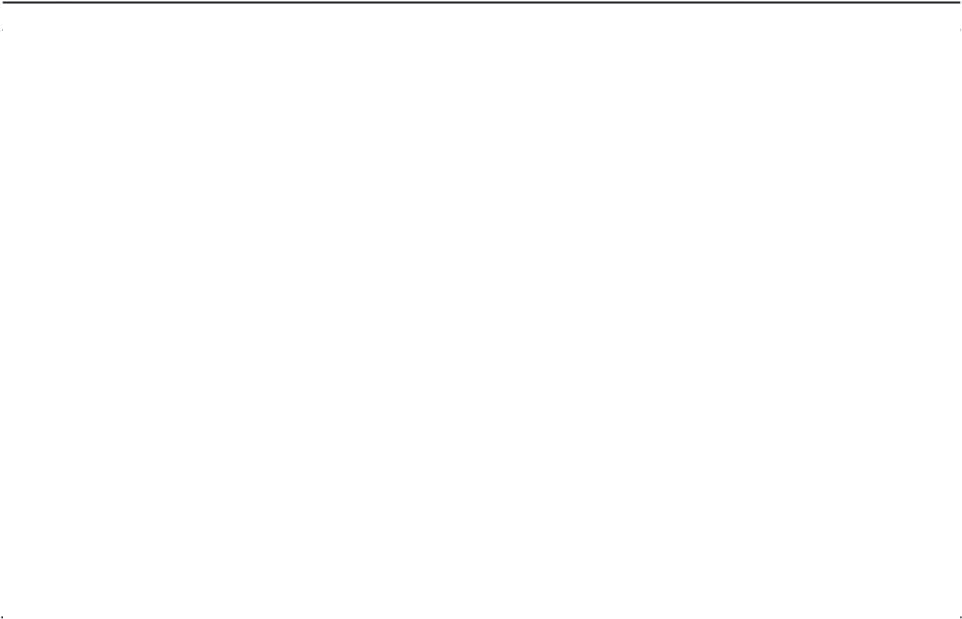
\*Toxoplasmosis, neurocysticercosis mumps.

**Figure 592-2** Cranial measurements.

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| **Table 592-4** Diagnostic Guide for Determining Type and Severity of Lateral | and Posterior Deformational Plagiocephaly |
| TYPE  **CLINICAL FINDINGS LATERAL DEFORMATIONAL PLAGIOCEPHALY** | **POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)** |
| Occiput (vertex view) Ipsilateral occipital flattening; contralateral occipital bossing  Ear position (vertex view) Ipsilateral ear may be anteriorly displaced  Face, forehead (anterior, lateral, May be normal; more-severe cases may present and vertex views) with the following: mandibular asymmetry,  ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced  Other Torticollis, head position preference | Uniform occipital flattening  Normal  Temporal bossing, increase in vertical height in severe cases  Large size, history of limited activity or limited mobility |
| SEVERITY  **LATERAL DEFORMATIONAL PLAGIOCEPHALY** | **POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)** |
| Mild TDD 3-10 mm Type I Flattening restricted to the back  of the skull Moderate TDD 10-12 mm Type II Malposition of ear  Type III Forehead deformity Severe TDD >12 mm Type IV Malar deformity  Type V Vertical or temporal skull growth | CI: 0.82-0.9 Central posterior deformity  (“ping-pong ball depression”)  CI: 0.9-1.0 Central posterior deformity and  widening of posterior skull  CI: >1.0 Vertical head, head growth, or temporal bossing |

CI, cephalic index (cranial index); TDD, transcranial diameter difference.



**Figure 592-3** Types of deformational plagiocephaly.

**2824 Part XXVII** ◆ The Nervous System

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| **Table 593-1** | Types of Epileptic Seizures | |
| SELF-LIMITED SEIZURE TYPES | | CONTINUOUS SEIZURE TYPES |
| *Focal Seizures* | | *Generalized Status Epilepticus* |
| Focal sensory seizures | | Generalized tonic-clonic status epilepticus |
| * With elementary sensory symptoms (e.g., occipital and parietal lobe | | Clonic status epilepticus |
| seizures) | | Absence status epilepticus |
| * With experiential sensory symptoms (e.g., temporoparietooccipital | | Tonic status epilepticus |
| junction seizures) | | Myoclonic status epilepticus |
| Focal motor seizures | | *Focal Status Epilepticus* |
| * With elementary clonic motor signs | | Epilepsia partialis continua of Kojevnikov |
| * With asymmetrical tonic motor seizures (e.g., supplementary motor | | Aura continua |
| seizures) | | Limbic status epilepticus (psychomotor status) |
| * With typical (temporal lobe) automatisms (e.g., mesial temporal | | Hemiconvulsive status with hemiparesis |
| lobe seizures) | |
| PRECIPITATING STIMULI FOR REFLEX SEIZURES  Visual stimuli   * Flickering light—color to be specified when possible * Patterns * Other visual stimuli Thinking   Music Eating Praxis  Somatosensory Proprioceptive Reading  Hot water Startle |
| * With hyperkinetic automatisms | |
| * With focal negative myoclonus | |
| * With inhibitory motor seizures | |
| Gelastic seizures | |
| Hemiclonic seizures | |
| Secondarily generalized seizures | |
| Reflex seizures in focal epilepsy syndromes | |
| *Generalized Seizures* | |
| Tonic-clonic seizures (includes variations beginning with a clonic or | |
| myoclonic phase) | |
| Clonic seizures | |
| * Without tonic features | |
| * With tonic features | |
| Typical absence seizures | |
| Atypical absence seizures | |
| Absence with special features: | |
| * Eyelid myoclonia | |
| * Myoclonic absence | |
| Tonic seizures | |
| Myoclonic seizures | |
| Myoclonic atonic seizures | |
| Negative myoclonus | |
| Atonic seizures | |
| Reflex seizures in generalized epilepsy syndromes | |
| *Unknown* | |
| *Epileptic Spasms* | |

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| --- | --- | --- |
| **Table 593-1** | Types of Epileptic Seizures | |
| SELF-LIMITED SEIZURE TYPES | | CONTINUOUS SEIZURE TYPES |
| *Focal Seizures* | | *Generalized Status Epilepticus* |
| Focal sensory seizures | | Generalized tonic-clonic status epilepticus |
| * With elementary sensory symptoms (e.g., occipital and parietal lobe | | Clonic status epilepticus |
| seizures) | | Absence status epilepticus |
| * With experiential sensory symptoms (e.g., temporoparietooccipital | | Tonic status epilepticus |
| junction seizures) | | Myoclonic status epilepticus |
| Focal motor seizures | | *Focal Status Epilepticus* |
| * With elementary clonic motor signs | | Epilepsia partialis continua of Kojevnikov |
| * With asymmetrical tonic motor seizures (e.g., supplementary motor | | Aura continua |
| seizures) | | Limbic status epilepticus (psychomotor status) |
| * With typical (temporal lobe) automatisms (e.g., mesial temporal | | Hemiconvulsive status with hemiparesis |
| lobe seizures) | |
| PRECIPITATING STIMULI FOR REFLEX SEIZURES  Visual stimuli   * Flickering light—color to be specified when possible * Patterns * Other visual stimuli Thinking   Music Eating Praxis  Somatosensory Proprioceptive Reading  Hot water Startle |
| * With hyperkinetic automatisms | |
| * With focal negative myoclonus | |
| * With inhibitory motor seizures | |
| Gelastic seizures | |
| Hemiclonic seizures | |
| Secondarily generalized seizures | |
| Reflex seizures in focal epilepsy syndromes | |
| *Generalized Seizures* | |
| Tonic-clonic seizures (includes variations beginning with a clonic or | |
| myoclonic phase) | |
| Clonic seizures | |
| * Without tonic features | |
| * With tonic features | |
| Typical absence seizures | |
| Atypical absence seizures | |
| Absence with special features: | |
| * Eyelid myoclonia | |
| * Myoclonic absence | |
| Tonic seizures | |
| Myoclonic seizures | |
| Myoclonic atonic seizures | |
| Negative myoclonus | |
| Atonic seizures | |
| Reflex seizures in generalized epilepsy syndromes | |
| *Unknown* | |
| *Epileptic Spasms* | |

**Chapter 593** ◆ Seizures in Childhood **2825**

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| **Table 593-2** Classification for Epilepsy Syndromes Prognosis, and Therapeutic Options | with an Indication of Age of Onset, Duration of Active | | | Epilepsy, |
| **SPECIFIC AGE AT AGE AT**  **SYNDROMES ONSET REMISSION** | **PROGNOSIS** | **MONOTHERAPY OR ADD-ON**\* | **POSSIBLE ADD-ON**† | **SURGERY**† |
| EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD  Benign infantile Infant Infant Good seizures (nonfamilial)  Benign childhood 3-13 yr 16 yr Good epilepsy with  centrotemporal spikes  Early and late-onset 2-8 yr; 6-17 yr 12 yr or Good idiopathic occipital younger;  epilepsy 18 yr | | PB  CBZ, LEV, OXC, VPA  CBZ, LEV, OXC, VPA | —  —  — | No No  No |
| FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES  Benign familial Newborn to Newborn to neonatal convulsions young infant young infant  Benign familial Infant Infant infantile convulsions  Autosomal dominant Childhood nocturnal frontal  lobe epilepsy  Familial lateral Childhood to  temporal lobe adolescence epilepsy  Generalized Childhood to  epilepsies with adolescence febrile seizures plus | Good Good Variable  Variable Variable | PB  CBZ, PB  CBZ, GBP, OXC, PHT, TPM  CBZ, GBP, OXC, PHT, TPM, VPA  ESM, LTG, TPM, VPA | —  —  CLB, LEV, PB, PHT  CLB, LEV, PB, PHT  CLB, LEV | No No No  No No |
| STRUCTURAL–METABOLIC FOCAL EPILEPSIES  *Limbic Epilepsy*  Mesial temporal lobe School-age or Long lasting epilepsy with earlier  hippocampal sclerosis  Mesial temporal lobe Variable Long lasting epilepsy defined by  specific causes  Other types defined Variable Long lasting by location and  causes  *Neocortical Epilepsies*  Rasmussen syndrome 6-12 yr Progressive  Hemiconvulsion- 1-5 yr Chronic hemiplegia  syndrome  Other types defined Variable Long lasting by location and  cause  Migrating partial Infant No remission seizures of early  infancy | Variable  Variable Variable  Ominous Severe  Variable Ominous | CBZ, LEV, OXC, TPM, VPA  CBZ, LEV, OXC, TPM, VPA  CBZ, LEV, OXC, TPM, VPA  Plasmapheresis, immunoglobulins  CBZ, LEV, OXC, TPM, VPA  CBZ, LEV, OXC, TPM, VPA  Bromides, CBZ, LEV, PB, PHT, TPM, VPA | CLB, GBP, LAC, PB, PHT, ZON  CLB, GBP, LAC, PB, PHT, ZON  CLB, FBM, GBP, LAC, PB, PHT, ZON  CBZ, LAC, PB, PHT, TPM  CLB, GBP, LAC, PB, PHT, ZON  PHT, PB, CLB, GBP, LAC, ZON  BDZ, LAC, ZON | Temporal resection  Temporal resection  Lesionectomy ±  temporal resection  Functional hemispherectomy  Functional hemispherectomy  Lesionectomy ±  cortical resection No |
| GENERALIZED EPILEPSIES OF UNKNOWN CAUSE  Benign myoclonic 3 mo-3 yr 3-5 yr epilepsy in infancy  Epilepsy with 3-5 yr Variable myoclonic astatic  seizures  Childhood absence 5-6 yr 10-12 yr epilepsy  Epilepsy with 1-12 yr Variable myoclonic absences | Variable Variable  Good  Guarded | LEV, TPM, VPA ESM, TPM, VPA  ESM, LTG, VPA  ESM, VPA | BDZ, ZON  BDZ, ketogenic diet, LEV, LTG, steroids, ZON  Acetazolamide, ketogenic diet, ZON  BDZ, ZON | No No  No  No |

\*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.

Continued

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| **Table 593-2** Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Prognosis, and Therapeutic Options—cont’d | | | | | Epilepsy, |
| **SPECIFIC AGE AT** | **AGE AT** |  | **MONOTHERAPY** | **POSSIBLE** |  |
| **SYNDROMES ONSET** | **REMISSION** | **PROGNOSIS** | **OR ADD-ON**\* | **ADD-ON**† | **SURGERY**† |
| GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES  Juvenile absence 10-12 yr Usually Good ESM, LTG, VPA epilepsy lifelong  Juvenile myoclonic 12-18 yr Usually Good LEV, TPM, VPA epilepsy lifelong  Epilepsy with 12-18 yr Usually Good LEV, LTG, TPM, generalized lifelong VPA  tonic-clonic seizures only | | | | BDZ  BDZ, LTG, PB, PRM, ZON  BDZ, CBZ, ZON | No No No |
| REFLEX EPILEPSIES  Idiopathic 10-12 yr photosensitive  occipital lobe epilepsy  Other visual sensitive 2-5 yr epilepsies  Startle epilepsy Variable | Unclear  Unclear Long lasting | Variable  Variable Guarded | VPA  VPA  CBZ, GBP, OXC, PHT, TPM, VPA | BDZ, LEV, LTG, ZON  BDZ, LEV, LTG, ZON  CLB, LEV, PB, PHT, ZON | No  No  Lesionectomy ± cortical resection in some |
| EPILEPTIC ENCEPHALOPATHIES  Early myoclonic Newborn- encephalopathy and infant Ohtahara syndrome  West syndrome Infant  Dravet syndrome Infant (severe myoclonic  epilepsy in infancy)  Lennox-Gastaut 3-10 yr syndrome  Landau-Kleffner 3-6 yr syndrome  Epilepsy with 4-7 yr continuous spike  waves during slow-wave sleep | Poor,  Ohtahara syndrome evolves into West syndrome  Variable  No remission  No remission 8-12 yr  8-12 yr | Ominous  Variable Severe  Severe Guarded  Guarded | PB, steroids, VGB  ACTH, steroids, VGB  CLB, stiripentol, TPM, VPA  CLB, LTG, RFD, TPM, VPA  LEV, nocturnal DZP, steroids, VPA  LEV, nocturnal DZP, steroids, VPA | BDZ, ZON | No |
| BDZ, FBM, IVIG, TPM, ZON  BDZ, ZON | Lesionectomy ±  cortical resection No |
| BDZ, FBM, IVIG,  steroids, ZON BDZ, ESM, IVIG,  LTG  BDZ, ESM, IVIG, LTG | Callosotomy  Multiple subpial transections, rarely lesionectomy  No |
| PROGRESSIVE MYOCLONUS EPILEPSIES  Unverricht-Lundborg, Late infant to Lafora, ceroid adolescent lipofuscinoses, etc. | Progressive | Ominous | TPM, VPA, ZON | BDZ, PB | No |
| OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES  Benign neonatal Newborn Newborn Good LEV, PB seizures  Febrile seizures 3-5 yr 3-6 yr Good PB or VPA if  repeated and prolonged  Reflex seizures Variable n/a LEV, VPA  Drug or other Variable n/a Withdraw  chemically induced offending agent  seizures  Immediate and early Variable n/a LEV, PHT posttraumatic  seizures | | | | — | No |
| — | No |
| LTG, ZON | No |
| — | No |
| — | No |

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| **Table 593-4** | Identified Genes for Syndromic Epilepsy Syndromes\* | | |
| **SYNDROME** | | **GENE** | **PROTEIN** |
| Rett/atypical Rett syndromes | | *MECP2 CDKL5 FOXG1 MBD5 MEF2C* | Methyl CpG binding protein 2 Cyclin-dependent kinase-like 5 Forkhead box protein G1  Methyl-CpG-binding domain protein 5 Myocyte-specific enhancer factor 2C |
| Angelman/Angelman-like/Pitt-Hopkins syndromes | | *UBE3A SLC9A6 MBD5 TCF4 NRXN1 CNTNAP2* | Ubiquitin protein ligase E3A Sodium/hydrogen exchanger 6  Methyl-CpG-binding domain protein 5 Transcription factor 4  Neurexin-1  Contactin-associated protein-like 2 |
| Mowat-Wilson syndrome Creatine deficiency syndromes | | *ZEB2* | Zinc finger E-box-binding homeobox 2 |
| *GAMT GATM* | Guanidinoacetate *N*-methyltransferase Glycine amidinotransferase, mitochondrial |
| Neuronal ceroid lipofuscinosis (NCL) | | *PPT1 (CLN1) TPP1 (CLN2) CLN3*  *CLN5 CLN6*  *MFSD8 (CLN7) CLN8*  *CTSD (CLN10) KCTD7 (CLN14)* | Palmitoyl-protein thioesterase 1  Tripeptidyl-peptidase 1 Battenin  Ceroid-lipofuscinosis neuronal protein 5 Ceroid-lipofuscinosis neuronal protein 6  Major facilitator superfamily domain-containing protein 8 Ceroid-lipofuscinosis neuronal protein 8  Cathepsin D  BTB/POZ domain-containing protein KCTD7 |
| Adenosuccinate lyase deficiency | | *ADSL* | Adenylosuccinate lyase |
| Cerebral folate deficiency | | *FOLR1* | Folate receptor alpha |
| Epilepsy with variable learning and behavioral disorders | | *GRIN2A SYN1* | Glutamate receptor ionotropic, *N*-methyl-D-aspartate (NMDA) 2A Synapsin-1 |
| 17q21.31 microdeletion syndrome | | *KANSL1* | KAT8 regulatory nonspecific lethal (NSL) complex subunit 1 |
| Microcephaly with early-onset intractable seizures and developmental delay (MCSZ) | | *PNKP* | Bifunctional polynucleotide phosphatase/kinase |

\*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

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| **Table 593-5** | Childhood Epileptic Syndromes with Generally Good Prognosis | |
| **SYNDROME** | | **COMMENT** |
| Benign neonatal familial convulsions | | Dominant, may be severe and resistant for a few days Febrile or afebrile seizures (benign) occur later in a minority |
| Infantile familial convulsions | | Dominant; seizures often in clusters |
| Febrile convulsions plus syndromes (see Table 593-2) | | Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal |
| Benign myoclonic epilepsy of infancy | | Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise) |
| Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes) | | Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG |
| Idiopathic occipital partial epilepsy | | Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus  Later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign |
| Petit mal absence epilepsy | | Cases with absences only; some have generalized seizures  In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission |
| Juvenile myoclonic epilepsy | | Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood |

#### EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

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Counsel parents about risk of recurrence and

how to provide first aid and manage fever.

Determine risk factors for later epilepsy

(Table 593-7)

**Low risk**

**Intermediate or high risk**

No therapy or

investigations are necessary

1. Consider EEG and imaging
2. Consider intermittent oral diazepam or, in exceptional cases that recur, continuous therapy

* History
* Exam
* Manage acute febrile seizure and acute illness (first aid, midazolam, diazepam, diagnostic tests) as needed.
* Determine risk factors for recurrence and estimate risk of recurrence of the febrile seizures (Table 593-6).

**Figure 593-1** Management of febrile seizures.

|  |  |
| --- | --- |
| **Table 593-6** | Risk Factors for Recurrence of Febrile Seizures |
| MAJOR  Age <1 yr  Duration of fever <24 hr Fever 38-39°C (100.4-102.2°F) | |
| MINOR  Family history of febrile seizures Family history of epilepsy Complex febrile seizure Daycare  Male gender  Lower serum sodium at time of presentation | |

Having no risk factors carries a recurrence risk of approximately 12%; 1 risk factor, 25-50%; 2 risk factors, 50-59%; 3 or more risk factors, 73-100%.

|  |  |
| --- | --- |
| **Table 593-8** | Selected Epilepsy Syndromes by Age of Onset |
| NEONATAL PERIOD  Benign familial neonatal seizures (BFNS) Early myoclonic encephalopathy (EME) Ohtahara syndrome | |
| INFANCY  Epilepsy of infancy with migrating focal seizures West syndrome  Myoclonic epilepsy in infancy (MEI) Benign infantile seizures  Benign familial infantile epilepsy Dravet syndrome  Myoclonic encephalopathy in nonprogressive disorders | |
| CHILDHOOD  Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures)  Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)  Epilepsy with myoclonic atonic (previously astatic) seizures Benign epilepsy with centrotemporal spikes (BCECTS) Late-onset childhood occipital epilepsy (Gastaut type)  Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE) Epilepsy with myoclonic absences  Lennox-Gastaut syndrome  Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)  Landau-Kleffner syndrome Childhood absence epilepsy (CAE) | |
| ADOLESCENCE–ADULT  Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME)  Epilepsy with generalized tonic–clonic seizures alone Progressive myoclonus epilepsies (PME)  Autosomal dominant epilepsy with auditory features (ADEAF) Other familial temporal lobe epilepsies | |
| AGE-RELATED (AGE OF ONSET LESS SPECIFIC)  Familial focal epilepsy with variable foci (childhood to adult) Reflex epilepsies | |
| SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY  Benign neonatal seizures (BNS) Febrile seizures (FS) | |
| EPILEPTIC ENCEPHALOPATHIES  EME  Ohtahara syndrome  Migrating partial seizures of infancy West syndrome  Dravet syndrome  Myoclonic encephalopathy in nonprogressive disorders Epilepsy with myoclonic astatic seizures  Lennox-Gastaut syndrome  Epileptic encephalopathy with CSWS Landau-Kleffner syndrome | |
| OTHER SECONDARY GENERALIZED EPILEPSIES  Generalized epilepsy secondary to neurodegenerative disease Progressive myoclonus epilepsies | |

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis:

* Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed.
* Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
* Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
* Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
* Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.

Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

**Table 593-9**

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| --- | --- | --- |
| **Table 593-7** | Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure | |
| **RISK FACTOR** | | **RISK FOR SUBSEQUENT EPILEPSY** |
| Simple febrile seizure | | 1% |
| Recurrent febrile seizures | | 4% |
| Complex febrile seizures (more than 15 min duration or recurrent within 24 hr) | | 6% |
| Fever <1 hr before febrile seizure | | 11% |
| Family history of epilepsy | | 18% |
| Complex febrile seizures (focal) | | 29% |
| Neurodevelopmental abnormalities | | 33% |

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Did the child have a seizure?

NO YES

Benign paroxysmal

vertigo Breath holding Cough syncope

Familial choreoathetosis Hereditary chin trembling Shuddering attacks Narcolepsy

Night terror Pseudoseizures Rage attack

Benign myoclonus of infancy

Tics

*Initial Seizure*

Fasting blood sugar, calcium, metabolic studies dictated by history and physical; EEG? CT scan? MRI?

CSF examination?

*Studies and Examination*

*Recurrent Seizures* Drug compliance? Improper dose?

Incorrect drug? Metabolic disorder?

Underlying structural lesion? Drug interaction?

CNS degenerative disease? Intractable seizures?

*Abnormal Symptomatic Seizures* Treat underlying cause

(hypoglycemia, urea cycle abnormality, meningitis, temporal lobe tumor, etc.)

Antiepileptic drugs if necessary

*Normal*

Isolated first seizure with normal EEG

Negative family history No continuous drug

treatment Close observation Prescribe rescue

medications (rectal diazepam) for seizures longer than 5 min

*Normal (except EEG) Consider drug therapy*

*Follow-up*

*Good Control*

Regular follow-up Antiepileptic drug levels Monitor toxicity (CBC,

liver function, behavioral, learning)

EEG as indicated

*Poor Control*

Consider hospitalization Prolonged EEG

recording and video monitoring for possible epilepsy surgery candidacy

Readjust medication Reconsider underlying

pathology with reinvestigation with CT or MRI

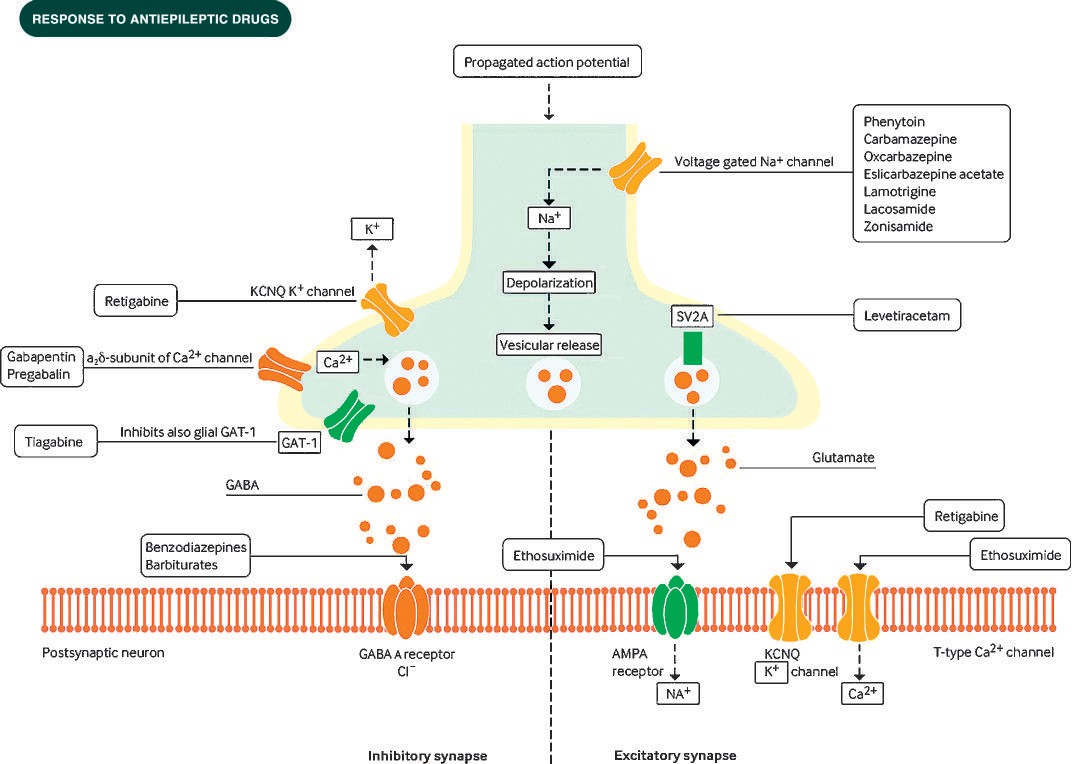
Frequent follow-up

**Figure 593-4** Approach to the child with a suspected convulsive disorder.

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| **Table 593-10** | Sports and Special Considerations for the Child with Epilepsy\* |
| **SPORTS TYPE** | **SPECIAL CONSIDERATIONS** |
| Body contact sports | If there are more than occasional seizures, physician evaluation of benefits and risks of participation should be made based on the child’s condition. No contraindications in general except for boxing. |
| Noncontact sports | Generally recommended. Anxiety and fatigue can cause a problem in some children.  Individualization based on clinical history must be the rule. |
| Gymnastics | A fall can result if the child experiences a sudden seizure, especially with trampolines, parallel bars, and rope climbing, which should be avoided.  Individual consideration remains the basic determinant. |
| Swimming | The child should always be under supervision, and scuba diving should be discouraged in poorly controlled epileptics. |

### \*Specific advice should be individualized depending on the patient’s clinical condition. Many patients actually have fewer seizures when they are active than when they are idle.

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###### **Figure 593-5** Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory *(left hand side)* and excitatory *(right hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored. AMPA, α-amino- 3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults.* BMJ, *348:bmj.g254, 2014.)*

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| **Table 593-11** Comparison of Recommendations for the Treatment of Pediatric Epilepsy | | | | | | | |
| **SEIZURE TYPE OR EPILEPSY SYNDROME** | **FDA APPROVED** | **SIGN (2005)** | **NICE (2012)** | **AAN (2004)** | **ILAE (2013)**\* | **PEDIATRIC EXPERT CONSENSUS SURVEY (NORTH AMERICA–2005)** | **PEDIATRIC EXPERT CONSENSUS SURVEY (EUROPE–2007)** |
| Partial-onset | CBZ,  ezogabine, lacosamide, LEV, LTG, OXC, PB,  perampanel, PHT, TPM, VGB | CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA | CBZ, LEV, LTG, OXC, VPA | CBZ, GBP, LTG, OXC, PB, PHT, TPM | A: OXC  B: None  C: CBZ, PB, PHT, TPM, VGB, VPA  D: CLB, CZP, LTG, ZNS | CBZ, OXC | CBZ, OXC |
| BCECT | None | Not  specifically mentioned | CBZ, LEV, LTG, OXC, VPA | Not surveyed | A, B: None C: CBZ, VPA D: GBP, LEV,  OXC, STM | CBZ, OXC | VPA |
| Childhood absence epilepsy | ESM, VPA | ESM, LTG, VPA | ESM, LTG, VPA | LTG | A: ESM, VPA  B: None C: LTG  D: None | ESM | VPA |
| Juvenile myoclonic epilepsy | LEV, LTG, TPM | VPA | LEV, LTG, TPM, VPA | Not surveyed | A, B, C: None D: TPM, VPA | LTG, VPA | VPA |
| Lennox- Gastaut syndrome | CLB, FLB, LTG,  rufinamide (atonic), TPM | CLB, LTG, VPA | VPA | Not surveyed | Not reviewed | LTG, VPA | VPA |
| Infantile spasms | VGB | Nitrazepam, TPM, VGB, VPA | Corticosteroids, VGB | ACTH, VGB  (updated IS guidelines 2012) | Not reviewed | ACTH, VGB | VGB |
| Primary generalized tonic-clonic seizures | LEV, LTG, TPM | TPM, VPA | LTG, TPM, VPA | No evidence given | A: None B: None  C: CBZ, PB, PHT, TPM, VPA  D: OXC |  |  |

\*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

*Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion,* Epileptic Disord *9:353–412, 2007; and Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia *54(3):551–563, 2013.*

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| **Table 593-12** | Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs | | |
| **FINDING** | | **RECOMMENDATION** | **LEVEL OF RECOMMENDATION** |
| VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome | | If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome | B |
| AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes | | If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome | B |
| Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes | | If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes | C |
| Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of <7 | | Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of <7 | C |

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

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| **Table 593-13** | Dosages of Selected Antiepileptic Drugs | | | | |
| **MEDICATION** | **FDA APPROVAL (AGE APPROVED)** | **MAINTENANCE ORAL**  **DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED** | **USUAL DOSING** | **THERAPEUTIC LEVELS** | **PREPARATIONS** |
| Acetazolamide | Absence seizures (adults) | 1-12 mo; 10 <1 yr: 20-30 | bid or tid | 10-15 mg/L | 125, 250, 500 mg tabs |
| Bromide |  | 50-100 | bid or qd | 10-15 mEq/L | Supplied as triple bromide soln (240 mg/ mL of bromide salt) |
| Carbamazepine\* | Partial and GTC (all ages) | 10-20 | tid or qid  SR usually bid | 3-12 mg/L | 150, 300 mg ER caps  100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs  100 mg/5 mL susp |
| Clobazam† | LGS (all ages above 2 yr) | 10-20 mg/day | bid or tid | 60-200 μg/L | 5 mg, 10 mg, 20 mg tabs  2.5 mg/mL soln |
| Clonazepam† | Absence sz, LGS, myoclonic sz (all ages) | 0.05-0.2 | bid or tid | 25-85 μg/L | 0.5, 1, 2 mg tabs  0.125, 0.25, 0.5 mg orally disintegrating tabs |
| Diazepam | Partial sz (all ages  >6 mo) | 0.25-1.5  0.01-0.25 IV  0.2-0.5 mg/kg rectal (according to age; see Table 593-15) | bid or tid | 100-700 μg/L | 2, 5, 10 mg tabs  5 mg/mL, 5 mg/5 mL soln Rectal gel that can be  dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5,  20 mg |
| Ethosuximide | Absence sz (>3 yr) | 20-30 | bid or tid | 40-100 mg/L | 250 mg caps  250 mg/5 mL syrup, soln |
| Ezogabine | Partial sz (adults) | No pediatric dose approved | tid | — | 50, 200, 300, 400 mg tabs |
| Felbamate | LGS (>2 yr) Partial sz (>14 yr) | 15-45 | bid or tid | 50-110 mg/L | 400, 600 mg tabs 600 mg/5 mL susp |
| Gabapentin‡ | Partial sz (>3 yr) | 30-60 | tid | 2-20 mg/L | 100, 300, 400 mg caps,  600, 800 mg tabs |
| Lacosamide | Partial sz (>17 yr) | No FDA approved dose.  4-12 | bid | <= 15 μg/L | 50, 100, 150, 200 mg tabs 10 mg/mL oral soln |

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| **Table 593-13** Dosages of Selected Antiepileptic Drugs—cont’d | | | | | |
| **MEDICATION** | **FDA APPROVAL (AGE APPROVED)** | **MAINTENANCE ORAL**  **DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED** | **USUAL DOSING** | **THERAPEUTIC LEVELS** | **PREPARATIONS** |
| Lamotrigine | LGS, partial and tonic–clonic sz (age  >2 yr) | 5-15§  1-5¶ | tid bid | 1-15 mg/L | 25, 100, 150, 200 mg tabs  5, 25 mg chewable dispersible tabs  25, 50, 100, 200 mg ODTs  25, 50, 100, 200, 250,  300 mg ER tabs |
| Levetiracetam† | Myoclonic, partial and tonic–clonic sz (age  >4-6 yr) | 20-40 | bid or tid | 6-20 mg/L | 250, 500, 750 mg tabs  100 mg/mL soln  500, 750 mg SR (ER) tabs |
| Lorazepam | Status epilepticus (all ages) | 0.05-0.1 | bid or tid | 20-30 μg/L | 0.5, 1, 2 mg tabs  2 mg/mL soln |
| Methsuximide (or methsuximide) | Absence sz (children and older) | 10-30 | bid or tid | 10-50 mg/L | 150, 300 mg caps |
| Nitrazepam | – | 0.25-1 | bid or tid | <200 μg/L | 5 mg tabs |
| Oxcarbazepine\* | Partial sz (>2 yr) | 20-40 | bid | 13-28 mg/L | 150, 300, 600 mg tabs 300 mg/5 mL susp |
| Perampanel | Partial sz (>12 yr) | 2-12 mg per day (older than 12 yr) | qhs | - | 2 mg, 4 mg, 6 mg, 8 mg,  10 mg, 12 mg tabs |
| Phenobarbital | Myoclonic, partial, and tonic–clonic sz and status (all ages) | <5 yr, 3-5  >5 yr, 2-3 | bid or qd | 10-40 mg/L | 15, 30, 60, 90, 100 mg  tabs  4 mg/mL soln |
| Phenytoin | Partial, tonic–clonic sz and status (all ages) | <3 yr, 8-10  >3 yr, 4-7 | tabs, susp: tid caps: qd | 5-20 mg/L | 50 mg tabs  30,100 mg caps 125 mg/5 mL susp |
| Pregabalin | Partial sz (adults) | 2-14 | bid | Up to  10 μg/mL | 25, 50, 75, 100, 150, 200,  225, 300 mg caps  20 mg/mL soln |
| Primidone | Partial and tonic– clonic sz (all ages) | 10-20 | bid or tid | 4-13 mg/L | 50, 250 mg tabs, susp |
| Rufinamide† | LGS (age >4 yr) | 30-45 | bid | <60 μg/mL | 200, 400 mg tabs |
| Sulthiame |  | 5-15 | bid or tid | 1.5-20 μg/mL | 50, 200 mg caps Not available in all  countries |
| Tiagabine | Partial sz (age >2 yr) | 0.5-2 | bid, tid, qid | 80-450 μg/L | 2, 4, 12, 16 mg tabs |
| Topiramate† | LGS, partial and tonic–clonic sz (all ages) | 3-9, slow titration | bid or tid | 2-25 mg/L | 25, 100, 200 mg tabs  15, 25 mg sprinkle caps |
| Valproate | Absence, myoclonic, partial and tonic– clonic sz (age >2 yr) | 15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day) | Sprinkle caps: bid  Soln: tid | 50-100 mg/L | 250 mg caps  125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln |
| Vigabatrin | Infantile spasms and partial sz (age  >1 mo) | 50-150 | bid | 20-160 μg/mL | 500 mg tabs  500 mg powder for soln |
| Zonisamide | Partial sz (age >16 yr) | 4-8 | bid or qd | 10-40 mg/L | 100 mg caps |

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

\*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

†Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

‡Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

§Child on enzyme inducers.

Available in some European countries.

¶Child on valproate.

cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

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| **Table 593-14** Some | Common Adverse Effects of Antiepileptic Drugs\* |
| **ANTIEPILEPTIC DRUG** | **SIDE EFFECT(S)** |
| Acetazolamide | Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome |
| Benzodiazepines | Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea |
| Bromide | Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life |
| Carbamazepine | Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity |
| Ezogabine | Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria  Serious: blue discoloration of the skin and retinal pigmentation that requires close ophthalmologic monitoring in follow up, urinary retention |
| Felbamate | Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness  Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurological disorders) |
| Gabapentin | In children: acute onset of aggression, hyperactivity  In adults: euphoria and behavioral disinhibition, weight gain |
| Lacosamide | Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed) |
| Lamotrigine | Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity |
| Levetiracetam | CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: behavioral symptoms are common  In adults: depressive mood |
| Oxcarbazepine | Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia |
| Perampanel | Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder |
| Phenobarbital and other barbiturates | Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome |
| Phenytoin and other hydantoins | Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia)  Serious: Stevens-Johnson syndrome, liver toxicity |
| Pregabalin | Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions, rhabdomyolysis |
| Primidone | Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome |
| Rufinamide | Nuisance: somnolence, vomiting  Serious: contraindicated in familial short QT interval |
| Succinimides | Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus |
| Tiagabine | Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus |
| Topiramate | Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever Serious: precipitation of glaucoma |
| Valproic acid | Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity |
| Vigabatrin | Nuisance: hyperactivity  Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up |
| Zonisamide | Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever |

\*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions. AED, antiepileptic drug; CNS, central nervous system.

**2850 Part XXVII** ◆ The Nervous System

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| **Table 593-16** Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures | |
| **CLASSIFICATION** | **CHARACTERIZATION** |
| Focal clonic | Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal  May occur synchronously or asynchronously in muscle groups on 1 side of the body May occur simultaneously but asynchronously on both sides  Cannot be suppressed by restraint Pathophysiology: epileptic |
| Focal tonic | Sustained posturing of single limbs  Sustained asymmetrical posturing of the trunk Sustained eye deviation  Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic |
| Generalized tonic | Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor  May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic |
| Myoclonic | Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate  May be generalized, focal, or fragmentary May be provoked by stimulation  Presumed pathophysiology: may be epileptic or nonepileptic |
| Spasms | May be flexor, extensor, or mixed extensor/flexor May occur in clusters  Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic |
| Motor automatisms | |
| Ocular signs | Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation  Presumed pathophysiology: nonepileptic |
| Oral-buccal-lingual movements | Sucking, chewing, tongue protrusions  May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic |
| Progression movements | Rowing or swimming movements  Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic |
| Complex purposeless movements | Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation  Presumed pathophysiology: nonepileptic |

*From Mizrahi EM, Kellaway P.* Diagnosis and management of neonatal seizures*. Philadelphia, 1998, Lippincott-Raven. Tab 4, p. 21.*

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| **Table 593-17** | Causes of Neonatal Seizures According to Common Age of Presentation |
| AGES 1-4 DAYS  Hypoxic–ischemic encephalopathy  Drug withdrawal, maternal drug use of narcotic or barbiturates Drug toxicity: lidocaine, penicillin  Intraventricular hemorrhage Acute metabolic disorders   * Hypocalcemia * Sepsis * Maternal hyperthyroidism, or hypoparathyroidism * Hypoglycemia * Perinatal insults, prematurity, small for gestational age * Maternal diabetes * Hyperinsulinemic hypoglycemia * Hypomagnesemia * Hyponatremia or hypernatremia * Iatrogenic or inappropriate antidiuretic hormone secretion Inborn errors of metabolism * Galactosemia * Hyperglycinemia * Urea cycle disorders   Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age) | |
| AGES 4-14 DAYS  Infection   * Meningitis (bacterial) * Encephalitis (enteroviral, herpes simplex) Metabolic disorders * Hypocalcemia * Diet, milk formula * Hypoglycemia, persistent * Inherited disorders of metabolism * Galactosemia * Fructosemia * Leucine sensitivity * Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome * Anterior pituitary hypoplasia, pancreatic islet cell tumor * Beckwith syndrome   Drug withdrawal, maternal drug use of narcotics or barbiturates Benign neonatal convulsions, familial and nonfamilial Kernicterus, hyperbilirubinemia  Developmental delay, epilepsy, neonatal diabetes syndrome | |
| AGES 2-8 WK  Infection   * Herpes simplex or enteroviral encephalitis * Bacterial meningitis Head injury * Subdural hematoma * Child abuse   Inherited disorders of metabolism   * Aminoacidurias * Urea cycle defects * Organic acidurias * Neonatal adrenoleukodystrophy Malformations of cortical development * Lissencephaly * Focal cortical dysplasia Tuberous sclerosis Sturge-Weber syndrome | |

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| **Table 597-9** | Selected Causes of Tremor in Children |
| BENIGN  Enhanced physiologic tremor Shuddering attacks Jitteriness  Spasmus nutans | |
| STATIC INJURY/STRUCTURAL  Cerebellar malformation  Stroke (particularly in the midbrain or cerebellum) Multiple sclerosis | |
| HEREDITARY/DEGENERATIVE  Familial essential tremor Fragile X premutation Wilson disease Huntington disease  Juvenile parkinsonism (tremor is rare) Pallidonigral degeneration | |
| METABOLIC  Hyperthyroidism  Hyperadrenergic state (including pheochromocytoma and neuroblastoma)  Hypomagnesemia Hypocalcemia Hypoglycemia  Hepatic encephalopathy Vitamin B12 deficiency Inborn errors of metabolism Mitochondrial disorders | |
| DRUGS/TOXINS  Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors | |
| PERIPHERAL NEUROPATHIES | |
| PSYCHOGENIC | |

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| **Table 593-19** | Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome—Uganda, 2012-2013\* | |
| **TYPE OF CASE** | **CONSENSUS CASE DEFINITION** | **MODIFIED CONSENSUS CASE DEFINITION** |
| Suspected case | Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person | Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person |
| Probable case | Suspected case of head nodding, with both major criteria:   * Age of onset of nodding ranging from 3-18 yr * Frequency of nodding 5-20 per minute Plus at least 1 of the following minor criteria: * Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) * Clustering in space or time with similar cases * Triggering by food or cold weather * Stunting or wasting * Delayed sexual or physical development * Psychiatric symptoms | Suspected case of head nodding, with 1 major criterion:   * Age of onset of nodding ranging from 3-18 yr   Plus at least 1 of the following minor criteria:   * Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) * Clustering in space or time with similar cases * Triggering by food or cold weather * Stunting or wasting * Psychiatric symptoms |
| Confirmed case | Probable case, with documented nodding episode   * Observed and recorded by a trained healthcare worker,   *or*   * Videotaped nodding episode, *or* * Video/EEG/EMG documenting head nodding as atonic seizures | Probable case, with documented nodding episode   * Observed and recorded by a trained healthcare worker, *or* * Videotaped nodding episode, *or* * Video/EEG/EMG documenting head nodding as atonic seizures |

\*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30–August 1, 2012, in Kampala, Uganda. Meeting report available at [http://www.who.int/neglected\_diseases/diseases/Nodding\_syndrom\_Kampala\_Report\_2012.pdf.](http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf) The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

*From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013.* MMWR Morb Mortal Wkly Rep *63:603–606, 2014, Table 1.*

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| **Table 593-18** | Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus | | |
| **DRUG**\* | | **ROUTE** | **DOSAGE** |
| Lorazepam | | Intravenous Intranasal | 0.1 mg/kg up to 4 mg total, may repeat in 5-10 min  0.1 mg/kg |
| Midazolam  Diazepam | | Intravenous  Intramuscular Intranasal Buccal | 0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min 0.08-0.23 mg/kg/hr maintenance  0.2 mg/kg  0.2 mg/kg  0.5 mg/kg |
| Intravenous Rectal | 0.15 mg/kg up to a max total dose of 10 mg, may repeat in 5-10 min 2-5 yr: 0.5 mg/kg  6-11 yr: 0.3 mg/kg  ≥12 yr: 0.2 mg/kg |
| Fosphenytoin | | Intravenous | 20 mg/kg PE, then 3-6 mg/kg/24 hr, loading rate up to 50 mg PE per min |
| Phenobarbital† | | Intravenous | 5-20 mg/kg |
| Pentobarbital coma† | | Intravenous | 13.0 mg/kg, then 1-5 mg/kg/hr |
| Propofol† | | Intravenous | 1 mg/kg (bolus), then 1-15 mg/kg/hr (infusion) |
| Thiopental† | | Intravenous | 5 mg/kg/1st hr, then 1-2 mg/kg/hr |
| Valproate† | | Intravenous | Loading: 25 mg/kg, then 30-60 mg/kg/24 hr |
| Lacosamide† | | Intravenous | Loading: 4 mg/kg then 4-12 mg/kg/24 hr |
| Levetiracetam | | Intravenous | 20-60 mg/kg |
| Topiramate | | Enterally | 5-10 mg/kg/24 hr (loading dose) then same or lower for maintenance |

\*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.

†May cause PR prolongation.

PE, phenytoin sodium equivalents.

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| **Table 593-3** Identified Genes for Epilepsy Syndromes\*† | | |
| **EPILEPSY TYPE** | **GENE** | **PROTEIN** |
| INFANTILE ONSET  Benign familial neonatal seizures  Benign familial neonatal infantile seizures Early familial neonatal infantile seizures  Early infantile epileptic encephalopathy (EIEE) | *KCNQ2 KCNQ3 SCN2A SCN2A CDKL5 (EIEE2) ARX (EIEE1) TSC1*  *TSC2*  *SCN1A (EIEE6) PCDH19(EIEE9) KCNQ2 (EIEE7) STXBP1 (EIEE4) SLC2A1* | Potassium voltage-gated channel Potassium voltage-gated channel Sodium channel protein type 2α Sodium channel protein type 2α Cyclin-dependent kinase-like 5 Aristaless-related homeobox Hamartin  Tuberin  Sodium channel protein type 1α Protocadherin-19  Potassium voltage-gated channel Syntaxin binding protein 1  Solute carrier family 2, facilitated glucose transporter member 1  α-Aminoadipic semialdehyde dehydrogenase (antiquitin)  DNA polymerase subunit gamma-1 Sodium channel protein type 2α Phospholipase C β1  Renin receptor  α2-Spectrin  Mitochondrial glutamate carrier 1 Pyridoxine-5′-phosphate oxidase Sodium channel protein type 1α Sodium channel protein type 1β  γ-Aminobutyric acid receptor subunit γ2 Sodium channel protein type 1α |
|  | *ALDH7A1* |
| Generalized epilepsy with febrile seizures plus (early onset) | *POLG*  *SCN2A (EIEE11) PLCβ1 (EIEE12) ATP6AP2 SPTAN1 (EIEE5) SLC25A22 (EIEE3) PNPO*  *SCN1A SCN1B GABRG2 SCN2A* |
| CHILDHOOD ONSET  Childhood onset epileptic encephalopathies | *SCN1A PCDH19 SLC2A1 POLG SCN2A*  *GLUT-1* deficiency syndrome, *SLC2A1*gene  *SCN1A SCN1B GABRG2 SCN2A EFHC1 CACNB4 GABRA1 EPM2A NHLRC1 CSTB PRICKLE1*  *PPT1, TPP1,CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8*  *CHRNA4 CHRNB2 CHRNA2* | Sodium channel protein type 1α Protocadherin-19  Solute carrier family 2, facilitated GTM1 DNA polymerase subunit γ1  Sodium channel protein type 2α  Solute carrier family 2, facilitated GTM1  Sodium channel protein type 1α Sodium channel protein type 1β  γ-Aminobutyric acid receptor subunit γ2 Sodium channel protein type 1α  EF-hand domain-containing protein 1 Voltage-dependent L-type calcium channel γ-Aminobutyric acid receptor subunit α1 Laforin  NHL repeat-containing protein 1 (Malin) Cystatin-B  Prickle-like protein 1  Multiple proteins causing neuronal ceroid lipofuscinosis  Neuronal acetylcholine receptor α4 Neuronal acetylcholine receptor β2 Neuronal acetylcholine receptor α2 |
| Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder  Generalized epilepsy with febrile seizure plus |
| Juvenile myoclonic epilepsy (more commonly presents in adolescence) |
| Progressive myoclonic epilepsy (different forms present from infancy through adulthood) |
| Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood) |
| ADOLESCENT ONSET  Juvenile myoclonic epilepsy (JME) Progressive myoclonic epilepsy (PME)  Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)  Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)  Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood) | See Childhood Onset JME See Childhood Onset PME  See Childhood Onset AD-NFLE See Childhood Onset AD-LTLE *LGI1* | Leucine-rich glioma-inactivated protein 1 |

\*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing ([http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).](http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests))

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| **Table 594-2** | Comparison of Generalized Seizures and Some Disorders That Can Mimic Them | | | | |
| **CONDITION** | | **PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)** | **PRODROME** | **ICTAL SYMPTOMS** | **POSTICTAL SYMPTOMS** |
| Generalized seizures | | Sleep deprivation, television, video games, visual patterns, and photic stimulation | Rarely irritability or nonspecific behavioral changes | Usually 2-3 min Consciousness might be  preserved if atonic, or in some, tonic seizures  Synchronous bilateral movements  Tongue biting | Delayed recovery with postictal depression, incontinence (may be ictal also) |
| Syncope: vasovagal  Syncope with reflex anoxic seizures  Syncope: trigeminal vagal Syncope: orthostatic | | Fatigue, emotional stress, dehydration, vomiting, choking, swallowing  Minor bump to head, upsetting surprises  Cold water on face Standing up, bathing,  awakening | Blurring of vision, tinnitus, dizziness  Crying in  breath-holding spells | Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures | Rapid recovery with no postictal depression |
| Hyperekplexia | | Auditory and tactile stimuli | None | Tonic stiffening, cyanosis if severe, nonfatigable nose- tap–induced startles | Depending on severity, may have postictal depression |
| Cardiac | | Exercise | None | Loss of consciousness, often only few seconds, pallor | Rarely |
| Psychogenic | | Suggestion, stress | None | Eyes closed Asynchronous flailing limb  movements that vary between attacks  No injury, closed eyelids May respond to suggestion  during “loss of consciousness” Usually longer than 2-3 min | No postictal depression |

*Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy,* Pediatr Neurol *37(5):309–316, 2007.*

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| **Table 594-3** | Differential Diagnoses of Various Types of Paroxysmal Dyskinesia | | | | | |
| Features | | PKD | PNKD MR1+ | PNKD MR1− | PED | PHD |
| Nomenclature | | PKC | PDC, FPC | PDC, FPC | PEDt | ADNFLE |
| Inheritance | | AD–16q | AD–2q35 | AD–2q13 | AD/AR | AD–20q13, 15q24, 1q21, 8p21 |
| Age at onset (yr) | | 1-20 | <1-12 | 1-23 | Usually childhood | Usually childhood |
| Triggers | | Sudden whole-body movement | Coffee, alcohol, stress | Exercise | After 10-15 minutes of exercise | Sleep |
| Clinical features | | Chorea, athetosis, ballismus, dystonia | Chorea, athetosis, dystonia, ballismus | Chorea, athetosis, dystonia, ballismus | Mainly leg dystonia | Wakes up with dystonic posture |
| Usual duration | | <1-5 min | 10 min to 1 hr | 10 min to 2-3 hr | 10-15 min | <1 min |
| Frequency | | 1-20/day | 1/week | 1/week | Unclear | Several/night |
| Associations | | Infantile seizures, migraine, writer’s cramp, essential tremor | Migraine | Epilepsy | RE-PED-WC |  |
| Medication | | Carbamazepine Phenytoin Oxcarbazepine | Clonazepam Benzodiazepine | Clonazepam Benzodiazepine | Acetazolamide L-DOPA | Carbamazepine Oxcarbazepine |
| Prognosis | | Excellent | Excellent, worse than PKD | Minimally worse than PNKD MR1+ | Poor medication response | Excellent |

AD, autosomal-dominant; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; AR, autosomal-recessive; FPC, familial paroxysmal choreoathetosis; MR1+, myofibrillogenesis regulator 1-positive; MR1−, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer’s cramp.

*From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:*

Swaiman’s pediatric neurology*, ed 5, Philadelphia, 2012, WB Saunders, Table 65-1.*

**2864 Part XXVII** ◆ The Nervous System

|  |  |
| --- | --- |
| **Table 595-1** Classification of Headaches (ICHD-3 Beta Code | Diagnosis) |
| MIGRAINE  Migraine with or without aura  Migraine with typical aura (with or without headache) Migraine with brainstem aura  Hemiplegic migraine (sporadic or familial types 1, 2, 3, or other genetic loci)  Retinal migraine Chronic migraine  Complications of Migraine  Status migrainosus  Persistent aura without infarction Migrainous infarction  Migraine aura-triggered seizure  Episodic Syndromes That May Be Associated with Migraine  Recurrent gastrointestinal disturbance  Cyclical vomiting syndrome Abdominal migraine Benign paroxysmal vertigo  Benign paroxysmal torticollis | HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER  Headache attributed to ischemic stroke or transient ischemic attack Headache attributed to nontraumatic intracerebral hemorrhage Headache attributed to nontraumatic subarachnoid hemorrhage (SAH)  Headache attributed to nontraumatic acute subdural hemorrhage (ASDH)  Headache attributed to unruptured vascular malformation Headache attributed to unruptured saccular aneurysm Headache attributed to arteriovenous malformation (AVM) Headache attributed to dural arteriovenous fistula (DAVF) Headache attributed to cavernous angioma  Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)  Headache attributed to arteritis  Headache attributed to giant cell arteritis (GCA)  Headache attributed to primary angiitis of the central nervous system (PACNS)  Headache attributed to secondary angiitis of the central nervous system (SACNS)  Headache attributed to cervical carotid or vertebral artery disorder Headache or facial or neck pain attributed to cervical carotid or  vertebral artery dissection Post-endarterectomy headache  Headache attributed to carotid or vertebral angioplasty Headache attributed to cerebral venous thrombosis (CVT) Headache attributed to other acute intracranial arterial disorder Headache attributed to an intracranial endovascular procedure Angiography headache  Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)  Headache attributed to intracranial arterial dissection Headache attributed to genetic vasculopathy  Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)  Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)  Headache attributed to another genetic vasculopathy Headache attributed to pituitary apoplexy |
| TENSION-TYPE HEADACHE (TTH)  Infrequent episodic tension-type headache associated with or without pericranial tenderness  Frequent episodic tension-type headache associated with or without pericranial tenderness  Chronic tension-type headache associated with or without pericranial tenderness  Probable tension-type headaches |
| TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)  Cluster headache (episodic or cluster) Paroxysmal hemicrania (episodic or cluster)  Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)  Episodic SUNCT Chronic SUNCT  Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)  Episodic SUNA Chronic SUNA Hemicrania continua  Probable trigeminal autonomic cephalalgias |
| HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER  Headache attributed to increased cerebrospinal fluid pressure Headache attributed to idiopathic intracranial hypertension (IIH)  Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes  Headache attributed to intracranial hypertension secondary to hydrocephalus  Headache attributed to low cerebrospinal fluid pressure Postdural puncture headache  Cerebrospinal fluid fistula headache  Headache attributed to spontaneous intracranial hypotension Headache attributed to noninfectious inflammatory disease Headache attributed to neurosarcoidosis  Headache attributed to aseptic (noninfectious) meningitis Headache attributed to other noninfectious inflammatory disease Headache attributed to lymphocytic hypophysitis  Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)  Headache attributed to intracranial neoplasm  Headache attributed to colloid cyst of the third ventricle Headache attributed to carcinomatous meningitis Headache attributed to hypothalamic or pituitary hyper- or  hyposecretion  Headache attributed to intrathecal injection Headache attributed to epileptic seizure Hemicrania epileptica  Postictal headache  Headache attributed to Chiari malformation type I (CM1) Headache attributed to other nonvascular intracranial disorder |
| OTHER PRIMARY HEADACHE DISORDERS  Primary cough headache Primary exercise headache  Primary headache associated with sexual activity Primary thunderclap headache  Cold-stimulus headache (external application, ingestion, or inhalation) External-pressure headache  External-compression headache External-traction headache Primary stabbing headache Nummular headache  Hypnic headache  New daily persistent headache (NDPH) |
| HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK  Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head  Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head  Acute or persistent headache attributed to whiplash Acute or persistent headache attributed to craniotomy |

**Chapter 595** ◆ Headaches **2865**

|  |  |
| --- | --- |
| **Table 595-1** Classification of Headaches (ICHD-3 Beta Code | Diagnosis)—cont’d |
| HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL  Headache attributed to use of or exposure to a substance Nitric oxide (NO) donor-induced headache Phosphodiesterase (PDE) inhibitor-induced headache Carbon monoxide (CO)-induced headache  Alcohol-induced headache  Monosodium glutamate (MSG)-induced headache Cocaine-induced headache  Histamine-induced headache  Calcitonin gene-related peptide (CGRP)-induced headache Headache attributed to exogenous acute pressor agent  Headache attributed to occasional or long-term use of nonheadache medication  Headache attributed to exogenous hormone Medication-Overuse Headache (MOH) Ergotamine-overuse headache  Triptan-overuse headache  Simple analgesic-overuse headache Paracetamol (acetaminophen)-overuse headache Acetylsalicylic acid-overuse headache  Other non-steroidal antiinflammatory drug (NSAID)-overuse headache Opioid-overuse headache  Combination analgesic-overuse headache Headache Attributed to Substance Withdrawal Caffeine-withdrawal headache  Opioid-withdrawal headache Estrogen-withdrawal headache | HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE  Headache attributed to disorder of cranial bone Headache attributed to retropharyngeal tendonitis Headache attributed to craniocervical dystonia Headache attributed to acute glaucoma Headache attributed to refractive error  Headache attributed to heterophoria or heterotropia (latent or persistent squint)  Headache attributed to ocular inflammatory disorder Headache attributed to trachelitis  Headache attributed to disorder of the ears  Headache attributed to acute or chronic or recurring rhinosinusitis Headache attributed to temporomandibular disorder (TMD)  Head or facial pain attributed to inflammation of the stylohyoid ligament  Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure |
| HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER  Headache attributed to somatization disorder Headache attributed to psychotic disorder |
| PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS  Classical trigeminal neuralgia  Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain  Painful trigeminal neuropathy  Painful trigeminal neuropathy attributed to acute herpes zoster Postherpetic trigeminal neuropathy  Painful posttraumatic trigeminal neuropathy  Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque  Painful trigeminal neuropathy attributed to space-occupying lesion Painful trigeminal neuropathy attributed to other disorder Glossopharyngeal neuralgia  Classical nervus intermedius (facial nerve) neuralgia  Nervus intermedius neuropathy attributed to herpes zoster Occipital neuralgia  Optic neuritis  Headache attributed to ischemic ocular motor nerve palsy Tolosa-Hunt syndrome  Paratrigeminal oculosympathetic (Raeder) syndrome Recurrent painful ophthalmoplegic neuropathy Burning mouth syndrome (BMS)  Persistent idiopathic facial pain (PIFP) Central neuropathic pain  Central neuropathic pain attributed to multiple sclerosis (MS) Central post-stroke pain (CPSP) |
| HEADACHE ATTRIBUTED TO INFECTION  Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis  Persistent headache attributed to past bacterial meningitis or meningoencephalitis  Acute or chronic headache attributed to intracranial fungal or other parasitic infection  Headache attributed to brain abscess Headache attributed to subdural empyema  Headache attributed to systemic infection (acute or chronic) |
| HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS  Headache attributed to hypoxia and/or hypercapnia High-altitude headache  Headache attributed to airplane travel Diving headache  Sleep apnea headache Dialysis headache  Headache attributed to arterial hypertension Headache attributed to pheochromocytoma  Headache attributed to hypertensive crisis with or without hypertensive encephalopathy  Headache attributed to preeclampsia or eclampsia Headache attributed to autonomic dysreflexia Headache attributed to hypothyroidism  Headache attributed to fasting Cardiac cephalalgia  Headache attributed to other disorder of homoeostasis |

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).*

Cephalalgia *33(9):629–808, 2013.*

**2866 Part XXVII** ◆ The Nervous System

**595.1 Migraine**

*Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O’Brien*

##### Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and may be associated with nausea, vomiting, light sensitivity, and sound sensitivity. Compared to adults, pediatric migraine is shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (i.e., hemiplegic, “Alice in Wonderland” syndrome) (Tables 595-2 to 595-6). In addition, a number of migraine variants have been described and, in children, include abdominal related symptoms without headache, and compo- nents of the painless periodic syndromes of childhood (see Table 595- 1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

**EPIDEMIOLOGY**

##### Up to 75% of children report having a significant headache by the time they are 15 yr old. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr, and up to 28% of older

1. At least 2 attacks fulfilling criteria B to D
2. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
3. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
4. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
5. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

Migraine with Brainstem Aura

**Table 595-4**

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).* Cephalalgia *33(9):629–808, 2013, Table 7.*

1. At least 5 attacks fulfilling criteria B to D
2. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
3. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
4. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
5. Not better accounted for by another ICHD-3 diagnosis

Migraine Without Aura

**Table 595-2**

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).* Cephalalgia *33(9):629–808, 2013, Table 4.*

1. At least 5 episodes fulfilling criteria C and D
2. A current or past history of 1.1 *Migraine without aura* or 1.2

*Migraine with aura*

1. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
2. At least 50% of episodes are associated with at least 1 of the following 3 migrainous features:
   1. Headache with at least 2 of the following 4 characteristics:
      1. Unilateral location
      2. Pulsating quality
      3. Moderate or severe intensity
      4. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
3. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

Vestibular Migraine with Vertigo

**Table 595-5**

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).* Cephalalgia *33(9):629–808, 2013 (Table 8).*

1. At least 2 attacks fulfilling criteria B and C
2. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
3. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
4. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

Migraine with Typical Aura

**Table 595-3**

1. Headache (tension-type-like and/or migraine-like) on 15 or

more days per month for more than 3 mo and fulfilling criteria B and C

1. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
2. On 8 or more days per month for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for 1.1 *Migraine without aura*
   2. Criteria B and C for 1.2 *Migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
3. Not better accounted for by another ICHD-3 diagnosis

Chronic Migraine

**Table 595-6**

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).* Cephalalgia *33(9):629–808, 2013, Table 6.*

*From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version).* Cephalalgia *33(9):629–808, 2013, Table 9.*

Abnormal neurologic examination

Abnormal or focal neurologic signs or symptoms

* Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
* Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase

Seizures or very brief auras (<5 min) Unusual headaches in children

* Atypical auras including basilar-type, hemiplegic
* Trigeminal autonomic cephalalgia including cluster headaches in child or adolescent
* An acute secondary headache (i.e., headache with known underlying illness or insult)

Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache

Brief cough headache in a child or adolescent

Headache worst on first awakening or that awakens the child from sleep

Migrainous headache in the child with no family history of migraine or its equivalent

Indications for Neuroimaging in a Child with Headaches

**Table 595-7**

1. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D
2. Lasting from 30 min to 7 days
3. At least 2 of the following 4 characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
4. Both of the following:
   1. No nausea or vomiting
   2. No more than 1 of photophobia or phonophobia
5. Not better accounted for by another ICHD-3 beta diagnosis

Infrequent Episodic Tension-Type Headache

**Table 595-9**

**Chapter 595** ◆ Headaches **2869**

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| --- | --- | --- | --- | --- | --- |
| **Table 595-8** | Drugs Used in the Management of Migraine Headaches in Children | | | | |
| **DRUG** | | **DOSE** | **MECHANISM** | **SIDE EFFECTS** | **COMMENTS** |
| ACUTE MIGRAINE  *Analgesics*  Acetaminophen  Ibuprofen | | 15 mg/kg/dose  7.5-10 mg/kg/dose | Analgesic effects  Antiinflammatory and analgesic  5-HT1b/1d agonist  Same Same  Same  Same Same  Same | Overdose, fatal hepatic necrosis  GI bleeding stomach upset, kidney injury | Effectiveness limited in migraine  Avoid overuse (2-3 times per wk)  Avoid overuse (more than 4-6 times per mo)  Avoid overuse (more than 4-6 times per mo)  May be effective for menstrual migraine prevention  Avoid overuse (more than 4-6 times per mo)  May be effective for menstrual migraine prevention  Avoid overuse (more than 4-6 times per mo)  Available in tablets and melts Avoid overuse (more than 4-6  times per mo)  Avoid overuse (more than 4-6 times per mo)  Available in tablets and melts Avoid overuse (more than 4-6  times per mo) |
| *Triptans*  Almotriptan\* (ages 12-17 yr)  Eletriptan | | 12.5 mg  40 mg | Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort  Same |
| Frovatriptan | | 2.5 mg | Same |
| Naratriptan | | 2.5 mg | Same |
| Rizatriptan\* (ages 6-17 yr) | | 5 mg for child weighing  <40 kg, 10 mg | Same |
| Sumatriptan  Zolmitriptan | | Oral: 25 mg, 50 mg,  100 mg  Nasal: 10 mg  SC: 6 mg  Oral: 2.5 mg, 5 mg  Nasal: 5 mg | Same  Same |

Continued

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| --- | --- | --- | --- | --- | --- |
| **Table 595-8** Drugs | Used in the Management | of | Migraine Headaches in Children—cont’d | | |
| **DRUG** | **DOSE** | **MECHANISM** | | **SIDE EFFECTS** | **COMMENTS** |
| PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)  *Calcium Channel Blockers*  Flunarizine† 5 mg hs Calcium channel blocking agent  *Anticonvulsants*  Valproic acid 20 mg/kg/24 hr (begin ↑ Brain GABA 5 mg/kg/24 hr)  Topiramate 100-200 mg divided bid ↑ Activity of GABA  Levetiracetam 20-60 mg/kg divided bid Unknown  Gabapentin 900-1800 mg divided bid Unknown | | | | Headache, lethargy, dizziness  Nausea, pancreatitis, fatal hepatotoxicity Fatigue, nervousness  Irritability, fatigue  Somnolence, fatigue aggression, weight gain | May ↑ to 10 mg hs  ↑ 5 mg/kg every 2 wk Increase slowly over 12-16 wk  Increase every 2 wk starting at 20 mg/kg divided bid  Begin 300 mg, ↑ 300 mg/wk |
| *Antidepressants*  Amitriptyline | 1 mg/kg/day | ↑ CNS serotonin and norepinephrine | | Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion | Increase by 0.25 mg/kg every 2 wk  Morning sleepiness reduced by administration at dinnertime |
| *Antihistamines*  Cyproheptadine  *Antihypertensive*  Propranolol  *Others*  Coenzyme Q10  Riboflavin Magnesium Butterbur  OnabotulinumtoxinA | 0.2-0.4 mg/kg divided bid; max: 0.5 mg/ kg/24 hr  10-20 mg tid  1-3 mg/kg/day  50-400 mg daily  9 mg/kg divided tid 50-150 mg daily  100 units (age 11-17 yr) | H1-receptor and serotonin agonist  Nonselective  β-adrenergic blocking agent  Increases fatty acid oxidation in mitochondria  Cofactor in energy metabolism  Cofactor in energy metabolism  May act similar to a calcium channel blocker  Inhibits acetylcholine release from nerve endings | | Drowsiness, thick bronchial secretions  Dizziness, lethargy  No adverse effects reported  Bright yellow urine, polyuria and diarrhea  Diarrhea or soft stool Burping  Ptosis, blurred vision, hematoma at injection site | Preferred in children who cannot swallow pills; not well tolerated in adolescents |
| Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression) |
| Fat soluble; ensure brand contains small amount of vitamin E to help absorption |
| Used off label in children |
| SEVERE INTRACTABLE  Prochlorperazine  Metoclopramide  Ketorolac  Valproate sodium injection  Dihydroergotamine IV  Nasal spray | 0.15 mg/kg/IV; max dose 10 mg  0.2 mg/kg IV; 10 mg max dose  0.5 mg/kg IV; 15 mg max dose  15 mg/kg IV: 1,000 mg max dose  0.5 mg/dose every 8 hr  (<40 kg)  1.0 mg/dose every 8 hr  (>40 kg)  0.5-1.0 mg/dose  0.5 mg/spray | Dopamine antagonist  Dopamine antagonist  Antiinflammatory and analgesic  ↑ Brain GABA | | Agitation, drowsiness, muscle stiffness, akinesia and akathisia  Drowsiness, urticaria, agitation, akinesia and akathisia  GI upset, bleeding  Nausea, vomiting, somnolence, thrombocytopenia  Nausea, vomiting, vascular constriction, phlebitis | May have increased effectiveness when combined with ketorolac and fluid hydration  Caution in asthma patients  Would avoid in hepatic disease  Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase). |

\*FDA approved in the pediatric population.

†Available in Europe.

↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

Cortical tuber Subependymal nodule

Subependymal giant cell astrocytoma Facial angiofibroma or forehead plaque

Ungual or periungual fibroma (non-traumatic) Hypomelanotic macules (>3)

Shagreen patch

Multiple retinal hamartomas Cardiac rhabdomyoma Renal angiomyolipoma

Pulmonary lymphangioleiomyomatosis

Major Features of TSC

**Table 596-3**

Cerebral white matter migration lines Multiple dental pits

Gingival fibromas Bone cysts

Retinal achromatic patch Confetti skin lesions Nonrenal hamartomas Multiple renal cysts Hamartomatous rectal polyps

Minor Features of TSC

**Table 596-4**

**Chapter 596** ◆ Neurocutaneous Syndromes **2875**

|  |  |  |
| --- | --- | --- |
| **Table 596-2** | Frequency of Lesions Associated with Neurofibromatosis Type 2 | |
| **FREQUENCY OF ASSOCIATION WITH NF-2** | | |
| NEUROLOGIC LESIONS | |  |
| Bilateral vestibular schwannomas | | 90-95% |
| Other cranial nerve schwannomas | | 24-51% |
| Intracranial meningiomas | | 45-58% |
| Spinal tumors | | 63-90% |
| Extramedullary | | 55-90% |
| Intramedullary | | 18-53% |
| Peripheral neuropathy | | Up to 66% |
| OPHTHALMOLOGIC LESIONS | |  |
| Cataracts | | 60-81% |
| Epiretinal membranes | | 12-40% |
| Retinal hamartomas | | 6-22% |
| CUTANEOUS LESIONS | |  |
| Skin tumors | | 59-68% |
| Skin plaques | | 41-48% |
| Subcutaneous tumors | | 43-48% |
| Intradermal tumors | | Rare |

|  |  |  |
| --- | --- | --- |
| **Table 596-1** | Diseases Associated with Multiple Café-Au-Lait Spots | |
| **DISEASE** | | **MAJOR FEATURES** |
| Ataxia telangiectasia | | Progressive ataxia, lymphoreticular malignancy |
| Bannayan-Riley-Ruvalcaba syndrome | | Macrosomia, megalencephaly, lipomas, intestinal polyps |
| Basal cell nevus syndrome | | Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies |
| Bloom syndrome | | Short stature, photosensitivity, chromosome breaks, malignancy |
| Fanconi anemia | | Limb anomalies, renal anomalies, pancytopenia |
| Gaucher disease | | Jewish predilection, ataxia, mental retardation |
| Hunter syndrome | | Thickened skin, coarse facies, skin papules, joint contractures |
| Jaffe-Campanacci syndrome | | Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies |
| Maffucci syndrome | | Venous malformations, enchondromas |
| McCune-Albright syndrome | | Polyostotic fibrous dysplasia, precocious puberty |
| Multiple lentigines syndrome | | Multiple lentigines, hypertelorism, pulmonic stenosis |
| Multiple mucosal neuroma syndrome | | Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia |
| Neurofibromatosis | | Neurofibromas, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies |
| Russell-Silver syndrome | | Short stature, asymmetry, limb anomalies |
| Tuberous sclerosis | | White macules, multiple hamartomas, central nervous system anomalies |
| Watson syndrome | | Pulmonic stenosis, axillary freckles, low intelligence |
| Legius syndrome | | Axillary freckling macrocephaly, a Noonan-like facial dysmorphism, lipomas |

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| **Table 597-2** Selected Causes of Ataxia in Childhood | |
| CONGENITAL   * Agenesis of vermis of the cerebellum * Aplasia or dysplasia of the cerebellum * Basilar impression * Cerebellar dysplasia with microgyria, macrogyria, or agyria * Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3) * Chiari malformation * Dandy-Walker syndrome * Encephalocele * Hydrocephalus (progressive) * Hypoplasia of the cerebellum | METABOLIC   * Abetalipoproteinemia * Argininosuccinic aciduria * Ataxia with vitamin E deficiency (AVED) * Congenital disorders of glycosylation * GM2 gangliosidosis (late) * Hartnup disease * Hyperalaninemia * Hyperammonemia I and II (urea cycle defects) * Hypoglycemia * Kearns-Sayre syndrome * Leigh disease * Maple syrup urine disease (intermittent) * Myoclonic epilepsy with ragged red fibers (MERRF) * Metachromatic leukodystrophy * Mitochondrial complex defects (I, III, IV) * Multiple carboxylase deficiency (biotinidase deficiency) * Neuronal ceroid-lipofuscinosis * Neuropathy, ataxia, retinitis pigmentosa (NARP) * Niemann-Pick disease (late infantile) * 5-Oxoprolinuria * Pyruvate decarboxylase deficiency * Refsum disease * Sialidosis * Triose-phosphate isomerase deficiency * Tryptophanuria * Wernicke encephalopathy |
| DEGENERATIVE AND/OR GENETIC   * Acute intermittent cerebellar ataxia * Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration * Ataxia-telangiectasia * Biemond posterior column ataxia * Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia * Cockayne syndrome * Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva) * Familial ataxia with macular degeneration * Friedreich ataxia * Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism * Hereditary cerebellar ataxia with myotonia and cataracts * Hypertrophic interstitial neuritis * Marie ataxia * Marinesco-Sjögren syndrome * Multiple-system atrophy * Pelizaeus-Merzbacher disease * Periodic attacks of vertigo, diplopia, and ataxia–autosomal- dominant inheritance * Posterior and lateral column difficulties, nystagmus, and muscle atrophy * Progressive cerebellar ataxia and epilepsy * Ramsay Hunt syndrome (myoclonic seizures and ataxia) * Roussy-Lévy disease * Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias * Vanishing white matter syndrome |
| NEOPLASTIC   * Frontal lobe tumors * Hemispheric cerebellar tumors * Midline cerebellar tumors * Neuroblastoma * Pontine tumors (primarily gliomas) * Spinal cord tumors |
| PRIMARY PSYCHOGENIC   * Conversion reaction |
| TOXIC   * Alcohol * Benzodiazepines * Carbamazepine * Clonazepam * Lead encephalopathy * Neuroblastoma * Phenobarbital * Phenytoin * Primidone * Tic paralysis poisoning |
| ENDOCRINOLOGIC   * Acquired hypothyroidism * Cretinism |
| INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY   * Acute cerebellar ataxia * Acute disseminated encephalomyelitis * Autoimmune (anti-glutamic acid decarboxylase, anti–γ-aminobutyric acidB receptor antibodies) * Cerebellar abscess * Cerebellitis * Coxsackievirus * Diphtheria * Echovirus * Fisher syndrome * Infectious mononucleosis (Epstein-Barr virus infection) * Infectious polyneuropathy * Japanese B encephalitis * Mumps encephalitis * *Mycoplasma* pneumonia * Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome) * Pertussis * Polio * Postbacterial meningitis * Rubeola * Tuberculosis * Typhoid * Varicella |
| TRAUMATIC   * Acute cerebellar edema * Acute frontal lobe edema |
| VASCULAR   * Angioblastoma of cerebellum * Basilar migraine * Cerebellar embolism * Cerebellar hemorrhage * Cerebellar thrombosis * Posterior cerebellar artery disease * Vasculitis * von Hippel-Lindau disease |

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| **Table 597-3** | Treatable Causes of Inherited Ataxia | | | |
| **DISORDER** | | **METABOLIC ABNORMALITY** | **DISTINGUISHING CLINICAL FEATURES** | **TREATMENT** |
| Acute disseminated encephalomyelitis | | Demyelination | Positive MRI findings | Steroids, IVIG, rituximab |
| Ataxia with vitamin E deficiency | | Mutation in α-tocopherol transfer protein | Ataxia, areflexia, retinopathy | Vitamin E |
| Bassen-Kornzweig syndrome | | Abetalipoproteinemia | Acanthocytosis, retinitis pigmentosa, fat malabsorption | Vitamin E |
| Hartnup disease | | Tryptophan malabsorption | Pellagra rash, intermittent ataxia | Niacin |
| Familial episodic ataxia type 1 and type 2 | | Mutations in potassium channel (KCNA1) and α1A voltage-gated calcium channel, respectively | Episodic attacks, worse with pregnancy or birth control pills | Acetazolamide |
| Multiple carboxylase deficiency | | Biotinidase deficiency | Alopecia, recurrent infections, variable organic aciduria | Biotin |
| Mitochondrial complex defects | | Complexes I, III, IV | Encephalomyelopathy | Possibly riboflavin, CoQ10, dichloroacetate |
| Opsoclonus-myoclonus-ataxia syndrome | | Paraneoplastic or spontaneous autoimmune | Underlying neuroblastoma or autoantibodies | Steroids, IVIG, rituximab |
| Pyruvate dehydrogenase deficiency | | Block in E-M and Krebs cycle interface | Lactic acidosis, ataxia | Ketogenic diet, possibly dichloroacetate |
| Refsum disease | | Phytanic acid, α-hydroxylase | Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis | Dietary restriction of phytanic acid |
| Urea cycle defects | | Urea cycle enzymes | Hyperammonemia | Protein restriction, arginine, benzoate, α-ketoacids |

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.

*Modified from Stumpf DA: The inherited ataxias.* Pediatr Neurol *1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman’s pediatric neurology*, ed 5, Philadelphia, 2012, WB Saunders, Table 67-1.*

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| **Table 597-4** | Autosomal-Recessive Cerebellar Ataxias | | | | | |
| **ATAXIA** | | **CHROMOSOME** | **GENE** | **GENE PRODUCT** | **MECHANISM** | **AGE OF ONSET (yr)** |
| Friedreich ataxia | | 9q13 | *X25* | Frataxin | GAA repeat | 2-51 |
| Friedreich ataxia 2 | | 9p23–p11 | Unknown | Unknown | Unknown | 5-20 |
| AVED | | 8q13 | *TTP1* | TTPA | Missense mutation, deletion, insertion | 2-52 |
| Ataxia-telangiectasia | | 11q22.3 | *ATM* | ATM | Missense and deletion mutations | Infancy |
| ATLD | | 11q21 | *hMRE11* | MRE11A | Missense and deletion mutations | 9-48 mo |
| Ataxia-ocular apraxia 1 | | 9p13.3 | *APTX* | Aprataxin | Frameshift, missense, nonsense mutations | 2-18 |
| SCAR1 | | 9q34 | *SETX* | Senataxin | Frameshift, missense, nonsense mutations | 9-22 |
| SCAR2 | | 9q34–qter | Unknown | Unknown | Unknown | Congenital |
| SCAR3 | | 6p23–p21 | Unknown | Unknown | Unknown | 3-52 |
| SCAR4 | | 1p36 | Unknown | Unknown | Unknown | 23-39 |
| SCAR5 | | 15q24–q26 | Unknown | Unknown | Unknown | 1-10 |
| SCAR6 | | 20q11–q13 | Unknown | Unknown | Unknown | Infancy |
| SCAR7 | | 11p15 | Unknown | Unknown | Unknown | Childhood |
| SCAR8 | | 11p15 | *SYNE1* | SYNE1 | Splice site mutation, nonsense mutations | 17-46 |

Continued

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| **Table 597-4** | Autosomal-Recessive Cerebellar Ataxias—cont’d | | | | | |
| **ATAXIA** | | **CHROMOSOME** | **GENE** | **GENE PRODUCT** | **MECHANISM** | **AGE OF ONSET (yr)** |
| SCAR9 | | 1q41 | *ADCK3* | ADCK3 | Splice site mutation, missense, nonsense mutations | 3-11 |
| Ataxia, Cayman type | | 19q13.3 | *ATCAY* | Caytaxin | Missense mutation | Birth |
| IOSCA | | 10q24 | *C10orf2* | Twinkle | Missense, silent mutations | 9-24 mo |
| Progressive myoclonic epilepsy | | 21q22.3 | *CST6* | Cystatin B | 5′ dodecamer repeat | 6–13 |
| ARSACS | | 13q12 | *SACS* | Sacsin | Frameshift and nonsense mutations | 1–20 |
| Congenital disorders of glycosylation | | Multiple | Multiple | Multiple |  | Birth |

ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal-recessive.

*From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman’s pediatric neurology*, ed 5, Philadelphia, 2012, WB Saunders, Table 67-2.*

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| **Table 597-5** | Autosomal-Dominant Cerebellar Ataxias | | | | | | | |
| **ATAXIA** | **CHROMOSOME** | **GENE** | **GENE PRODUCT** | **MECHANISM** | **AGE OF ONSET (yr)** | **NORMAL REPEAT** | **EXPANDED REPEAT** | **DURATION OF EPISODES** |
| POLYGLUTAMINE EXPANSION | |  |  |  |  |  |  |  |
| SCA1 6p23 | | *SCA1* | Ataxin-1 | CAG repeat | 6-60 | 6-44\* | 39-82\* |
| SCA2 12q24 | | *SCA2* | Ataxin-2 | CAG repeat | 2-65 | 15-24 | 35-59 |
| SCA3/MJD 14q24.3-q31 | | *MJD1* | Ataxin-3 | CAG repeat | 11-70 | 13-47\* | 45-84\* |
| SCA6 19q13 | | *CACNA1A* | CACNA1A | CAG repeat | 16-v73 | 4-20 | 21-33 |
| SCA7 3p21.1-p12 | | *SCA7* | Ataxin-7 | CAG repeat | Birth-53 | 4-35 | 37-460 |
| SCA17 6q27 | | *SCA17* | TBP | CAG repeat | 3-48 | 25-42 | 45-66 |
| DRPLA 12p13.31 | | *DRPLA* | Atrophin-1 | CAG repeat | 4-55 mo | 7-34 | 53-93 |
| NONCODING EXPANSION | |  |  | CTG repeat in 3′ UTR  ATTCT repeat in intron 9 CAG repeat in  5′ UTR  TGGAA repeat insertion in intron of BEAN and TK |  |  |  |  |
| SCA8 13q21 | | *SCA8* | SCA8 RNA | 18-72 | 2-91\* | 110-155\* |
| SCA10 22q13 | | *SCA10* | Ataxin-10 | 14-45 | 10-29 | 750-4500 |
| SCA12 5q31-q33 | | *SCA12* | P2R2B | 8-55 | 7-32 | 55-78 |
| SCA31 16q22.1 | | *BEAN/TK2* | BEAN/TK2 | 45-72 | Rarely | 2.5-3.8 kb |
|  | |  |  |  | (0.23%) |  |
|  | |  |  |  | 1.5-2.0 kb |  |
| OTHER MUTATIONS | |  |  | Missense mutation  Fibroblast growth factor deficiency  Deletion, missense mutations  Truncation mutation  Missense mutations  Deletion, missense mutation  Missense mutations |  |  |  |  |
| PKC-γ | 10-69 |
| SCA14 19q13.4 | | *PKC-γ* |
| SCA27 13q34 | | *FGF14* | FGF14 | 15-20 |
| SCA5 11p11-q11 | | *SPTBN2* | β-3 | 10-68 |
|  | |  | spectrin |  |
| SCA11 15q14-q21.3 | | *TTBK2* | TTBK2 | 15-43 |
| SCA13 19q13.3-q13.4 | | *KCNC3* | KCNC3 | <1-60 |
| SCA15 3p24.2-3pter | | *ITPR1* | ITPR1 | Child–adult |
| SCA28 18p11.22-q11.2. | | *AFG3L2* | AFG3L2 | 12-36 |

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| **Table 597-8** | Drugs That Can Induce Chorea | |
| DOPAMINE RECEPTOR | | CALCIUM CHANNEL |
| BLOCKING AGENTS (UPON | | BLOCKERS |
| WITHDRAWAL OR AS A | | Cinnarizine |
| TARDIVE SYNDROME) | | Flunarizine |
| Phenothiazines | | Verapamil |
| Butyrophenones | |
| OTHERS  Lithium Baclofen Digoxin  Tricyclic antidepressants Cyclosporine  Steroids/oral contraceptives Theophylline  Propofol |
| Benzamides | |
| ANTIPARKINSONIAN DRUGS | |
| L-DOPA | |
| Dopamine agonists | |
| Anticholinergics | |
| ANTIEPILEPTIC DRUGS | |
| Phenytoin | |
| Carbamazepine | |
| Valproic acid | |
| PSYCHOSTIMULANTS | |
| Amphetamines | |
| Methylphenidate | |
| Cocaine | |

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| **Table 600-4** | Clinical Features That May Distinguish ADEM from First Attack of MS | | |
|  | | **ADEM** | **MS** |
| Age | | <10 yr | >10 yr |
| Stupor/coma | | + | – |
| Encephalopathy | | + | – |
| Fever/vomiting | | + | – |
| Family history | | No | 20% |
| Sensory complaints | | + | + |
| Optic neuritis | | Bilateral | Unilateral |
| Manifestations | | Polysymptomatic | Monosymptomatic |
| CSF | | Pleocytosis (lymphocytosis) | Oligoclonal bands |
| Response to steroids | | + | + |
| Follow-up | | No new lesions | New lesions |

Some features that may help distinguish an initial acute episode of demyelination from a first attack of MS in children. Final diagnosis of MS is based on follow-up evaluation and possibly MRI.

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| **Table 597-6** | Etiologic Classification of Choreic Syndromes |
| GENETIC CHOREAS  Huntington disease (rarely presents with chorea in childhood)  Huntington disease–like 2 and other Huntington disease –like syndromes  Dentatorubropallidoluysian atrophy Neuroacanthocytosis  Leigh syndrome and other mitochondrial disorders Ataxia telangiectasia  Benign hereditary chorea Wilson disease  Spinocerebellar ataxia (types 2, 3, or 17)  Pantothene kinase–associated neurodegeneration (PKAN) Paroxysmal kinesigenic choreoathetosis  Paroxysmal nonkinesigenic choreoathetosis Fahr syndrome  Rett syndrome | |
| STRUCTURAL BASAL-GANGLIA LESIONS  Vascular chorea in stroke, vasculitis, Moyamoya disease  Mass lesions (e.g., central nervous system lymphoma, metastatic brain tumors)  Joubert syndrome and related disorders Multiple sclerosis plaques  Extrapontine myelinolysis Trauma | |
| PARAINFECTIOUS AND AUTOIMMUNE DISORDERS  Sydenham chorea  Systemic lupus erythematosus Chorea gravidarum  Antiphospholipid antibody syndrome Postinfectious or postvaccinal encephalitis  Anti–N-methyl-D-aspartate (NMDA)–receptor antibody syndrome (Limbic encephalitis)  Paraneoplastic choreas | |
| INFECTIOUS CHOREA  HIV encephalopathy Toxoplasmosis Cysticercosis Diphtheria  Bacterial endocarditis Neurosyphilis  Scarlet fever  Viral encephalitis (mumps, measles, varicella) | |
| METABOLIC DRUG OR TOXIC ENCEPHALOPATHIES  Acute intermittent porphyria Hypo-/hypernatremia Hypocalcemia Hyperthyroidism Hypoparathyroidism Hepatic/renal failure  Carbon monoxide poisoning Manganese poisoning Mercury poisoning Organophosphate poisoning Pheochromocytoma | |
| DRUG-INDUCED CHOREA (see Table 597-8) | |

+, More likely to be present; −, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

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| **Table 597-1** | Selected Types of Involuntary Movement in Childhood | |
| **TYPE** | | **CHARACTERISTICS** |
| Stereotypies (see Chapter 24) | | Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition |
| Tics (see Chapter 24) | | Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement |
| Tremor | | Oscillating, rhythmic movements about a fixed point, axis, or plane |
| Dystonia (see Chapter 597.3) | | Intermittent and sustained involuntary muscles contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality |
| Chorea (see Chapter 597.2) | | Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly |
| Ballism | | Involuntary, high amplitude, flinging movements typically occurring proximally. Ballism is essentially a large amplitude chorea |
| Athetosis | | Slow, writhing, continuous, involuntary movements |
| Myoclonus | | Sudden, quick, involuntary muscle jerks |

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| **Table 597-7** Genetic Choreas | | | | | |
|  | **MODE OF INHERITANCE** | **GENE, LOCATION** | **PROTEIN PRODUCT** | **USUAL AGE AT ONSET (yr)** | **CLINICAL SIGNS** |
| HDL2\* | AD† | *JPH3*, 16q | Junctophilin-3 | 20-40 | Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity |
| SCA17 | AD† | *TBP*, 6q | TBP | 10-30 | Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline |
| DRPLA | AD† | *DRPLA*, 12p | Atrophin-1 | About 20 | Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or United States |
| SCA3/MJD | AD† | *MJD*, 14q | Ataxin-3 | 35-40 | Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features |
| SCA2 | AD† | *Ataxin-2*, 12q | Ataxin-2 | 30-35 | Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyporeflexia |
| Chorea- acanthocytosis | AR | *VPS13A*  (formerly  *CHAC*), 9q | Chorein | 20-50 | Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis |
| McLeod syndrome | X-linked, recessive | *XK*, Xp | XK-protein | 40-70 | Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen |
| Neuroferritinopathy | AD | *FTL*, 19q | FTL | 20-55 | Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen |
| AT and ATLD | AR | *ATM*, 11q (*AT*) *MRE11*, 11q *(ATLD)* | ATM (AT) MRE11 (ATLD) | Childhood | Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus  In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high α-fetoprotein in serum and high concentrations of carcinoembryonic antigen |
| AOA 1 and 2 | AR | *APTX*, 9p *(AOA 1) SETX*, 9q  *(AOA 2)* | Aprataxin (AOA 1)  Senataxin (AOA 2) | Childhood or adolescence (later onset in AOA 2) | Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotor apraxia type 1: hypoalbuminemia and hypercholesterolemia; ataxia with oculomotor apraxia type 2: raised α-fetoprotein in serum |
| Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome) | AR | *PANK2,* 20p | Pantothenate kinase 2 | Childhood, but also adult- onset subtype | Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, “eye of the tiger” sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes |

Continued

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| **Table 597-7** | Genetic Choreas—cont’d | | | | | |
|  | | **MODE OF INHERITANCE** | **GENE, LOCATION** | **PROTEIN PRODUCT** | **USUAL AGE AT ONSET (yr)** | **CLINICAL SIGNS** |
| Lesch-Nyhan syndrome | | X-linked, recessive | *HPRT,* Xq | Hypoxanthine- guanine phosphoribosyl- transferase | Childhood | Chorea, dystonia, hypotonia,  self-injurious behavior with biting of fingers and lips, mental retardation; short stature, renal calculi, hyperuricemia |
| Wilson disease | | AR | *ATP7B,* 13q | Copper transporting  P-type adenosine triphosphatase (ATPase) | <40 | Parkinsonian features, dystonia, tremor, rarely chorea, behavioral and cognitive change, corneal Kayser-Fleischer rings, liver disease |
| PKC syndrome and ICCA syndrome | | AD | Unknown, 16p | Unknown | <1-40 | Paroxysmal movement disorders presenting with recurrent brief episodes of abnormal involuntary movements with dramatic response to low-dose carbamazepine (PKC); recurrent brief episodes of abnormal involuntary movements in association with infantile convulsions (ICCA) |
| Benign hereditary chorea | | AD | *TITF-1,* 14q;  other | Thyroid transcription factor 1 | Childhood | Chorea, mild ataxia; genetically heterogeneous |

\*HDL1, HDL3, and HDL4 are very rare conditions (only 1 family known) and therefore not included in the table.

†Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size.

AD, autosomal dominant; AOA, ataxia with oculomotor apraxia (types 1 or 2); AR, autosomal recessive; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia–like disorder; DRPLA, dentatorubropallidoluysian atrophy; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MJD, Machado-Joseph disease; PKC, paroxysmal kinesigenic choreoathetosis; SCA, spinocerebellar ataxia (types 2, 3, or 17).

*Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas,* Lancet Neurol *5:589–602, 2006.*

Infectious vasculitis Bacterial, fungal, parasitic

Spirochetal (syphilis, Lyme disease, leptospirosis)

Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths

Necrotizing vasculitides Classic polyarteritis nodosa Wegener granulomatosis

Allergic angiitis and granulomatosis (Churg-Strauss syndrome) Necrotizing systemic vasculitis overlap syndrome Lymphomatoid granulomatosis

Vasculitis associated with collagen vascular disease Systemic lupus erythematosus

Rheumatoid arthritis Scleroderma Sjögren syndrome

Vasculitis associated with other systemic diseases Behçet disease

Ulcerative colitis Sarcoidosis

Relapsing polychondritis Kohlmeier-Degos disease

Takayasu arteritis Hypersensitivity vasculitides

Henoch-Schönlein purpura Drug-induced vasculitides Chemical vasculitides

Essential mixed cryoglobulinemia Miscellaneous

Vasculitis associated with neoplasia Vasculitis associated with radiation Cogan syndrome

Dermatomyositis-polymyositis

X-linked lymphoproliferative syndrome Kawasaki disease

Classification of Cerebral Vasculitis

**Table 601-2**

|  |  |
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| **Table 601-4** | Potential Risk Factors for Hemorrhagic Stroke in Children |
| **MAJOR CATEGORIES** | **EXAMPLES** |
| Vascular disorder | Arteriovenous malformations  Cavernous malformations (“cavernomas”) Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm  Choroid plexus angiomas (pure intraventricular hemorrhage)  Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1)  Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis |
| Blood disorder | Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome  Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of  the newborn)  Disseminated intravascular coagulopathy |
| Trauma | Middle meningeal artery injury (epidural hematoma)  Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage  Hemorrhagic contusions (coup and contrecoup)  Nonaccidental trauma (subdural hematomas of different ages)  Iatrogenic (neurosurgical procedures, angiography)  Rupture of arachnoid cyst |

Primary central nervous system vasculitis

*From Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children,* Stroke *39:2644–2691, 2008, Table 5, p. 8.*

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| **Table 597-10** Causes of Dystonia in Childhood | |
| STATIC INJURY/STRUCTURAL DISORDERS  Cerebral palsy Hypoxic–ischemic injury Kernicterus  Head trauma Encephalitis Tumors  Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)  Congenital malformations | DRUGS/TOXINS  Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)  Calcium channel blockers  Stimulants (amphetamine, cocaine, ergot alkaloids) Anticonvulsants (carbamazepine, phenytoin) Thallium  Manganese Carbon monoxide Ethylene glycol Cyanide Methanol  Wasp sting |
| HEREDITARY/DEGENERATIVE DISORDERS  DYT1 (9q34, encodes torsinA) DYT2 (autosomal-recessive)  DYT3 (X-linked dystonia-parkinsonism syndrome of Lubag–Xq13) DYT4  DYT5 (14q22.1-2, encodes GTP cyclohydrolase I, leading to dopa- responsive dystonia or Segawa disease)  DYT6 (8p21-q22) DYT7 (18p)  DYT8 (2q33-q35, causing paroxysmal nonkinesigenic choreoathetosis [PNKC])  DYT9 (1p, causing paroxysmal nonkinesigenic dyskinesia [PNKD] and spasticity)  DYT10 (16p11.2-q12.1, causing paroxysmal kinesigenic choreoathetosis [PKC])  DYT11 (heterogeneous, causing familial myoclonus-dystonia) Rapid-onset dystonia-parkinsonism (DYT12)  Fahr disease (often caused by hypoparathyroid disease)  Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, formerly Hallervorden-Spatz disease, caused by mutations in PANK2)  Huntington disease (particularly the Westphal variant, IT15-4p16.3)  Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)  Neuronal ceroid-lipofuscinoses (NCL) Rett syndrome  Striatal necrosis Leigh disease Neuroacanthocytosis  HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)  Ataxia-telangiectasia Tay-Sachs disease Sandhoff’s disease Niemann-Pick type C GM1 gangliosidosis  Metachromatic leukodystrophy (MLD) Lesch-Nyhan disease |
| PAROXYSMAL DISORDERS  Paroxysmal kinesigenic choreoathetosis (PKC) Paroxysmal nonkinesigenic choreoathetosis (PNKC) Exercise-induced dystonia  Complex migraine  Alternating hemiplegia of childhood (AHC) Paroxysmal torticollis of infancy |
| DISORDERS THAT MIMIC DYSTONIA  Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)  Arnold-Chiari malformation type II Atlantoaxial subluxation Syringomyelia  Posterior fossa mass  Cervical spine malformation (including Klippel-Feil syndrome) Skew deviation with vertical diplopia causing neck twisting Juvenile rheumatoid arthritis  Sandifer syndrome (associated with hiatal hernia in infants) Spasmus nutans  Tics  Infant masturbation Spasticity  Myotonia Rigidity  Stiff-person syndrome  Isaac syndrome (neuromyotonia) Startle disease (hyperekplexia) Neuroleptic malignant syndrome Central herniation with posturing Psychogenic dystonia |
| METABOLIC DISEASE  Glutaric aciduria types 1 and 2  Acyl-coenzyme A (CoA) dehydrogenase deficiencies  Dopa-responsive dystonia (tyrosine hydroxylase deficiency, guanosine triphosphate [GTP] cyclohydrolase 1 deficiency, DYT5)  Dopamine agonist-responsive dystonia (aromatic l-amino acid decarboxylase deficiency, aminolevulinic acid dehydrase [ALAD])  Biotin responsive basal ganglia disease Mitochondrial disorders  Wilson disease Vitamin E deficiency Homocystinuria  Methylmalonic aciduria Tyrosinemia |

*From Sanger TD, Mink JW: Movement disorders. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman’s pediatric neurology: principles and practice*, ed 5, Philadelphia, 2012, WB Saunders, Box 68-2.*

**Chapter 597** ◆ Movement Disorders **2893**

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| **Table 597-11** Examples of Primary and Secondary Dystonia in Childhood | |
| **DIAGNOSIS ADDITIONAL CLINICAL FEATURES** | **DIAGNOSIS ADDITIONAL CLINICAL FEATURES** |
| Aicardi-Goutières Encephalopathy, developmental  syndrome regression  Acquired microcephaly Sterile pyrexias  Lesions on the digits, ears (chilblain) Epilepsy  CT: calcification of the basal ganglia | Leigh syndrome Motor delays, weakness, hypotonia Ataxia, tremor  Elevated lactate  MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus |
| Lesch-Nyhan syndrome Male  (X-linked) Self-injurious behavior Hypotonia  Oromandibular dystonia, inspiratory stridor  Oculomotor apraxia Cognitive impairment Elevated uric acid |
| Alternating hemiplegia Episodic hemiplegia/quadriplegia of childhood Abnormal ocular movements  Autonomic symptoms Epilepsy  Global developmental impairment Environmental triggers for spells |
| Aromatic amino acid Developmental delay decarboxylase Oculogyric crises  deficiency (AADC) Autonomic dysfunction Hypotonia |
| Myoclonus dystonia Myoclonus  Head, upper limb involvement |
| Niemann-Pick type C Hepatosplenomegaly  Hypotonia  Supranuclear gaze palsy Ataxia, dysarthria Epilepsy  Psychiatric symptoms |
| ARX gene mutation Male  (X-linked) Cognitive impairment Infantile spasms, epilepsy Brain malformation |
| Benign paroxysmal Episodic  torticollis of infancy Cervical dystonia only  Family history of migraine |
| Neuroacanthocytosis Oromandibular and lingual dystonia |
| Neurodegeneration with Cognitive impairment  brain iron accumulation Retinal pigmentary degeneration, optic atrophy |
| Complex regional pain Lower limb involvement syndrome Prominent pain |
| Dopa-responsive Diurnal variation dystonia (DRD) | Rapid onset dystonia Acute onset  parkinsonism (DYT12) Distribution face > arm > leg  Prominent bulbar signs |
| Drug-induced dystonia |
| Rett syndrome Female  Developmental regression following a period of normal development  Stereotypic hand movements Acquired microcephaly Epilepsy |
| Dystonia-deafness optic Sensorineural hearing loss in early neuropathy syndrome childhood  Psychosis  Optic atrophy in adolescence |
| DYT1 dystonia Lower limb onset followed by generalization |
| Spinocerebellar ataxia 17 Ataxia  (SCA17) Dementia, psychiatric symptoms Parkinsonism |
| Glutaric aciduria type 1 Macrocephaly  Encephalopathic crises MRI: striatal necrosis |
| Tics Stereotyped movements Premonitory urge, suppressible |
| GM1 gangliosidosis Short stature, skeletal dysplasia type 3 Orofacial dystonia  Speech/swallowing disturbance Parkinsonism  MRI: putaminal hyperintensity |
| Tyrosine hydroxylase Infantile encephalopathy, hypotonia deficiency Oculogyric crises, ptosis  Autonomic symptoms  Less diurnal fluctuation than DRD |
| Huntington disease Parkinsonism Epilepsy  Family history of Huntington disease |
| Kernicterus Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia  MRI: hyperintense lesions in the globus pallidus |

**Chapter 598** ◆ Encephalopathies **2897**

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| **Table 598-1** | Classification of Cerebral Palsy and Major Causes | | |
| **MOTOR SYNDROME (APPROX. % OF CP)** | | **NEUROPATHOLOGY/MRI** | **MAJOR CAUSES** |
| Spastic diplegia (35%) | | Periventricular leukomalacia  Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles | Prematurity Ischemia Infection  Endocrine/metabolic (e.g., thyroid) |
| Spastic quadriplegia (20%) | | Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations | Ischemia, infection Endocrine/metabolic, genetic/  developmental |
| Hemiplegia (25%) | | Stroke: in utero or neonatal  Focal infarct or cortical, subcortical damage Cortical malformations | Thrombophilic disorders Infection Genetic/developmental  Periventricular hemorrhagic infarction |
| Extrapyramidal (athetoid, dyskinetic) (15%) | | Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scaring globus pallidus, caudate,  putamen, brainstem  No lesions: ? dopa-responsive dystonia | Asphyxia Kernicterus Mitochondrial Genetic/metabolic |

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| **Table 598-2** | Clinical Manifestations of Mitochondrial Encephalomyopathies | | | | | | | |
| **TISSUE** |  | **SYMPTOMS/SIGNS** | **MELAS** | **MERRF** | **NARP** | **KSS** | **LEIGH** | **LHON** |
| CNS |  | Regression | + | + |  | + | + |  |
| Seizures | + | + |  |  |
|  |  |  |
|  | Ataxia | + | + | + | + |  |  |
| Cortical blindness | + |  |
|  |  |  |  |  |
|  | Deafness | + |  | + |  |  |  |
|  | Migraine | + |  |  |  |  |  |
|  | Hemiparesis | + |  |  |  |  |  |
|  | Myoclonus Movement disorder | +  + | + |  |  |  | + |
| Nerve |  | Peripheral neuropathy | + | + | + | + |  |  |
| Muscle |  | Ophthalmoplegia |  |  |  | + |  |  |
| +  + | +  + | + | +  +  + | + |
| Weakness  RRF on muscle biopsy Ptosis |
| Eye |  | Pigmentary retinopathy |  |  | + | + |  |  |
| + | + |
| Optic atrophy Cataracts |  | + |
| Heart |  | Conduction block Cardiomyopathy |  |  |  | +  + |  | + |
| Blood |  | Anemia  Lactic acidosis | + | + |  | + | + |  |
| Endocrine | | Diabetes mellitus Short stature | + | + |  | +  + |  |  |
| Kidney | | Fanconi syndrome | + | + |  | + |  |  |

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia and retinitis pigmentosa; RRF, ragged red fibers.

**Chapter 598** ◆ Encephalopathies **2903**

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| **Table 598-3** | Clinical Features of Congenital Leigh Syndrome or Leigh-Like Syndrome | |
| NEUROLOGIC MANIFESTATIONS | | NONNEUROLOGIC MANIFESTATIONS |
| *Brainstem* | | *Dysmorphic Features* |
| Bradypnea, hypopnea, episodes of apnea | | Lip cleft |
| Bradycardia | | Short distal phalanges |
| Tetraparesis | | Single palmar crease |
| Hypotonia (floppy infant) | | Rostral vertebrae |
| Failure to thrive, poor sucking | | Round face |
| Swallowing difficulties, dysphagia, poor feeding, poor sucking | | Frontal bossing |
| Vomiting | | Flat nasal root |
| Spasticity, brisk tendon reflexes | | Microcephaly |
| Dysphasia, dysarthria | | Thin lips |
| Squint | | Small chin |
| Absence of optic or acoustic blink | | Long, featureless philtrum |
| *Other Cerebral Manifestations* | | Hypospadia |
| Stroke-like episodes | | *Others* |
| Delay of developmental milestones | | Inguinal hernia |
| Paralysis of vertical gaze | | Stiff neck |
| Myoclonic jerks of limbs or eyelids | | Retinal dystrophy, retinopathy |
| Hypothermia | | Deafness, hypoacusis |
| Drowsiness, dizziness | | Hypertrophic, dilated cardiomyopathy |
| Psychomotor (mental) retardation | | Pancreatitis |
| Ataxia, tremor | | Diarrhea |
| Seizures, convulsions | | Urinary excretion of Krebs-cycle intermediates |
| Growth retardation | | Intrauterine growth retardation |
| Dystonia | | Hypertrichosis |
| Clumsiness, dullness | | Villous atrophy |
| Nystagmus, uncoordinated eye movement, slow saccades | | Nephrotic syndrome |
| Optic atrophy | | Nephropathy |
| Visual loss | | Hyperhidrosis |
| Facial dyskinesia | | Scoliosis |
| Ocular apraxia | |  |
| Drooling | |  |
| Gaze fixation difficulty | |  |
| *Peripheral Nervous System Manifestations* | |  |
| Cranial nerve palsies | |  |
| Generalized wasting | |  |
| Bilateral ptoses | |  |
| Chronic progressive external ophthalmoplegia, strabismus | |  |
| Reduced tendon reflexes | |  |
| Polyneuropathy | |  |
| Muscle weakness | |  |
| Myopathy | |  |

*From Finsterer J: Leigh and Leigh-like syndrome in children and adults.* Pediatr Neurol *39:223–235, 2008, Table 1.*

1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other central nervous system regions.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of resembling diseases.
   1. Differential diagnosis from clinical viewpoints.

Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.

* 1. Differential diagnosis from radiologic viewpoints.

Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

**Table 598-4**

Acute disseminated encephalomyelitis (ADEM) Multiple sclerosis (including tumefactive MS) Acute hemorrhagic leukoencephalopathy Clinically isolated syndrome (CIS) Neuromyelitis optica spectrum disorder

*N*-methyl-D-aspartate receptor (NMDAR) antibody and other autoimmune encephalitis

Vasculitis/angiopathies

Hashimoto encephalitis (anti–thyroid peroxidase [TPO] antibody) Familial hemophagocytic lymphohistiocytosis

Langerhans cell histiocytosis Lymphoma

Gliomatosis cerebri Glioma

Sarcoidosis

Mitochondrial disorders (Leigh syndrome) Vitamin E deficiency

Vitamin B12 deficiency Celiac disease

Herpes simplex virus (HSV), enterovirus, arbovirus, Powassan and other viral encephalitides

Rabies

Subacute sclerosing pan-encephalitis (SSPE) (chronic measles) Charcot-Marie-Tooth syndrome

Leukoencephalopathies (Aicardi-Goutières syndrome) Vanishing white matter disease

Schilder disease (possibly an adrenoleukodystrophy) X-linked adrenoleukodystrophy

Griscelli syndrome type 2

Differential Diagnosis of Demyelinating Disorders

**Table 600-1**

|  |  |  |  |
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| **Table 598-5** Autoimmune Encephalitis in Children | | | |
| **TUMOR MECHANISMS ASSOCIATION** | **SYNDROME** | **ANCILLARY TEST** | **TREATMENT/ PROGNOSIS** |
| DEMONSTRATED IMMUNE MECHANISMS  Anti-NMDAR Antibodies against Age and gender encephalitis NR1 subunit of related: 41% in  NMDAR, disrupt females older  function by than 12 yr; <6%  crosslinking and in girls younger internalization of than 12 yr. No receptors tumors identified  in young boys | Psychiatric symptoms, seizures, orofacial dyskinesias and other abnormal movements, autonomic dysfunction | EEG: almost always abnormal; it may show “extreme delta brush” pattern  Brain MRI: nonspecific findings in ~35%  CSF: pleocytosis and/or increased protein in  >80%  EEG: temporal lobe epileptic activity; focal or generalized slowing  MRI: increased T2 and FLAIR signal in limbic region  CSF: pleocytosis and increased proteins | 80% complete recovery after immunotherapy and tumor removal  (if appropriate). Frequently second- line drug\* immunotherapy is required. Relapses in  ~15% of patients If autoantigens are intracellular, poor  response to immunotherapy  If autoantigens are on the cell surface,  ~80% are responsive to immunotherapy |
| Limbic Antibodies against Extremely rare in encephalitis intraneuronal children (see  antigens: Hu, Ma2, text) amphiphysin, GAD  Antibodies against synaptic antigens: GABABR, mGluR5 | Severe short-term memory loss, seizures |
| STRONGLY SUSPECTED IMMUNE MECHANISMS  Opsoclonus- Most patients do not Neuroblastoma myoclonus and have detectable occurs in 50% of other cerebellar- antibodies (a few children <2 year brainstem patients have Hu old; teratoma in encephalitis antibodies) teenagers and  young adults  Bickerstaff GQ1b antibodies No tumor encephalitis association  Hashimoto TPO antibodies No tumor encephalitis association | Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling  Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome  Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia  Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy  Abnormal movement and behavior disorder | CSF abnormalities suggesting B-cell activation  MRI: in some cases cerebellar atrophy  MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum)  Nerve conduction studies: abnormal in  ~44% (predominant axonal degeneration, less frequent demyelination)  48% hypothyroidism, MRI often normal  EEG: slow activity CSF: elevated protein | Partial response to immunotherapy in neuroblastoma- related opsoclonus  High response to immunotherapy in teratoma-associated opsoclonus  Often good outcome with steroids, IVIG and/or plasma exchange  Steroid-responsive. Partial responses are frequent |
| Rasmussen Most likely immune No tumor encephalitis mediated (unclear association  mechanism)  Basal ganglia Antibodies to D2R in No tumor encephalitis some cases association | MRI: progressive unilateral hemispheric atrophy  Variable basal ganglia T2/FLAIR abnormalities | Limited response to immunotherapy. Patients may need functional hemispherectomy  Mostly monophasic, can relapse |
| POSSIBLE IMMUNE MECHANISMS | Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction | MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord  Brain MRI, usually normal | Steroid-responsive but may require chronic steroid or other immunosuppressive therapy |
| CLIPPERS No antibodies No tumor |
| association |
| ROHHAD Unknown. Neural crest tumor | Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation | Symptomatic; in some patients limited response to immunotherapy |
| Autoimmune and in ~50% of |
| genetic origin cases† |
| postulated. |

\*Includes rituximab and cyclophosphamide.

†Exact frequency is unknown.

CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; GABABR, γ-aminobutyric acid-B receptor, GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.

**2908 Part XXVII** ◆ The Nervous System

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| **Table 598-6** Differential | Diagnosis of Anti-NMDAR Encephalitis in Children |
| **DISORDER** | **COMMENTS** |
| Viral encephalitis | Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis. |
| Relapsing post–herpes simplex virus encephalitis | Occurs ~4-6 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir), or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis. |
| New-onset psychosis | Because most patients with anti-NMDAR encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered. As the disease evolves, the development of neurological symptoms usually reveals the diagnosis. |
| Drugs/toxins | The acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others). Carbon monoxide. |
| Neuroleptic malignant syndrome | The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis. |
| Limbic encephalitis | Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes. |
| Encephalitis lethargica | This is an ill-defined entity, likely representing multiple disorders. Criteria include: acute or subacute encephalitis with at least 3 of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Approximately, 50% of patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis. |
| Childhood disintegrative disorder/late-onset autism | Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. While the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have substantial clinical recovery. |
| Kleine-Levin syndrome | Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae. |
| Inborn errors of metabolism | Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including  3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson, and Lesch-Nyhan syndromes. Pantothenate kinase associated neurodegeneration, porphyria, and urea cycle defects should also be considered. |
| Monoamine neurotransmitter disorders | Deficiency of dopamine, serotonin or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters. |
| Demyelinating disorders | Acute disseminated encephalomyelitis and neuromyelitis optica are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMO the presence of aquaporin 4 antibodies in serum or CSF is associated with relapses and poor prognosis. |
| CNS vasculitis | CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large vessel angiitis, and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter, not restricted to vascular territories with frequent leptomeningeal and/or local enhancement. |
| Systemic rheumatic disorders | Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood- forming cells, and blood vessels. |

CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction.

**Chapter 599** ◆ Neurodegenerative Disorders of Childhood **2911**

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| **Table 599-1** | Neurometabolic Conditions Associated with Developmental Regression | | |
| **AGE AT ONSET (yr)** | | **CONDITIONS** | **COMMENTS** |
| <2 with hepatomegaly | | Fructose intolerance Galactosemia  Glycogenosis (glycogen storage disease) types I-IV Mucopolysaccharidosis types I and II  Niemann-Pick disease, infantile type Tay-Sachs disease  Zellweger syndrome  Gaucher disease (neuronopathic form) Carbohydrate-deficient glycoprotein syndromes | Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)  Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)  Hypoglycemia, cardiomegaly (type II) Coarse facies, stiff joints  Gray matter disease, failure to thrive  Seizures, cherry-red macula, edema, coarse facies Hypotonia, high forehead, flat facies  Extensor posturing, irritability Dysmyelination, cerebellar hypoplasia |
| <2, without hepatomegaly | | Krabbe disease Rett syndrome  Maple syrup urine disease Phenylketonuria  Menkes kinky hair disease  Subacute necrotizing encephalopathy of Leigh disease Canavan disease  Neurodegeneration with brain iron accumulation disease | Irritability, extensor posturing, optic atrophy, and blindness Girls with deceleration of head growth, loss of hand skills,  hand wringing, impaired language skills, gait apraxia Poor feeding, tremors, myoclonus, opisthotonos  Light pigmentation, eczema, seizures Hypertonia, irritability, seizures, abnormal hair White matter disease  White matter disease, macrocephaly White matter disease, movement disorder |
| 2-5 | | Niemann-Pick disease types III and IV Wilson disease  Gangliosidosis type II Neuronal ceroid lipofuscinosis  Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])  Ataxia-telangiectasia Huntington disease (chorea)  Neurodegeneration with brain iron accumulation syndrome  Metachromatic leukodystrophy Adrenoleukodystrophy | Hepatosplenomegaly, gait difficulty  Liver disease, Kayser-Fleischer ring; deterioration of cognition is late  Gray matter disease Gray matter disease Gray matter disease  Basal ganglia disease Basal ganglia disease Basal ganglia disease  White matter disease  White matter disease, behavior problems, deteriorating school performance, quadriparesis |
| 5-15 | | Adrenoleukodystrophy Multiple sclerosis  Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)  Schilder disease Refsum disease  Sialidosis II, juvenile form  Subacute sclerosing panencephalitis | Same as for adrenoleukodystrophy in 2-5 yr olds White matter disease  Gray matter disease  White matter disease, focal neurologic symptoms Peripheral neuropathy, ataxia, retinitis pigmentosa Cherry-red macula, myoclonus, ataxia, coarse facies  Diffuse encephalopathy, myoclonus; may occur years after measles |

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| --- | --- | --- | --- | --- | --- | --- |
| **Table 600-5** | MRI Characteristics for Dissemination in Space That Increase the Likelihood of a Pediatric Multiple Sclerosis Diagnosis | | | | | |
| **BARKHOF\*** | | **MIKAELOFF (KIDMUS)†** | **CALLEN (MS VS ADEM)‡** | **CALLEN (DIAGNOSTIC MS)§** | **VERHEY (DIFFERENTIAL)** | **POLMAN (2010 REVISED MCDONALD CRITERIA)¶** |
| 3 of 4:  ≥9 T2 lesions or 1 gadolinium enhancing  ≥3 Periventricular  ≥1 Infratentorial  ≥1 Juxtacortical | | 1 of 2:  Lesions perpendicular to long axis of the corpus callosum  Sole presence of  well-defined lesions | 2 of 3:  Absence of a diffuse bilateral lesion pattern  Presence of black holes  ≥2 Periventricular lesions | 2 of 3:  ≥5 Lesions on  T2-weighted images 2 Periventricular  lesions  ≥1 Brainstem lesions | 2 of 2:  ≥1 Periventricular lesions  ≥1 Hypointense lesions on T1 images | 2 of 4:  ≥1 Periventricular  ≥1 Juxtacortical  ≥1 Infratentorial  ≥1 Spinal cord |

\*Barkhof F, Filippi M, Miller DH, et al: Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059– 2069, 1997.

†Mikaeloff Y, Adamsbaum C, Husson HM, et al: MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 127:1942–1947, 2004.

‡Callen DJ, Shroff MM, Branson HM, et al: Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 72:968–973, 2009.

§Callen DJ, Shroff MM, Branson HM, et al: MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 72:961–967, 2009.

Verhay LH, Branson HM, Shroff MM, et al: MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol* 10:1065–1073, 2011.

¶Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 69:292–302, 2011. ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.

*From Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions.* Mult Scler *19(10):1261–1267, 2013, Appendix 3, p. 1267.*

**2912 Part XXVII** ◆ The Nervous System

**Gal-GalNAc NANA**

**Gal**

 **Glc-Ceramide** *(GM1 Ganglioside)*

**GalNAc NANA**

Gal

**Gal**



**GM1 gangliosidoses**

β*-Galactosidase*

*Neurodegeneration, HSM, CRS,*

*skeletal deformities*



**Tay-Sachs Disease**

β*-Hexosaminidase A*

*Neurodegeneration, CRS, large head, acoustic startle*

 **Glc-Ceramide** *(GM2)*

**GalNac-Gal-Gal-Glc-Ceramide** *(Globoside)*

GalNac



**Sandhoff disease**

β*-Hexosaminidase A & B*

*Similar to Tay-Sachs, may have HSM, dysostosis multiplex*

**NANA**

###### GalNAc

 **Gal ** **Glc-Ceramide** *(GM3) Neuraminidase*

###### NANA

**Gal-Gal-Glc-Ceramide**

**Gal**



**Fabry disease**

Gal

α*-Galactosidase*

*Angiokeratomas, kidney/heart disease, burning dysesthesias*

**Glc-Ceramide**

(Lactosyl Ceramide)

*Sphingomyelinase*

###### Gal

β*-Galactosidase*

**Phosphorylcholine-Ceramide**

**Niemann-Pick A/B**

Choline P

**Glc-Ceramide**

###### Glc

**Gaucher disease**

β*-Glucosidase*

*Most common HSM, osteoporosis, CNS disease rare*

Gal

*Neurodegeneration HSM*

**Ceramide**

**Farber disease**

*Painful joint deformities, subcutaneous lipid nodules, hoarse cry*

β-Galactosidase

###### Fatty Acid

Ceramidase

SO3H

**Gal-Ceramide**

**Krabbe**

**Sphingosine**

*Spasticity, irritability, blindness, failure to thrive*

*Arylsulfatase A*

**MLD**

*Spasticity, dementia, areflexia*

**SO3H-Gal-Ceramide**

###### **Figure 599-1** Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

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| **Table 599-2** | Clinical and | Genetic Characteristics of the | Neuronal Ceroid Lipofuscinoses (NCL) | |
| **NCL TYPE** | **GENE\*** | **PROTEIN** | **AGE OF ONSET** | **CLINICAL PRESENTATION** |
| Congenital | *CLN10* | Cathepsin‡ | Birth (but can present later) | Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms |
| Infantile  Variant infantile | *CLN1 CLN1* | Palmitoyl-protein thioesterase-1 (PPT1)‡ | 6-24 months  3 yr to adulthood | Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss  Chronic course  Initial visual loss followed then by slow mental and motor decline and seizures |
| Late infantile | *CLN2 CLN5 CLN6 CLN7 CLN8* | Tripeptidyl peptidase-1 (TPP1)‡ Partially soluble protein Membrane protein  Membrane protein Membrane protein | 2-8 yr  5-10 yr | Seizures, often severe and intractable; cognitive and motor decline; and visual loss  Severe epilepsy, progressive with mental retardation |
| Juvenile | *CLN3* | Membrane protein | 4-10 yr | Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures |

\*Note that all the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in DNAJC5) is not well characterized and is not included in the table.

†Direct genetic testing is available for all.

‡Enzyme testing available.

**2920 Part XXVII** ◆ The Nervous System

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| **Table 600-2** | IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System | |
| **DISORDER** | | **IPMSSG 2012** |
| CIS | | * A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, unless caused by fever |
| Monophasic ADEM | | * A first polyfocal clinical CNS event with presumed inflammatory cause * Encephalopathy that cannot be explained by fever is present   MRI typically shows diffuse, poorly demarcated, large, **>**1-2 cm lesions involving predominantly the cerebral white matter; T1 hypointense white matter lesions are rare; deep gray-matter lesions (e.g., thalamus or basal ganglia) can be present   * No new symptoms, signs or MRI findings after 3 mo of the incident ADEM |
| Recurrent ADEM | | * See multiphasic ADEM |
| Multiphasic ADEM | | * New event of ADEM 3 mo or more after the initial event that can be associated with new or reemergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent |
| MS | | Any of the following:   * Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than 1 area of the CNS * Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ages 2-12 yr and only apply to cases without an ADEM onset) |
| NMO | | All are required:   * Optic neuritis * Acute myelitis   At least 2 of 3 supportive criteria   * Contiguous spinal cord MRI lesion S3 vertebral segments * Brain MRI not meeting diagnostic criteria for MS * Anti–aquaporin-4 immunoglobulin G–seropositive status * ADEM followed 3 mo later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS |

The 2001 McDonald MRI criteria for DIS require 3 of the following 4 MRI features: 29 T2 lesions or 1 gadolinium-enhancing lesion; 23 periventricular lesions; 21 infratentorial lesion(s); 21 juxtacortical lesion(s). The DIT criteria require subsequent white-matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.

The 2010 Revised McDonald MRI criteria for DIS require the presence of at least 2 of the following 4 criteria: 21 lesions in each of the 4 locations; periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of newT2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MS, multiple sclerosis; NMO, neuromyelitis optica.

*Modified from Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune- mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler 19(10):1261–1267, 2013, Appendix 1, p. 1266.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 600-3** | Symptoms and Signs of Multiple Sclerosis by Site | | |
|  | | **SYMPTOMS** | **SIGNS** |
| Cerebrum | | Cognitive impairment  Hemisensory and motor Affective (mainly depression) Epilepsy (rare)  Focal cortical deficits (rare) | Deficits in attention, reasoning, and executive function (early); dementia (late)  Upper motor neuron signs |
| Optic nerve | | Unilateral painful loss of vision | Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect |
| Cerebellum and cerebellar pathways | | Tremor  Clumsiness and poor balance | Postural and action tremor, dysarthria Limb incoordination and gait ataxia |
| Brainstem | | Diplopia, oscillopsia Vertigo  Impaired swallowing  Impaired speech and emotional lability Paroxysmal symptoms | Nystagmus, internuclear and other complex ophthalmoplegias  Dysarthria Pseudobulbar palsy |
| Spinal cord | | Weakness  Stiffness and painful spasms Bladder dysfunction  Erectile impotence Constipation | Upper motor neuron signs Spasticity |
| Other | | Pain Fatigue  Temperature sensitivity and exercise intolerance |  |

*Modified from Compston A, Coles A: Multiple sclerosis,* Lancet *372:1502–1517, 2008, p. 1503.*

**Chapter 600** ◆ Demyelinating Disorders of the Central Nervous System **2923**

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| --- | --- | --- | --- | --- |
| **Table 600-6** | Overview of Available | and Emerging Therapies in | Pediatric Multiple Sclerosis | |
| **MEDICATION** | **MEDICATION CLASS** | **MECHANISM IN MS** | **SIDE EFFECTS** | **STUDIES DESCRIBING DRUG EFFICACY IN PEDIATRIC MS** |
| FIRST-LINE THERAPIES  Interferon-α or β Immunomodulator | | Modulates T cells and cytokine production | Flu-like symptoms; transaminitis; leukopenia; tissue necrosis at injection site (rare)  Flushing, lipodystrophy at injection sites | Retrospective Prospective multicenter |
| Glatiramer acetate\* | Immunomodulator | Modulates T cells and reduces antigen presentation | Prospective single center Prospective multicenter |
| SECOND-LINE THERAPIES  Natalizumab\* Monoclonal antibody | | Targets α4-integrin; prevents T-cell migration into CNS and other tissues  DNA alkylation; effects include cytotoxic immune cell depletion  Disrupts DNA synthesis; effects include cytotoxic immune cell depletion  Targets/inactivates interleukin-2 receptor; inhibits activated T cells  Targets CD20, a marker of immature B cells; depletes B-cell populations  Disrupts purine metabolism; effects include cytotoxic immune cell depletion  Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments  Impairs immune cell proliferation via pyrimidine synthesis inhibition | Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)  Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility  Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections  Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions  PML (rate undefined); infusion- related side effects | Retrospective Prospective multicenter  Retrospective multicenter Retrospective single center  Retrospective multicenter  No efficacy assessments available in pediatric MS |
| Cyclophosphamide Chemotherapeutic | |
| Mitoxantrone\* Chemotherapeutic | |
| Daclizumab Monoclonal antibody | |
| Rituximab Monoclonal antibody | |
| Azathioprine | Chemotherapeutic | Transaminitis; leukopenia; lymphoma | No efficacy assessments available in pediatric MS |
| Fingolimod\*† | Immunomodulator | Systemic viral infection; cardiac arrhythmia; macular edema; transaminitis | FDA approved for adult MS in September 2010; no reports of use in pediatric MS to date  FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date |
| Teriflunomide\*† | Immunomodulator | Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity |
| EMERGING THERAPIES  Vitamin D† Vitamin/hormone | | Modulates immune cell expression | Hypercalcemia and kidney stones at a serum 25(OH) vitamin D level >100 ng/mL  Headache; infusion-related side effects; theoretical risk of PML (undefined) | Prospective trials in pediatric and adult MS are currently underway  Recently completed phase III trial in adult MS; no use in pediatric MS to date  FDA approved for adult MS in March 2013; no use in pediatric MS to date  Recently completed phase III trial in adult MS; no use in pediatric MS to date  Recently completed phase III trial in adult MS; no use in pediatric MS to date |
| Ocrelizumab Monoclonal antibody | | Targets CD20, a marker of immature B cells; depletes B-cell populations |
| Dimethyl fumarate† Immunomodulator | | Neuroprotectant; antioxidant | Flushing reaction; gastrointestinal upset; headache |
| Alemtuzumab | Monoclonal antibody | Anti-CD52 antibody target; depletes mature T cells  Modulates T cell and cytokine production | Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)  Transaminitis |
| Laquinimod† | Immunomodulator |

\*FDA approved for the treatment of adult MS.

†Orally administered therapy.

CNS, central nervous system; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

**Chapter 601** ◆ Pediatric Stroke **2927**

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| --- | --- |
| **Table 601-1** Risk | Factors for Arterial Ischemic Stroke in Children |
| **MAJOR CATEGORY** | **EXAMPLES** |
| Arteriopathy | Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA])  Postvaricella and other viruses angiopathy (PVA) Systemic/secondary vasculitis (e.g., Takayasu arteritis) Moyamoya disease/syndrome  Arterial infection (e.g., bacterial meningitis, tuberculosis) Fibromuscular dysplasia  Traumatic or spontaneous carotid or vertebral artery dissection Vasospasm (e.g., Call-Fleming syndrome)  Migraine (migrainous infarction?)  Congenital arterial hypoplasia (e.g., PHACES syndrome) |
| Cardiac | Complex congenital heart diseases (cyanotic ≫ acyanotic) Cardiac catheterization/procedure (e.g., balloon atrial septostomy) Ventricular assistive device use  Cardiac surgery Arrhythmia  Valvular heart disease Endocarditis  Cardiomyopathy, severe ventricular dysfunction Intracardiac lesions (e.g., atrial myxoma)  Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli]) |
| Hematologic | Sickle cell anemia  Iron-deficiency anemia  Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A)  Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy) |
| Other including metabolic/genetic etiologies | Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis) Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia) Illicit drugs and toxins (e.g., cocaine)  Extracorporeal membrane oxygenation (ECMO) Hereditary dyslipoproteinemia  Familial hypoalphalipoproteinemia Familial hypercholesterolemia  Type IV, type III hyperlipoproteinemia Tangier disease  Progeria  Fabry disease (α-galactosidase A deficiency)  Subacute necrotizing encephalomyelopathy (Leigh disease) Sulfite oxidase deficiency  11β-Ketoreductase deficiency 17α-Hydroxylase deficiency  Purine nucleoside phosphorylase deficiency Ornithine transcarbamylase deficiency Neurofibromatosis type 1  HERNS  Heritable disorders of connective tissue Ehlers-Danlos syndrome (type IV) Marfan syndrome  Pseudoxanthoma elasticum  Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase) Menkes syndrome  Organic acidemias Methylmalonic academia Propionic academia Isovaleric academia Glutaric aciduria type II  Mitochondrial encephalomyopathies MELAS  MERRF  MERRF/MELAS overlap syndrome Kearns-Sayre syndrome  See also: stroke mimics (see Chapter 601.4) |

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

*Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children.* Stroke *39:2644–2691, 2008, Table 2, p. 6.*

**2930 Part XXVII** ◆ The Nervous System

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| --- | --- | --- |
| **Table 601-3** | Common Risk Factors for Cerebral Sinovenous Thrombosis in Children | |
| **MAJOR CATEGORIES** | | **EXAMPLES** |
| Blood coagulation | | Prothrombotic conditions  Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium  Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia  Drugs and toxins (e.g., L-asparaginase, oral contraceptives)  Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation)  Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome  Inborn errors of metabolism (e.g., homocystinuria) |
| Blood vessel | | Infection/thrombophlebitis  Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome  Sepsis  Trauma: skull fractures, closed hear trauma  Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas) |

|  |  |
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| **Table 601-4** | Potential Risk Factors for Hemorrhagic Stroke in Children |
| **MAJOR CATEGORIES** | **EXAMPLES** |
| Vascular disorder | Arteriovenous malformations  Cavernous malformations (“cavernomas”) Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm  Choroid plexus angiomas (pure intraventricular hemorrhage)  Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1)  Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis |
| Blood disorder | Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome  Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of  the newborn)  Disseminated intravascular coagulopathy |
| Trauma | Middle meningeal artery injury (epidural hematoma)  Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage  Hemorrhagic contusions (coup and contrecoup)  Nonaccidental trauma (subdural hematomas of different ages)  Iatrogenic (neurosurgical procedures, angiography)  Rupture of arachnoid cyst |

|  |  |
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| **Table 601-4** | Potential Risk Factors for Hemorrhagic Stroke in Children |
| **MAJOR CATEGORIES** | **EXAMPLES** |
| Vascular disorder | Arteriovenous malformations  Cavernous malformations (“cavernomas”) Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm  Choroid plexus angiomas (pure intraventricular hemorrhage)  Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1)  Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis |
| Blood disorder | Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome  Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of  the newborn)  Disseminated intravascular coagulopathy |
| Trauma | Middle meningeal artery injury (epidural hematoma)  Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage  Hemorrhagic contusions (coup and contrecoup)  Nonaccidental trauma (subdural hematomas of different ages)  Iatrogenic (neurosurgical procedures, angiography)  Rupture of arachnoid cyst |

|  |  |  |
| --- | --- | --- |
| **Table 601-3** | Common Risk Factors for Cerebral Sinovenous Thrombosis in Children | |
| **MAJOR CATEGORIES** | | **EXAMPLES** |
| Blood coagulation | | Prothrombotic conditions  Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium  Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia  Drugs and toxins (e.g., L-asparaginase, oral contraceptives)  Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation)  Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome  Inborn errors of metabolism (e.g., homocystinuria) |
| Blood vessel | | Infection/thrombophlebitis  Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome  Sepsis  Trauma: skull fractures, closed hear trauma  Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas) |

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| **Table 601-3** | Common Risk Factors for Cerebral Sinovenous Thrombosis in Children | |
| **MAJOR CATEGORIES** | | **EXAMPLES** |
| Blood coagulation | | Prothrombotic conditions  Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium  Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia  Drugs and toxins (e.g., L-asparaginase, oral contraceptives)  Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation)  Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome  Inborn errors of metabolism (e.g., homocystinuria) |
| Blood vessel | | Infection/thrombophlebitis  Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome  Sepsis  Trauma: skull fractures, closed hear trauma  Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas) |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 601-5** | Differential Diagnosis of Stroke-Like Episodes in Children | | |
| **DISORDER** | | **CLINICAL DISTINCTION FROM STROKE** | **IMAGING DISTINCTION FROM STROKE** |
| Migraine | | Evolving or “marching” symptoms, short duration, complete resolution, headache, personal or family history of migraine | Typically normal Migrainous infarction is rare |
| Seizure | | Positive symptoms, Todd paralysis is postseizure and limited | Normal or may identify source of seizures (e.g., malformation, old injury, etc.) |
| Infection | | Fever, encephalopathy, gradual onset, meningismus | Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis |
| Demyelination | | Gradual onset, multifocal symptoms, encephalopathy  Accompanying optic neuritis or transverse myelitis | Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion |
| Hypoglycemia | | Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms | Bilateral, symmetrical  May see restricted diffusion Posterior dominant pattern |
| Watershed infarction caused by global hypoxic–ischemic encephalopathy | | Risk factor (e.g., hypotension, sepsis, heart disease), bilateral deficits | Bilateral, symmetric restricted diffusion in border zones between major arteries (watershed zones) |
| Hypertensive encephalopathy (posterior reversible leukoencephalopathy) | | Documented hypertension, bilateral visual symptoms, encephalopathy | Posterior dominant, bilateral, patchy lesions involving gray and white matter, usually no restricted diffusion |
| Inborn errors of metabolism | | Preexisting delays/regression, multisystem disease, abnormal biochemical profiles | May have restricted diffusion lesions but bilateral, symmetrical, not within vascular territories. MR spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) |
| Vestibulopathy | | Symptoms limited to vertigo, imbalance (i.e., no weakness). Gradual onset | Normal |
| Acute cerebellar ataxia | | Sudden-onset bilaterally symmetric ataxia; postviral | Normal |
| Channelopathy | | Syndromic cluster of symptoms not localizing to single lesion. Gradual onset, progressive evolution | Normal |
| Alternating hemiplegia | | History contralateral events Choreoathetosis/dystonia | Normal |

**2934 Part XXVII** ◆ The Nervous System

Primary CNS

Vasculitis

Secondary CNS

Vasculitis

Antibody-mediated

encephalitis

Angiography

positive

Angiography

negative Brain biopsy positive

See Table 602-1

Intracellular Receptor/Cell

antigen surface antigen

Progressive

Non-progressive

**Inflammatory brain disease**

###### **Figure 602-1** CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

|  |  |
| --- | --- |
| **Table 602-1** | Causes of Secondary CNS Vasculitis |
| VIRAL INFECTIONS  Varicella zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19 | |
| BACTERIAL INFECTIONS  *Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia* spp. | |
| FUNGAL INFECTIONS  Aspergillosis, mucormycosis, coccidioidomycosis, candidosis | |
| PARASITIC INFECTIONS  Cysticercosis | |
| SYSTEMIC VASCULITIDES  Wegener granulomatosis, Churg-Strauss syndrome, Behçet disease, polyarteritis nodosa, Henoch-Schönlein purpura, Kawasaki disease, giant-cell arteritis, Takayasu arteritis | |
| CONNECTIVE TISSUE DISEASES  Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease | |
| MISCELLANEOUS  Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease,  graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine) | |

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   * Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   * Seizures or (refractory) seizure status
   * Diffuse neurologic deficit including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   * Headaches
   * Meningitis symptoms, abnormal level of consciousness
   * Psychiatric symptoms including hallucinations, pseudoseizures

*Differential diagnosis approach:*

* + Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features

1. Laboratory tests
   * Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   * Endothelial markers: von Willebrand factor (vWF) antigen
   * Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

*Differential diagnosis approach:*

* + Infections/postinfectious inflammation: cultures, serologies, Gram stains
  + Autoimmune encephalitis: check neuronal antibodies in CSF and blood
  + Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
  + Thromboembolic conditions: procoagulatory profile

1. Neuroimaging
   * Parenchymal imaging on MRI:
     + Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
     + Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   * Vessel imaging
2. Brain biopsy

Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

**Table 602-2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 602-3** | Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome | | |
|  | | **PCNSV** | **RCVS** |
| Precipitating factor | | None | Postpartum onset or onset after exposure to vasoactive substances |
| Onset | | More insidious, progressive course | Acute onset followed by a monophasic course |
| Headaches | | Chronic and progressive | Acute, thunderclap type |
| CSF findings | | Abnormal (leucocytosis and high total protein concentration) | Normal to near normal |
| MRI | | Abnormal in almost all patients | Normal in 70% of patients |
| Angiography | | Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible | Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk |
| Cerebral biopsy | | Vasculitis | No vasculitic changes |
| Drug treatment | | Prednisone with or without cytotoxic agents | Nimodipine |

CSF, cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.

*From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis.* Lancet *380:767–776, 2012, Table 2.*

**Chapter 603** ◆ Central Nervous System Infections **2937**

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| **Table 603-1** Cerebrospinal Fluid Findings in Central Nervous System Disorders | | | | | |
| **CONDITION** | **PRESSURE (mm H2O)** | **LEUKOCYTES (mm3)** | **PROTEIN**  **(mg/dL)** | **GLUCOSE**  **(mg/dL)** | **COMMENTS** |
| Normal | 50-80 | <5, ≥75% Lymphocytes | 20-45 | >50 (or 75%  serum glucose) |  |
| COMMON FORMS OF MENINGITIS  Acute bacterial Usually elevated  meningitis (100-300)  Partially treated Normal or bacterial meningitis elevated  Viral meningitis or Normal or slightly meningoencephalitis elevated  (80-150) | | 100-10,000 or more; usually 300-2,000; PMNs  predominate  5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time  Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course | Usually 100-500  Usually 100-500  Usually 50-200 | Decreased, usually <40 (or  <50% serum glucose)  Normal or decreased  Generally normal; may be decreased to  <40 in some viral diseases, particularly mumps (15-20% of cases) | Organisms usually seen on Gram stain and recovered by culture  Organisms may be seen on Gram stain  Pretreatment may render CSF sterile. Antigen may be detected by agglutination test  HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF |
| UNCOMMON FORMS OF MENINGITIS  Tuberculous Usually elevated meningitis  Fungal meningitis Usually elevated  Syphilis (acute) and Usually elevated leptospirosis  Amebic (*Naegleria*) Elevated meningoencephalitis | | 10-500; PMNs early, but lymphocytes predominate through most of the course  5-500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response  50-500; lymphocytes predominate  1,000-10,000 or more; PMNs predominate | 100-3,000; may  be higher in presence of block  25-500  50-200  50-500 | <50 in most cases; decreases with time if treatment is not provided  <50; decreases with time if treatment is not provided  Usually normal  Normal or slightly decreased | Acid-fast organisms almost never seen on smear.  Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF  Budding yeast may be seen. Organisms may be recovered in culture.  Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection  Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive  Mobile amebas may be seen by hanging-drop examination of CSF at room temperature |
| BRAIN ABSCESSES AND PARAMENINGEAL FOCUS | | |  | Normal unless abscess ruptures into ventricular system  Normal  Normal Normal  Normal or slightly decreased |  |
| Brain abscess | Usually elevated | 5-200; CSF rarely acellular; | 75-500 | No organisms on smear or |
|  | (100-300) | lymphocytes predominate; |  | culture unless abscess |
| if abscess ruptures into | | |  | ruptures into ventricular |
| ventricle, PMNs | | |  | system |
| predominate and cell | | |  |  |
| count may reach >100,000 | | |  |  |
| Subdural empyema | Usually elevated  (100-300) | 100-5,000; PMNs  predominate | 100-500 | No organisms on smear or  culture of CSF unless |
|  | | |  | meningitis also present; |
|  | | |  | organisms found on tap of |
|  | | |  | subdural fluid |
| Cerebral epidural | Normal to slightly | 10-500; lymphocytes | 50-200 | No organisms on smear or |
| abscess | elevated | predominate |  | culture of CSF |
| Spinal epidural | Usually low, with | 10-100; lymphocytes | 50-400 | No organisms on smear or |
| abscess | spinal block | predominate |  | culture of CSF |
| Chemical (drugs, | Usually elevated | 100-1,000 or more; PMNs | 50-100 | Epithelial cells may be seen |
| dermoid cysts, |  | predominate |  | within CSF by use of |
| myelography dye) | | |  | polarized light in some  children with dermoids |

Continued

**2938 Part XXVII** ◆ The Nervous System

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| **Table 603-1** | Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont’d | | | | |
| **PRESSURE**  **CONDITION (mm H2O)** | | **LEUKOCYTES (mm3)** | **PROTEIN**  **(mg/dL)** | **GLUCOSE**  **(mg/dL)** | **COMMENTS** |
| NONINFECTIOUS CAUSES  Sarcoidosis Normal or elevated slightly  Systemic lupus Slightly elevated erythematosus with  CNS involvement  Tumor, leukemia Slightly elevated  to very high  Acute disseminated Normal or encephalomyelitis elevated  Autoimmune Normal encephalitis | | 0-100; mononuclear  0-500; PMNs usually predominate; lymphocytes may be present  0-100 or more; mononuclear or blast cells  ~100 lymphocytes  ~100 lymphocytes | 40-100  100  50-1,000  Normal to elevated Normal to elevated | Normal  Normal or slightly decreased  Normal to decreased (20-40)  Normal Normal | No specific findings  No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF  Cytology may be positive  MRI adds to diagnosis  Anti-NMDAR antibody– positive |

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

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| **Table 603-4** | Antibiotics Used for the Treatment of Bacterial Meningitis\* | | | |
| **DRUGS** | **0-7 DAYS** | **Neonates** | **8-28 DAYS** | **INFANTS AND CHILDREN** |
| Amikacin†‡ | 15-20 divided q12h |  | 30 divided q8h | 20-30 divided q8h |
| Ampicillin | 150 divided q8h |  | 200 divided q6h or q8h | 300 divided q6h |
| Cefotaxime | 100-150 divided q8h or q12h |  | 150-200 divided q6h or q8h | 225-300 divided q6h or q8h |
| Ceftriaxone§ | — |  | — | 100 divided q12h or q24h |
| Ceftazidime | 100-150 divided q8h or q12h |  | 150 divided q8h | 150 divided q8h |
| Gentamicin†‡ | 5 divided q12h |  | 7.5 divided q8h | 7.5 divided q8h |
| Meropenem | — |  | — | 120 divided q8h |
| Nafcillin | 75 divided q8h or q12h |  | 100-150 divided q6h or q8h | 200 divided q6h |
| Penicillin G | 150,000 divided q8h or q12h |  | 200,000 divided q6h or q8h | 300,000 divided q4h or q6h |
| Rifampin | — |  | 10-20 divided q12h | 10-20 divided q12h or q24h |
| Tobramycin†‡ | 5 divided q12h |  | 7.5 divided q8h | 7.5 divided q8h |
| Vancomycin†‡ | 20-30 divided q8h or q12h |  | 30-45 divided q6h or q8h | 60 divided q6h |

\*Dosages in mg/kg (units/kg for penicillin G) per day.

†Smaller doses and longer dosing intervals, especially for aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.

‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.

§Use in neonates is not recommended because of inadequate experience in neonatal meningitis.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al: Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 39(9):1267–1284, 2004,

|  |  |  |
| --- | --- | --- |
| **Table 606-1** | Clinical and Radiologic Mimics of Transverse Myelitis | |
| EXTRAAXIAL COMPRESSION DISEASE   1. Vertebral spine disorders    1. Trauma       1. Blunt       2. Penetrating       3. Surfing    2. Atlantoaxial subluxation       1. Trisomy 21       2. Mucopolysaccharidosis type IV       3. Grisel syndrome    3. Destructive lesions       1. Tuberculosis       2. Lymphoma       3. Langerhans cell histiocytosis    4. Scheuermann disease 2. Epidural disease    1. Tumor       1. Neuroblastoma       2. Wilms tumor       3. Ewing sarcoma    2. Abscess       1. Associated dermal sinus, vertebral body infection    3. Hematoma 3. Arachnoiditis    1. Tuberculosis    2. Cryptococcosis    3. Carcinomatous infiltration 4. Spinal nerve root inflammation    1. Guillain-Barré syndrome | | SPINAL CORD DISORDERS   1. Congenital malformation    1. Neurenteric cysts    2. Spinal cord tethering 2. Infection    1. Nonpolio enteroviruses    2. West Nile virus    3. Human T-lymphocyte virus 1    4. Neurocysticercosis 3. Vascular disorders    1. Arteriovenous malformation    2. Cavernomas    3. Cobb syndrome    4. Fibrocartilaginous embolization    5. Spinal cord infarction 4. Vasculitis    1. Systemic lupus erythematosus    2. Behçet disease 5. Nutritional disorders    1. Vitamin B12 deficiency (Subacute combined degeneration) 6. Toxic injury    1. Chemotherapy (e.g., methotrexate)    2. Radiation 7. Immune mediated    1. Acute disseminated encephalomyelitis    2. Neuromyelitis optica    3. Multiple sclerosis |

*Modified from Thomas T, Branson HM: Childhood transverse myelitis and its mimics.* Neuroimaging Clin N Am *23:267–278, 2013, Box 11.*

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| **Table 603-2** Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis | |
| VIRUSES  Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus) Arboviruses: Eastern equine, Western equine, Venezuelan equine,  St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever  Parechovirus  Herpes simplex (types 1, 2) Human herpesvirus type 6 Varicella-zoster virus Epstein-Barr virus Parvovirus B19 Cytomegalovirus Adenovirus  Variola (smallpox) Measles  Mumps Rubella  Influenza A and B Parainfluenza Rhinovirus  Rabies  Lymphocytic choriomeningitis Rotaviruses  Coronaviruses  Human immunodeficiency virus type 1 | PARASITES (NONEOSINOPHILIC)  *Toxoplasma gondii* (toxoplasmosis)  *Acanthamoeba* spp. *Naegleria fowleri* Malaria |
| POSTINFECTIOUS  Vaccines: rabies, influenza, measles, poliovirus Demyelinating or allergic encephalitis |
| SYSTEMIC OR IMMUNOLOGICALLY MEDIATED  *Acute Disseminated Encephalomyelitis (ADEM) Autoimmune Encephalitis*  Bacterial endocarditis Kawasaki disease  Systemic lupus erythematosus Vasculitis, including polyarteritis nodosa Sjögren syndrome  Mixed connective tissue disease Rheumatoid arthritis  Behçet syndrome Wegener granulomatosis  Lymphomatoid granulomatosis Granulomatous arteritis Sarcoidosis  Familial Mediterranean fever Vogt-Koyanagi-Harada syndrome |
| BACTERIA  *Mycobacterium tuberculosis* (early and late) *Leptospira* species (leptospirosis) *Treponema pallidum* (syphilis)  *Borrelia* species (relapsing fever) *Borrelia burgdorferi* (Lyme disease) *Nocardia* species (nocardiosis) *Brucella* species  *Bartonella* species (cat-scratch disease)  *Rickettsia rickettsii* (Rocky Mountain spotted fever)  *Rickettsia prowazekii* (typhus)  *Ehrlichia canis Coxiella burnetii*  *Mycoplasma pneumoniae Mycoplasma hominis Chlamydia trachomatis Chlamydia psittaci Chlamydia pneumoniae*  Partially treated bacterial meningitis |
| MALIGNANCY  Leukemia Lymphoma  Metastatic carcinoma  Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma) |
| DRUGS  Intrathecal infections (contrast media, serum, antibiotics, antineoplastic agents)  Nonsteroidal antiinflammatory agents OKT3 monoclonal antibodies Carbamazepine  Azathioprine  Intravenous immune globulins  Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid) |
| MISCELLANEOUS  Heavy metal poisoning (lead, arsenic) Foreign bodies (shunt, reservoir) Subarachnoid hemorrhage  Postictal state Postmigraine state  Mollaret syndrome (recurrent) Intraventricular hemorrhage (neonate) Familial hemophagocytic syndrome Postneurosurgery Dermoid–epidermoid cyst  Headache, neurologic deficits  CSF lymphocytosis (syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis [HaNDL]) |
| BACTERIAL PARAMENINGEAL FOCUS  Sinusitis Mastoiditis Brain abscess  Subdural-epidural empyema Cranial osteomyelitis |
| FUNGI  *Coccidioides immitis* (coccidioidomycosis) *Blastomyces dermatitidis* (blastomycosis) *Cryptococcus neoformans* (cryptococcosis) *Histoplasma capsulatum* (histoplasmosis) *Candida* species  Other fungi *(Alternaria, Aspergillus, Cephalosporium, Cladosporium, Drechslera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* spp.*, Zygomycetes)* |
| PARASITES (EOSINOPHILIC)  *Angiostrongylus cantonensis Gnathostoma spinigerum Baylisascaris procyonis Strongyloides stercoralis Trichinella spiralis*  *Toxocara canis*  *Taenia solium* (cysticercosis) *Paragonimus westermani Schistosoma* spp.  *Fasciola* spp. |

Compiled from Cherry JD: Aseptic meningitis and viral meningitis. In Feigin RD, Cherry JD, editors: *Textbook of pediatric infectious diseases*, ed 4, Philadelphia, 1998, WB Saunders, p. 450; Davis LE: Aseptic and viral meningitis. In Long SS, Pickering LK, Prober CG, editors: *Principles and practice of pediatric infectious disease*, New York, 1997, Churchill Livingstone, p. 329; and Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis therapy*, ed 2, Philadelphia, 2004, Elsevier, p. 961.

**2944 Part XXVII** ◆ The Nervous System

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| **Table 603-3** | Classification of Encephalitis by Cause and Source | |
| I. INFECTIONS: VIRAL   1. Spread: person to person only    1. Mumps: frequent in an unimmunized population; often mild    2. Measles: may have serious sequelae    3. Enteroviruses: frequent at all ages; more serious in newborns    4. Parechovirus    5. Rubella: uncommon; sequelae rare except in congenital rubella    6. Herpesvirus group       1. Herpes simplex (types 1 and 2, possibly 6): relatively common; sequelae frequent; devastating in newborns       2. Varicella-zoster virus: uncommon; serious sequelae not rare       3. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type       4. Epstein-Barr virus (infectious mononucleosis): not common    7. Pox group       1. Vaccinia and variola: uncommon, but serious CNS damage occurs    8. Parvovirus (erythema infectiosum): not common    9. Influenzas A and B    10. Adenovirus    11. Other: reoviruses, respiratory syncytial, parainfluenza, hepatitis B 2. Arthropod-borne agents 3. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:   Eastern equine California  Western equine Powassan  Venezuelan equine Dengue  St. Louis Colorado tick fever West Nile   1. Spread by warm-blooded mammals    1. Rabies: saliva of many domestic and wild mammalian species    2. Herpesvirus simiae (“B” virus): monkeys’ saliva    3. Lymphocytic choriomeningitis: rodents’ excreta   II. INFECTIONS: NONVIRAL   1. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis 2. *Mycoplasma pneumoniae:* interval of some days between respiratory and CNS symptoms 3. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component 4. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease 5. Cat-scratch disease 6. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis 7. Protozoal: *Plasmodium*, *Trypanosoma*, *Naegleria*, and   *Acanthamoeba* spp.; Toxoplasma gondii   1. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis | | 1. PARAINFECTIOUS: POSTINFECTIOUS, ALLERGIC, AUTOIMMUNE   Patients in whom an infectious agent or 1 of its components plays a contributory role in etiology, but the intact infectious agent is not isolated in vitro from the nervous system; it is postulated that in this group, the influence of cell-mediated antigen–antibody complexes plus complement is especially important in producing the observed tissue damage   * 1. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)   Measles  Rickettsial infections Rubella  Influenzas A and B Mumps  Varicella-zoster  M. *pneumoniae*   * 1. Associated with vaccines Rabies   Measles Vaccinia Yellow fever   * 1. Autoimmune encephalitis   2. Acute disseminated encephalomyelitis (ADEM) Paraneoplastic   Idiopathic   1. HUMAN SLOW-VIRUS DISEASES   Accumulating evidence that viruses frequently acquired earlier in life, not necessarily with detectable acute illness, participate in later chronic neurologic disease (similar events also known to occur in animals)   * 1. Subacute sclerosing panencephalitis; measles; rubella?   2. Creutzfeldt-Jakob disease (spongiform encephalopathy)   3. Progressive multifocal leukoencephalopathy   4. Kuru (Fore tribe in New Guinea only)   5. Human immunodeficiency virus  1. UNKNOWN: COMPLEX GROUP   This group constitutes more than two-thirds of the cases of encephalitis reported to the Centers for Disease Control and Prevention, Atlanta, Georgia; the yearly epidemic curve of these undiagnosed cases suggests that the majority are probably caused by enteroviruses and/or arboviruses.  There is also a miscellaneous group that is based on clinical criteria: Reye syndrome is 1 current example; others include the extinct von Economo encephalitis (epidemic during 1918-1928); myoclonic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease).  An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide. |

CNS, central nervous system.

*Modified from Behrman RE, editor: Nelson textbook of pediatrics, ed 14, Philadelphia, 1992, WB Saunders, p. 667. From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 967.*

Brainstem stroke Brainstem encephalitis

Acute anterior poliomyelitis

* Caused by poliovirus
* Caused by other neurotropic viruses Acute myelopathy
* Space-occupying lesions
* Acute transverse myelitis Peripheral neuropathy
* Guillain-Barré syndrome
* Post–rabies vaccine neuropathy
* Diphtheritic neuropathy
* Heavy metals, biologic toxins, or drug intoxication
* Acute intermittent porphyria
* Vasculitic neuropathy
* Critical illness neuropathy
* Lymphomatous neuropathy

Disorders of neuromuscular transmission

* Myasthenia gravis
* Biologic or industrial toxins
* Tic paralysis Disorders of muscle
* Hypokalemia
* Hypophosphatemia
* Inflammatory myopathy
* Acute rhabdomyolysis
* Trichinosis
* Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

Differential Diagnosis of Acute Flaccid Paralysis

**Table 607-4**

Cerebral hypotonia

* Benign congenital hypotonia
* Chromosome disorders
* Prader-Willi syndrome
* Trisomy
* Chronic nonprogressive encephalopathy
* Cerebral malformation
* Perinatal distress
* Postnatal disorders
* Peroxisomal disorders
* Cerebrohepatorenal syndrome (Zellweger syndrome)
* Neonatal adrenoleukodystrophy
* Other genetic defects
* Familial dysautonomia
* Oculocerebrorenal syndrome (Lowe syndrome)
* Other metabolic defects
* Acid maltase deficiency (see “Metabolic Myopathies”)
* Infantile GM gangliosidosis Spinal cord disorders

Spinal muscular atrophies

* Acute infantile
  + Autosomal dominant
  + Autosomal recessive
* Cytochrome-c oxidase deficiency
* X-linked
* Chronic infantile
  + Autosomal dominant
  + Autosomal recessive
* Congenital cervical spinal muscular atrophy
* Infantile neuronal degeneration
* Neurogenic arthrogryposis Polyneuropathies
* Congenital hypomyelinating neuropathy
* Giant axonal neuropathy
* Hereditary motor-sensory neuropathies Disorders of neuromuscular transmission
* Familial infantile myasthenia
* Infantile botulism
* Transitory myasthenia gravis

Fiber-type disproportion myopathies

* Central core disease
* Congenital fiber-type disproportion myopathy
* Myotubular (centronuclear) myopathy
* Acute
* Chronic
* Nemaline (nemaline rod) myopathy
* Autosomal dominant
* Autosomal recessive Metabolic myopathies
* Acid maltase deficiency (Pompe disease)
* Cytochrome-c oxidase deficiency
* Other mitochondrial disorders
* Muscular dystrophies
* Bethlem myopathy
* Congenital dystrophinopathy
* Congenital muscular dystrophy
* Merosin deficiency primary
* Merosin deficiency secondary
* Merosin positive
* Congenital myotonic dystrophy

Differential Diagnosis of Infantile Hypotonia

**Table 607-3**

**Chapter 605** ◆ Idiopathic Intracranial Hypertension/Pseudotumor Cerebri **2951**

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| --- | --- | --- |
| **Table 605-1** | Etiology of Childhood Pseudotumor Cerebri | |
| HEMATOLOGIC  Wiskott-Aldrich syndrome Iron-deficiency anemia Aplastic anemia  Sickle cell disease Polycythemia?  Bone marrow transplantation and associated treatments?  Prothrombotic states Fanconi anemia | | NUTRITIONAL  Hypovitaminosis A Vitamin A intoxication Hyperalimentation in  malnourished patient Vitamin D–dependent rickets |
| CONNECTIVE TISSUE DISORDERS  Antiphospholipid antibody syndrome  Systemic lupus erythematosus? Behçet disease |
| INFECTIONS  Acute sinusitis  Otitis media (lateral sinus thrombosis)  Mastoiditis Tonsillitis Measles Roseola  Varicella, recurrent varicella- zoster virus infection  Lyme disease?  HIV or associated treatment complications? | |
| ENDOCRINE  Menarche  Polycystic ovarian syndrome Hypothyroidism Hypoparathyroidism/  hyperparathyroidism Congenital adrenal hyperplasia Addison disease  Recombinant growth hormone |
| OTHER  Dural sinus thrombosis Obesity (in pubertal patients) Bariatric surgery  Head trauma  Superior vena cava syndrome Arteriovenous malformation Sleep apnea  Guillain-Barré syndrome Crohn disease Ulcerative colitis?  Turner syndrome |
| DRUGS  Tetracyclines Sulfonamides Nalidixic acid Fluoroquinolones  Corticosteroid therapy and withdrawal  Nitrofurantoin Cytarabine Cyclosporine Phenytoin Mesalamine Isotretinoin Amiodarone?  1-Deamino-8-D-arginine vasopressin (DDAVP)?  Lithium?  Levonorgestrel implants? Oral contraceptive pills | |
| POSSIBLE ASSOCIATIONS  Cystic fibrosis Cystinosis  Down syndrome Hypomagnesemia–hypercalciuria Galactokinase deficiency Galactosemia  Atrial septal defect repair Moebius syndrome Sarcoidosis? |
| RENAL  Nephrotic syndrome Chronic renal insufficiency? Post–renal transplantation? Peritoneal dialysis? | |

**Chapter 607** ◆ Evaluation and Investigation **2961**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 607-1** | Distinguishing Features of Disorders of the Motor System | | | | | | | |
| **LOCUS OF LESION** | **Face** | **WEAKNESS**  **Arms Legs** | | **Proximal– Distal** | **DEEP TENDON REFLEXES** | **ELECTRO- MYOGRAPHY** | **MUSCLE BIOPSY** | **OTHER** |
| Central | 0 | + | + | ≥ | Normal or  ↑ | Normal | Normal | Seizures, hemiparesis, and delayed development |
| Ventral horn cell | Late | ++++ | ++++ | ≥ | 0 | Fasciculations and fibrillations | Denervation pattern | Fasciculations (tongue) |
| Peripheral nerve | 0 | +++ | +++ | < | ↓ | Fibrillations | Denervation pattern | Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve biopsy |
| Neuromuscular junction | +++ | +++ | +++ | = | Normal | Decremental response (myasthenia); incremental response and BSAP (botulism) | Normal | Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism) |
| Muscle | Variable (+ to  ++++) | ++ | + | > | ↓ | Short duration, small-amplitude  motor unit potentials and myopathic polyphasic potentials | Myopathic pattern\* | Elevated muscle enzyme levels (variable) |

\*Can also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.

+ to ++++, varying degrees of severity; BSAP, brief duration, small amplitude, overly abundant motor unit potentials.

*From Volpe J:* Neurology of the newborn*, ed 4, Philadelphia, 2001, WB Saunders, p. 706.*

|  |  |  |  |
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| **Table 607-2** | Pattern of Weakness and Localization in the Floppy Infant | | |
| **ANATOMIC REGION OF HYPOTONIA** | | **CORRESPONDING DISORDERS** | **PATTERN OF WEAKNESS AND INVOLVEMENT** |
| Central nervous system | | Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma | Central hypotonia  Axial hypotonia more prominent Hyperactive reflexes |
| Motor neuron | | Spinal muscular atrophy | Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters |
| Nerve | | Peripheral neuropathies | Distal muscle groups involved Weakness with wasting |
| Neuromuscular junction | | Myasthenia syndromes Infantile botulism | Bulbar, oculomotor muscles exhibit greater degree of involvement |
| Muscle | | Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy | Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 608-4** | Specific Congenital Myopathies: Distinguishing Clinical Features | | | | | |
| **MYOPATHY** | | **NEONATAL HYPOTONIA AND WEAKNESS** | **SEVERE FORM WITH NEONATAL DEATH** | **FACIAL WEAKNESS** | **PTOSIS** | **EXTRAOCULAR MUSCULAR WEAKNESS** |
| Central core disease | | + | 0 | ± | 0 | 0 |
| Nemaline myopathy | | + | + | + | 0 | 0 |
| Myotubular myopathy (centronuclear myopathy) | | + | + | + | + | + |
| Congenital fiber-type disproportion | | + | ± | ± | 0 | + |

+, Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.

*From Volpe JJ:* Neurology of the newborn*, ed 5, Philadelphia, 2008, Elsevier Saunders, p. 820.*

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**Chapter 608** ◆ Developmental Disorders of Muscle **2967**

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| --- | --- | --- | --- | --- | --- | --- |
| **Table 608-2** Clinical Signs of Muscular Dystrophy | | | | | | |
| **DISTRIBUTION MOTOR FUNCTION OF WEAKNESS** | **RIGID SPINE** | **CARDIOMYOPATHY** | **RESPIRATORY IMPAIRMENT** | **DISEASE COURSE** | **INCREASED CK** | **OTHER SIGNS** |
| CONGENITAL-ONSET MUSCULAR DYSTROPHY  Congenital muscular Independent ambulation Upper limbs > dystrophy with merosin generally not achieved lower limbs deficiency in patients with absent  merosin  Congenital muscular Independent ambulation Upper limbs > dystrophy and generally not achieved lower limbs abnormal glycosylation  of dystroglycan (Walker-Warburg syndrome, muscle-eye- brain disease, congenital muscular  dystrophy type 1C, etc.)  Congenital muscular Ambulation achieved Axial muscles >  dystrophy with rigid limbs  spine syndrome type 1 (SEPN1)  Ullrich syndrome Ambulation achieved in Proximal and  ~50% but lost by axial middle teens | –  –  ++  ++ | Not frequent  Not frequent  –  – | ++  +  Early respiratory failure  Early respiratory failure | Slowly progressive  Slowly progressive  Progression of respiratory signs  > motor signs  Progression of respiratory and motor signs | ++  ++  N or +  N or + | White matter changes on brain MRI  Frequent structural brain changes  Scoliosis  Distal laxity |
| FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY  Duchenne muscular Independent ambulation Proximal > distal dystrophy achieved, but lost (pattern A)  before age of 13 yr  Emery-Dreifuss muscular Ambulation achieved in Scapuloperoneal dystrophy with lamin all cases except for (pattern B)  AC deficiency (type 2) rare cases with  congenital onset  Limb-girdle muscular Independent ambulation Proximal > distal dystrophy with lamin achieved, variable (pattern A)  AC deficiency (type 1B) progression  Limb-girdle muscular Ambulation achieved Proximal > distal dystrophy with calpain (pattern A)  deficiency (type 2A) | –  ++  +  + | ++  ++  ++  – | ++  In adulthood in the typical form, but also in childhood (congenital variants)  In adulthood Not frequent | Progression of motor, cardiac, and respiratory signs  Slowly progressive  Progression of cardiac signs > motor signs  Slow progression | ++  + (+)  + (+)  ++ | Mental retardation in 30%  Frequent association with Dunningham-type lipodystrophy  None None |

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| **Table 608-2** Clinical Signs of Muscular Dystrophy—cont’d | | | | | | | |
| **MOTOR FUNCTION** | **DISTRIBUTION OF WEAKNESS** | **RIGID SPINE** | **CARDIOMYOPATHY** | **RESPIRATORY IMPAIRMENT** | **DISEASE COURSE** | **INCREASED CK** | **OTHER SIGNS** |
| CHILDHOOD-ONSET AND ADULTHOOD-ONSET MUSCULAR DYSTROPHY | | |  | Not frequent  ++  +(+)  –  +  –  Uncommon and mild  Not frequent |  |  | None None  Mental retardation reported in some cases  None None  None  Neurosensory hearing loss and retinal degeneration  None |
| Becker muscular Independent ambulation | Proximal > distal | – | ++ | Progressive with | ++ |
| dystrophy achieved, variable | (pattern A) |  |  | substantial |  |
| progression | | |  | variability |  |
| Limb-girdle muscular Independent ambulation | Proximal > distal | – | ++ | Progression of | ++ |
| dystrophy with achieved, generally | (pattern A) |  |  | motor, cardiac, |  |
| sarcoglycan deficiency lost in the 2nd decade | | |  | and respiratory |  |
| (types 2C, 2D, 2E, 2F) | | |  | signs |  |
| Limb-girdle muscular Independent ambulation | Proximal > distal | – | ++ | Progressive | ++ |
| dystrophy with achieved, variable | (pattern A) |  |  |  |  |
| abnormal glycosylation progression | | |  |  |  |
| of dystroglycan (types | | |  |  |  |
| 2I, 2K, 2L, 2M, 2N, 2O) | | |  |  |  |
| Limb-girdle muscular Independent ambulation | Both pattern A | – | – | Progressive in | ++ |
| dystrophy with dysferlin always achieved | and pattern E |  |  | adulthood |  |
| deficiency (type 2B) | | |  |  |  |
| Limb-girdle muscular Independent ambulation | Proximal > distal | – | + | Progressive in | + (+) |
| dystrophy with achieved, generally | (pattern A); in |  |  | adulthood |  |
| telethonin deficiency lost in the 4th decade | some pattern |  |  |  |  |
| (type 2G) | B |  |  |  |  |
| Limb-girdle muscular Independent ambulation | Proximal > distal | – | – | Roughly half lose | ++ |
| dystrophy with titin achieved | (pattern A) but |  |  | ambulation in |  |
| deficiency (type 2J) | also pattern E |  |  | adulthood |  |
| Facioscapulohumeral Independent ambulation | Pattern D | – | – | Slowly progressive | N or + |
| dystrophy achieved, variable | | |  |  |  |
| progression | | |  |  |  |
| Emery-Dreifuss muscular Independent ambulation | Scapuloperoneal | + | ++ | Progression of | + (+) |
| dystrophy with merin achieved, variable | (pattern B) |  |  | cardiac signs > |  |
| deficiency (type 1) progression | | |  | motor signs |  |
| ADULT-ONSET MUSCULAR DYSTROPHY  Limb-girdle muscular Onset in adulthood, 8 : 1 dystrophy with ratio of men to women anoctamin deficiency  (type 2L)  Limb-girdle muscular Independent ambulation dystrophy type 1A achieved  (myotilin)  Limb-girdle muscular Independent ambulation dystrophy with caveolin achieved; rippling deficiency (type 1C) might be seen before  weakness | Mainly lower limbs pattern A, rarely pattern E  Proximal > distal (pattern A)  Proximal and distal | –  –  – | –  –  + | – | Slowly progressive in adulthood | ++ | None |
| –  – | Generally slowly progressive in adulthood  Slowly progressive, variable | +  ++ | Dysarthria in some cases  Cramps, rippling, percussion- induced repetitive contractions |

–, Absent; +, mild; ++, severe; +(+), variable; CK, creatine kinase; N, normal.

*From Mercuri E, Muntoni F: Muscular dystrophies.* Lancet *381:845–858, 2013, Table 2.*

**Chapter 608** ◆ Developmental Disorders of Muscle **2969**

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| **Table 608-3** Cardiac | Involvement in Muscular | Dystrophies | | |
| **ONSET AND FIRST SIGNS** | | **PROGRESSION** | **CARDIAC DEATH** | **SURVEILLANCE** |
| Duchenne muscular dystrophy | Dilated cardiomyopathy with reduced left- ventricular ejection fraction after 10 yr of age | Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients | Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established | Echocardiography every  2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified) |
| Becker muscular dystrophy | Dilated cardiomyopathy, generally after 10 yr of age | Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias | Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported | Echocardiography at least every 5 yr |
| Myotonic dystrophy | Cardiac abnormalities can occur as early as the 2nd decade of life | Conduction deficits occur in about 65% of adult patients | 20-30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death | ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias |
| EMERY-DREIFUSS MUSCULAR DYSTROPHY  X-linked recessive Conduction disturbances Emery-Dreifuss generally in the 2nd muscular dystrophy decade  (type 1) | | Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function | Sudden death is by far the most common cause of death and can be very unpredictable | ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops.  Defibrillator might be needed in some patients  ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality |
| Emery-Dreifuss Conduction disease and muscular dystrophy cardiac failure  2 and limb-girdle muscular dystrophy 1B | | Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) present in 92% of patients older than 30 yr | Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported |
| LIMB-GIRDLE MUSCULAR DYSTROPHY  Sarcoglycanopathies ECG and/or  echocardiographic abnormalities reported in 20-30% of patients (especially β and δ variants; less common in α variant)  Limb-girdle muscular Cardiac involvement dystrophy 2I reported in 29-62% of  limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr  Limb-girdle muscular Dilated, restrictive, dystrophy 1E hypertrophic  cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients | | Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy–like dystrophy  Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)  Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness | Typically by cardiac failure. Cardiac transplants reported  Cardiac failure. Cardiac transplants reported  Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope | No evidence-based standards of care exist, but experts have made recommendations  No evidence-based standards of care exist, but experts have made recommendations  No evidence-based standards of care exist, but experts have made recommendations |

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| **Table 608-3** | Cardiac Involvement in Muscular Dystrophies—cont’d | | | |
| **ONSET AND FIRST SIGNS** | | **PROGRESSION** | **CARDIAC DEATH** | **SURVEILLANCE** |
| CONGENITAL MUSCULAR DYSTROPHY  Congenital muscular Occasional reports of dystrophy merosin reduced left ventricular muscular dystrophy systolic function  type C1A  Fukuyama Systolic left-ventricular  congenital dysfunction may muscular dystrophy develop in the 2nd  decade  Muscular dystrophy Dilated cardiomyopathy type C1C reported in young  children | | Not well characterized  Symptomatic cardiac failure over time  Not well characterized  Not well characterized | Rare by cardiac failure  Death from congestive heart failure might occur by the age of 20 yr  Not reported | No evidence-based standards of care exist, but experts have made recommendations  No evidence-based standards of care exist, but experts have made recommendations  No evidence-based standards of care exist, but experts have made recommendations  No evidence-based standards of care exist, but experts have made recommendations |
| Facioscapulohumeral Uncommon muscular dystrophy | | Not reported |

ECG, electrocardiogram.

*From Mercuri E, Muntoni F: Muscular dystrophies.* Lancet *381:845–858, 2013, Table 3.*

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| **Table 609-1** | Channelopathies and Related Disorders | | | | |
| **DISORDER** | | **PATTERN OF CLINICAL FEATURES** | **INHERITANCE** | **CHROMOSOME** | **GENE** |
| CHLORIDE CHANNELOPATHIES  *Myotonia Congenita* Thomsen disease Becker disease | | Myotonia  Myotonia and weakness | Autosomal dominant Autosomal recessive | 7q35  7q35 | *CLC1 CLC1* |
| SODIUM CHANNELOPATHIES  Paramyotonia congenita Hyperkalemic periodic paralysis  Hypokalemic periodic paralysis | | Paramyotonia Periodic paralysis with  myotonia and paramyotonia Periodic paralysis | Autosomal dominant Autosomal dominant  Autosomal dominant | 17q13.1-13.3  17q13.1-13.3  17q13.1-13.3 | *SCNA4A CNA4A*  *SCNA4A* |
| POTASSIUM-AGGRAVATED MYOTONIAS  Myotonia fluctuans Myotonia  Myotonia permanens Myotonia Acetazolamide-responsive myotonia Myotonia | | | Autosomal dominant Autosomal dominant Autosomal dominant | 17q13.1-13.3  17q13.1-13.3  17q13.1-13.3 | *SCNA4A SCNA4A SCNA4A* |
| CALCIUM CHANNELOPATHIES  Hypokalemic periodic paralysis  Schwartz-Jampel syndrome (chondrodystrophic myotonia)  Rippling muscle disease Anderson syndrome  Brody disease Malignant hyperthermia | | Periodic paralysis Myotonia; dysmorphic  Muscle mounding, stiffness Periodic paralysis, cardiac  arrhythmia, distinctive facies Delayed relaxation, no  electromyogram myotonia Anesthetic-induced delayed  relaxation | Autosomal dominant Autosomal recessive  Autosomal dominant Autosomal dominant  Autosomal recessive Autosomal dominant | 1q31-32  1q34.1-36.1  1q41  17q23  16p12  19q13.1 | Dihydropyridine receptor  *Perlecan*  *Caveolin-3 KCNJ2-Kir2.1*  Calcium adenosine triphosphatase Ryanodine receptor |

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| **Table 609-2** | Autosomal Recessive Limb-Girdle Muscular Dystrophies | | |
| **TYPE** | **LOCATION** | **GENE PRODUCT** | **CLINICAL FEATURES** |
| LGMD2A | 15q | Calpain 3 | Onset at 8-15 yr, progression variable |
| LGMD2B | 2p13-16 | Dysferlin | Onset at adolescence, mild weakness; gene site is the same as for Miyoshi myopathy |
| LGMD2C | 13q12 | Sarcoglycan | Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD1) |
| LGMD2D | 17q12 | α-Sarcoglycan (adhalin) | Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD2) |
| LGMD2E | 4q12 | β-Sarcoglycan | Phenotype between Duchenne and Becker muscular dystrophies |
| LGMD2F | 5q33-34 | Sarcoglycan | Slowly progressive, growth retardation |

LGMD, limb-girdle muscular dystrophy.

*From Fenichel GM:* Clinical pediatric neurology: a signs and symptoms approach*, ed 5, Philadelphia, 2005, Elsevier Saunders, p. 176, Table 7-5.*

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| **Table 610-1** | Toxic Myopathies | |
| INFLAMMATORY  Cimetidine  D-Penicillamine Procainamide  L-Tryptophan L-DOPA | | MALIGNANT HYPERTHERMIA  Halothane Ethylene Diethyl ether Methoxyflurane Ethyl chloride  Trichloroethylene Gallamine Succinylcholine |
| NONINFLAMMATORY NECROTIZING OR VACUOLAR  Cholesterol-lowering agents Chloroquine  Colchicine Emetine  ε-Aminocaproic acid Labetalol  Cyclosporine and tacrolimus Isoretinoic acid (vitamin A  analog) Vincristine Alcohol | |
| MITOCHONDRIAL  Zidovudine |
| MYOTONIA  2,4-*d*-Chlorophenoxyacetic acid Anthracene-9-carboxycyclic acid Cholesterol-lowering drugs Chloroquine  Cyclosporine |
| MYOSIN LOSS  Nondepolarizing neuromuscular blocking agents  Intravenous glucocorticoids |
| RHABDOMYOLYSIS AND MYOGLOBINURIA  Cholesterol-lowering drugs (especially statins)  Alcohol Heroin Amphetamine Toluene Cocaine  ε-Aminocaproic acid Pentazocine Phencyclidine | |

**Chapter 611** ◆ Metabolic Myopathies **2987**

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| **Table 611-2** | Secondary Causes of Periodic Paralysis |
| HYPOKALEMIC  Thyrotoxic  Primary hyperaldosteronism (Conn syndrome) Renal tubular acidosis (e.g., Fanconi syndrome)  Juxtaglomerular apparatus hyperplasia (Bartter syndrome) Gastrointestinal potassium wastage  Villous adenoma Laxative abuse  Pancreatic non–insulin-secreting tumors with diarrhea Nontropical sprue  Barium intoxication Potassium-depleting diuretics Amphotericin B  Licorice Corticosteroids Toluene toxicity  *p*-Aminosalicylic acid Carbenoxolone | |
| HYPERKALEMIC  Addison disease Hypoaldosteronism  Excessive potassium supplementation Potassium-sparing diuretics  Chronic renal failure | |

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| **Table 611-1** | Metabolic and Mitochondrial Myopathies |
| GLYCOGEN METABOLISM DEFICIENCIES  Type II: α-1,4-Glucosidase (acid maltase) Type III: Debranching  Type IV: Branching  Type V: Phosphorylase (McArdle disease)\* Type VII: Phosphofructokinase (Tarui disease)\* Type VIII: Phosphorylase B kinase\*  Type IX: Phosphoglycerate kinase\* Type X: Phosphoglycerate mutase\* Type XI: Lactate dehydrogenase\* | |
| LIPID METABOLISM DEFICIENCIES  Carnitine palmitoyltransferase\*  Primary systemic/muscle carnitine deficiency Secondary carnitine deficiency  β-Oxidation defects Medications (valproic acid) | |
| PURINE METABOLISM DEFICIENCIES  Myoadenylate deaminase deficiency | |
| MITOCHONDRIAL MYOPATHIES  Alpers-Huttenlocher syndrome  Chronic progressive external ophthalmoplegia Kearns-Sayre syndrome  Pearson syndrome  Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)  Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) Myoclonic epilepsy with ragged red fibers (MERRF)  Leber hereditary optic neuropathy Leigh syndrome  Infantile myopathy and lactic acidosis | |

\*Deficiency can produce exercise intolerance and myoglobinuria.

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| **Table 612-1** | Classification of the Congenital Myasthenic Syndromes |
| PRESYNAPTIC DEFECTS   * Paucity of synaptic vesicles and decreased quantal release * Congenital myasthenic syndromes with episodic apnea (choline acetyltransferase deficiency) * Lambert-Eaton syndrome–like form | |
| SYNAPTIC DEFECTS   * End plate acetylcholinesterase deficiency | |
| POSTSYNAPTIC DEFECTS   * Primary acetylcholine receptor deficiency * Reduced receptor expression as a result of acetylcholine receptor mutations * Reduced receptor expression because of rapsyn mutations * Reduced receptor expression with plectin deficiency * Primary acetylcholine receptor kinetic abnormality with or without acetylcholine receptor deficiency * Slow-channel syndrome * Fast-channel syndrome * Sodium-channel mutations * *Dok7* mutations | |

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| **Table 612-2** Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes | | | | | | |
|  | **Presynaptic**  **CHOLINE ACETYLTRANSFERASE LEMS-LIKE**  **DEFICIENCY FORM** | **Synaptic**  **AChE DEFICIENCY** | **Postsynaptic** | | | |
| **PRIMARY AChR DEFICIENCY** | **SLOW- CHANNEL CMS** | **FAST- CHANNEL CMS** | ***DOK7***  **MUTATIONS** |
| Autosomal dominant inheritance |  |  |  | X (most mutations) |  |  |
| Episodic apnea triggered by stressors | X |  |  |  |  |  |
| Neonatal hypotonia and respiratory insufficiency | X X | X (in severe cases) | X (in severe cases) |  |  |  |
| Skeletal deformities |  | X | X |  | X (in  severe cases) |  |
| Delayed pupillary light responses |  | X |  |  |  |  |
| Prominent neck, wrist, and finger extensor weakness |  |  |  | X |  |  |
| Repetitive CMAPs after single stimulus |  | X |  | X |  |  |
| Progressive decrement with prolonged exercise or repetitive stimulation | X |  | X |  |  |  |
| Marked increment (>200%) with high-frequency repetitive stimulation | X |  |  |  |  |  |
| Decrement repairs with AChE inhibitors |  |  | X |  | X |  |
| Clinical improvement with AChE inhibitors |  |  |  |  | X |  |
| Clinical worsening with AChE inhibitors |  | X |  | X |  | X |

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

*From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman’s pediatric neurology*, ed 5, Philadelphia, 2012, Elsevier, Table 91-3.*

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| **Table 612-4** | Potential Therapies in Congenital Myasthenic Syndromes | |
| AChE | | Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries  If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors |
| AChR deficiency | | AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses  If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults |
| AChR fast channel | | AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses  If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults |
| AChR slow channel | | Quinidine sulfate   * Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 μg/mL * Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults   Avoid AChE inhibitors |
| ChAT | | AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses  If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults |
| Dok7 | | Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries  If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors |
| Laminin β2 | | Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries Avoid AChE inhibitors |
| MuSK | | AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults |
| Rapsyn | | AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses  If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults |

*Modified from Eyemard B, Hantaï D, Estounet B: Congenital myasthenic syndromes,* Handb Clin Neurol *113:1469-1480, 2013.*

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| **Table 612-3** | Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) | | | | |
| **GRADE** | | **0** | **1** | **2** | **3** |
| Talking | | Normal | Intermittent slurring or nasal speech | Constant slurring or nasal, but can be understood | Difficult to understand speech |
| Chewing | | Normal | Fatigue with solid food | Fatigue with soft food | Gastric tube |
| Swallowing | | Normal | Rare episode of choking | Frequent choking, necessitating changes in diet | Gastric tube |
| Breathing | | Normal | Shortness of breath with exertion | Shortness of breath at rest | Ventilator dependence |
| Impairment of ability to brush teeth or comb hair | | None | Extra effort, but no rest periods needed | Rest periods needed | Cannot do 1 of these functions |
| Impairment of ability to arise from a chair | | None | Mild, sometimes uses arms | Moderate, always uses arms | Severe, requires assistance |
| Double vision | | None | Occurs, but not daily | Daily, but not constant | Constant |
| Eyelid droop | | None | Occurs, but not daily | Daily, but not constant | Constant |
| TOTAL MG-ADL SCORE | | | | | |

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| *Table 612-5 Spin* | *al Muscular Atrophy Variants: Progressive or Severe Neonatal Anterior Horn Cell Disease Not Linked to*  *SMN* | |
| **VARIANT** | | **MAJOR FEATURES** |
| SMA with respiratory distress type 1 (SMARD1) | | Mild hypotonia, weak cry, distal contractures initially  Respiratory distress from diaphragmatic paralysis 1-6 mo, progressive distal weakness Autosomal recessive, locus 11q13.2, gene: immunoglobulin mu-binding protein 2 (IGHMBP2) |
| Pontocerebellar hypoplasia type 1 | | Arthrogryposis, hypotonia, weakness, bulbar deficits early; later, microcephaly, extraocular defects, cognitive deficits: pontocerebellar hypoplasia  Molecular defect unknown Likely autosomal recessive |
| X-linked infantile SMA with bone fractures | | Arthrogryposis, hypotonia, weakness, congenital bone fractures, respiratory failure Lethal course as in severe type 1 SMA  Most cases X-linked (X9/11.3-q11.2), a few cases likely autosomal recessive |
| Congenital SMA with predominant lower limb involvement | | Arthrogryposis, hypotonia, weakness, especially distal lower limbs early Nonprogressive but severe disability  Autosomal dominant or sporadic; locus 12q23-24 |

SMA, spinal muscular atrophy; *SMN,* survivor motor neuron gene.

**Chapter 613** ◆ Hereditary Motor-Sensory Neuropathies **2999**

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| **Table 613-1** Hereditary | Peripheral Neuropathies | | |
| **DISORDER (OMIM NO.)** | **CLINICAL FEATURES** | **NERVE CONDUCTION STUDIES** | **GENE OR LOCUS** |
| CMT1 (DEMYELINATING) |  |  |  |
| CMT1 A-F (HMSN type I) | Autosomal dominant. Onset 1st-4th decade. | Delayed motor and sensory |  |
|  | Predominant distal weakness, decreased | conduction studies. Motor |  |
|  | DTRs, mild distal sensory loss, hypertrophy of | studies typically <38 m/s |  |
|  | nerves common |  |  |
| 1A (118220) | Commonest form recognized, seen in all ages (but more adults) |  | *PMP22* duplication or point |
|  |  |  | mutation |
| 1B (118200) | Approximately 5% of CMT1 group |  | *MPZ* |
| 1C (601098) | Childhood onset, starts with abnormal gait, |  | *LITAF* |
|  | then distal weakness and wasting, occasional |  |  |
|  | nerve hypertrophy. Rarely, early-onset hearing |  |  |
|  | loss |  |  |
| 1D (607678) | Possible cranial nerve involvement. Late onset |  | *EGR2* |
|  | in childhood or early adulthood |  |  |
| 1E (118300) | Associated with deafness (29-45%) |  | *PMP22* |
| 1F (607734) |  |  | *NEFL* |
| Hereditary neuropathy with | Autosomal dominant. Recurrent | Significant slowing of motor and | *PMP 22* deletion |
| liability to pressure palsies | mononeuropathy simplex or multiplex | sensory conduction velocities in |  |
| (tomaculous neuropathy) | frequently related to trauma | clinically affected nerves but |  |
| (162500) |  | also in unaffected nerves |  |
| Slowed NCVs Asymptomatic | Often a miscellaneous group. Incidentally detected with no clinical symptoms.  Autosomal dominant | Moderately slowed conduction velocities | *ARHGEF10* |
| CMT2 (AXONAL) |  |  |  |
| CMT2 A-L (HMSN type II) | Autosomal dominant (A, B, D, E, F, G, I) | Nerve conduction velocities |  |
|  | Autosomal recessive (BI, B2, H, K) | greater than HMSN type I |  |
|  | Clinically similar to CMT type 1, except for later | (>38 m/s) but below normal |  |
|  | onset, absence of peripheral nerve | range occasionally |  |
|  | enlargement, and less marked weakness |  |  |
| 2A1 (118210) | CMT2A: prominent distal weakness, proximal |  | 2A1: *KIF1B* (one |
| 2A2 (609260) | weakness also present in 60%. Optic atrophy |  | family) |
|  | and central involvement reported. Main form |  | 2A2: *MFN2* |
|  | related to *MFN2* mutations |  |  |
| 2B (600882) | CMT2B: severe sensory loss: often |  | 2B: *RAB7* |
| 2B1 (605588) | complications with infections, arthropathy, |  | 2B1: *LMNA* |
|  | amputations, foot ulcers, distal weakness |  |  |
| 2B2 (605589) | Average onset 34 yr (Costa Rican family) |  | *?MED25* |
| 2C (606071) | Vocal cord, diaphragm, and respiratory |  | *TRP4* |
|  | involvement, decreased longevity. Allelic with |  | 12q23–q24 |
|  | congenital dSMA (600175) and |  | *TRP4* |
|  | scapuloperoneal muscular atrophy (181405) |  |  |
| 2D (601472) (allelic to | Upper limb predominance |  | *GARS* |
| dSMA) |  |  |  |
| 2E (607684) (1F dominant is allelic to CMT2E) | 30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement | Intermediate/slow nerve conduction studies | *NEFL* |

Continued

**3000 Part XXVIII** ◆ Neuromuscular Disorders

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| **Table 613-1** Hereditary | Peripheral Neuropathies—cont’d | | |
| **DISORDER (OMIM NO.)** | **CLINICAL FEATURES** | **NERVE CONDUCTION STUDIES** | **GENE OR LOCUS** |
| 2F (606595) | Trophic changes feet and knees |  | *HSPB1* (*HSP27*) |
| 2G (608591) | Onset age 9-76 yr, average age 20 yr, large |  | 12q12–q13 |
|  | Spanish family. Also severe form with early |  |  |
|  | onset |  |  |
| 2H (607731) | Pyramidal involvement, vocal cord involvement | Intermediate/slow nerve | *GDAP1* |
| 2H (allelic to CMT4A– |  | conduction studies |  |
| CMT4C2 in original |  |  |  |
| publication) |  |  |  |
| 2I (607677) | CMT I and J: possible late onset, pupillary |  | *MPZ* |
|  | anomalies, pain, hearing loss, dysphagia |  |  |
| 2J (607736) | Vocal cord paralysis, more severe early-onset |  | *MPZ* |
|  | form |  |  |
| 2K (607831) | Occasional proximal leg weakness (like dHMN |  | *GDAP1* |
|  | II), large Chinese family, with onset at age |  |  |
| 2L (608673) | 15-33 yr. Scoliosis |  | *HSPB8* |
|  |  |  | 12q24 |
| HMSN II with onset in early | Autosomal dominant or recessive. Weakness | Axonal pattern with axonal- | *MFN2*; *GDAP1* |
| childhood (EOHMSN) | within 1st 5 yr, rapid progression of weakness, | degenerative polyneuropathy. | Heterogeneous |
| Severe early-onset axonal | usually complete paralysis below elbows and | Absent SNAPs, no response to |  |
| neuropathy (SEOAN) | knees by teens, absent DTRs, moderate | stimulation in cerebral palsy |  |
|  | sensory changes in most cases. Normal CSF | nerve, upper limb nerves normal |  |
|  | protein. Occasional optic atrophy or spasticity | or mildly slowed. EMG: |  |
|  |  | denervation |  |
| Spinal muscular atrophy with | Autosomal recessive. Onset in infancy (3-6 mo), | Absent conduction in most cases | *IGHMBP2* |
| respiratory distress type 1 | respiratory failure, progressive distal |  |  |
| (SMARD1)/severe infantile | weakness, eventual plateau. No recovery |  |  |
| axonal neuropathy with |  |  |  |
| respiratory failure (SIANR) |  |  |  |
| Allelic to dHMN6 dSMA1 |  |  |  |
| (604320) |  |  |  |
| Hereditary motor and | Adult onset (after 30 yr). Autosomal dominant. | Motor and sensory axonal | 3q13 |
| sensory neuropathy | Slowly progressive proximal dominant area of | neuropathy. SNAPs, CMAPs, |  |
| (HMSN-P) (Okinawa type) | weakness. Fasciculations of extremities and | MNCVs, and SNCVs reduced or |  |
|  | trunk. Raised creatine kinase, hyperlipidemia, | absent |  |
|  | diabetes mellitus, eventual loss of ambulation, | EMG: fasciculations, fibrillations, |  |
|  | absent DTRs, sensory disturbances. Most | and neuromyotonic picture early |  |
|  | patients described from Japan | on |  |
| CMT3\* AND 4 | Onset 1st 2 yr, overall disability ?less severe than CMT4. Hypotonia, motor delay by 1st yr, poor coordination, ataxia, distal weakness (max. lower limbs), short stature. By 2nd decade, proximal weakness, hand and foot deformities. Nerve hypertrophy. Moderate to severe sensory loss. Scoliosis. Common cranial nerve involvement, nystagmus, deafness, and mild bifacial weakness. Raised CSF protein  Clinical picture similar to or slightly more severe than in CMT1 form, increased ataxia, areflexia, scoliosis. Nerve hypertrophy rare  Onset <2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes  Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness, absent DTRs  Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey  Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades  Closed gypsy pedigree; onset <10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy  Congenital hypomyelinating neuropathy | Motor conduction velocities usually <10 m/s. SAPs absent. EMG: chronic denervation  Moderate slowing of nerve conduction studies  25-35 m/s  9-20 m/s  15-30 m/s  4-37 m/s  10-20 m/s  5-20 m/s |  |
| CMT3 (Dejerine-Sottas | *PMP22*, *MPZ*, *PRX*, |
| syndrome) (145900) | *EGR2*, *FIG4* |
| CMT4 (A-J) |  |
| Autosomal recessive |  |
| 4A (214400) | *GDAP1* |
| 4B1 (601382) | *MTMR2*, *(MPZ)* |
| 4B2 (604563) | *SBF2*, *MTMR13* |
| 4C (601596) | *SH3TC2*  (*KIAA1985*) |
| 4D (601455) (HMSN-Lom) | *NDRG1* |
| 4E (605253) | *ERG2/KROX 20, MPZ* |

**Chapter 613** ◆ Hereditary Motor-Sensory Neuropathies **3001**

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| **Table 613-1** Hereditary | Peripheral Neuropathies—cont’d | | |
| **DISORDER (OMIM NO.)** | **CLINICAL FEATURES** | **NERVE CONDUCTION STUDIES** | **GENE OR LOCUS** |
| 4F (145900) | Severely affected at birth or by 7 yr; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young  Type Russe. Onset 8-16 yr. Origin Bulgaria Increased in Lebanese/Turkish. Onset infancy to  childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs  Onset by 5 yr. Severe disorder. Similarities to motor neuron disease  Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy | <5 m/s | *PRX* |
| 4G (605285) | 30-35 m/s | 10q22 |
| 4H (609311) | <10 m/s or absent | *FDG4* |
| 4J (611228) | 2-7 m/s; some cases higher | *FIG4* |
| CCFDN (604168) | 19-33 m/s | *CTDP1* |
| MIXED PATHOLOGY (AXONAL AND DEMYELINATING)  CMT X X-linked dominant. Onset 1st-2nd decade.  X-linked CMT Progressive wasting and weakness of distal  X1 (302800) limb musculature, especially hands, more marked in affected males than carrier females  X2 (302801) X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected  X3 (302802) X-linked recessive. ± Spasticity. Females unaffected  X4 (310490) X-linked (Cowchock syndrome). Severe neuropathy, females very mildly affected. Isolated case reports. Onset birth to early childhood. Slowly progressive. Many develop deafness by 5 yr. Mental retardation commonly seen. Occasional optic atrophy  X5 (311070) X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes  Intermediate forms of CMT Patients have neurophysiologic results that fall  between axonal and demyelinating ranges | | Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced  Mixed demyelinating/axonal  Mixed demyelinating/axonal  Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation  Axonal neuropathy–mild demyelinating changes  “Intermediate values” 30-40 m/s– most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB) | *GJB1*  Xp22.2  Xq26 Xq24–26.1  Xq21.32–q24  *PRPS1* |
| DI-CMTA  DI-CMTB (606482)  DI-CMTC (608323)  DI-CMTD (607791)  A–autosomal recessive form (608340) | Italian family American family  Myelin protein zero Overlap conditions:  Recessive CMT with *GADP1* mutations: (CMT2K and 4A) Spanish and Tunisian family–severe childhood forms reported. Also called  DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E) |  | 10q24.1–q25.1 |
| *DNM2* |
| *YARS* |
| *MPZ* |
| Overlap: |
| *GJB1* |
| *NF-L* |
| *GDAP1* |
| OTHER HMSN AND HMN SYNDROMES  HMSN V/spastic paraplegia Variable inheritance. Spasticity in lower limbs with HMSN type V/CMT5 causing difficulty walking and toe walking. (CMT with pyramidal signs) Autosomal recessive form associated with (600631) mental retardation. Lower limb marked  spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy  CMT with pyramidal signs: part of HMSN V but described without spasticity  HMSN VI (allelic CMT2A) Visual impairment due to optic atrophy.  Dominant and recessive forms. Onset in 1st decade. Distal weakness, often proximal involvement too. Less sensory involvement. Scoliosis  HMSN VII HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset | | Small/absent SNAPs. Motor studies axonal in type | *SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1*  CMT with pyramidal signs: *MFN2* |
| No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated | *MFN2* |

*Continued*

**3002 Part XXVIII** ◆ Neuromuscular Disorders

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| **Table 613-1** Hereditary Peripheral Neuropathies—cont’d | | |
| **DISORDER (OMIM NO.) CLINICAL FEATURES** | **NERVE CONDUCTION STUDIES** | **GENE OR LOCUS** |
| DISTAL HEREDITARY MOTOR NEURONOPATHIES (DHMN)  dHMNI (182960) Autosomal dominant. Juvenile onset. Distal weakness and wasting | Normal nerve conduction studies, occasional mild slowing. EMG neurogenic | *HSPB1*  7q34–q36 |
| dHMNII (608634) Autosomal dominant. Adult onset, distal weakness and wasting  dHMNIIjuv (158590) (Allelic CMT2F, CMT2L)  dHMNIII Autosomal recessive. Infantile to adult onset.  Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis  dHMNIV (607088) Autosomal recessive. Juvenile onset. Severe  Distal SMA type 3 muscle wasting and weakness and diaphragmatic paralysis  dHMNV (600794) (Allelic CMT2D)  Autosomal dominant. Upper limb predominance, occasional pyramidal features  dHMN type V (Silver Autosomal dominant. Prominent hand muscle syndrome) (270685) weakness and wasting, mild to severe  spasticity of lower limbs  dHMNVI (604320) (Allelic SMARD1)  Autosomal recessive. Severe infantile form with respiratory distress  dHMNVIIA (158580) Autosomal dominant. Onset with vocal cord paralysis  dHMNVIIB (607641) Autosomal dominant. Onset with vocal cord  paralysis and facial weakness  X-linked dHMN  dHMN/ALS4 (602433) X-linked recessive. Juvenile onset with distal  wasting and weakness  dHMN-J (Jerash) Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs  Congenital distal SMA Autosomal recessive. Onset from 6-10 yr with (600175) pyramidal features in 1 Jordanian family  Autosomal dominant congenital nonprogressive distal HMN with contractures  Peripheral neuropathy with Autosomal recessive. Increased in French agenesis of corpus Canadian populations. Progressive axonal callosum (Charlevoix neuropathy. CNS malformations—absence/ disease or Andermann hypoplasia of corpus callosum in most, early syndrome) (218000) onset, developmental delay, areflexia,  dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade  Hereditary neuralgic Autosomal dominant. Episodes of paralysis and amyotrophy (brachial muscle weakness initiated by severe pain. plexus neuropathy) Onset can be from birth or later childhood (162100) but usually adult onset. Outcome usually  good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism | EMG: denervation. Axonal neuropathy  Normal or mildly prolonged MNCVs distal to affected brachial plexus | *HSPB8, HSPB3*  *HSPB1*  11q13.3  11q13 *GARS BSCL2 IGHMBP2 DCTN1*  2q14 Xq13–q21  *SETX*  9p21.1–p12  12q23–q24  *SLC12A6 (KCC3)*  *SEPT9* |
| HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES  HSN (HSAN) 1 (162400) Type 1: Autosomal dominant. Onset 2nd–5th  decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement | Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity  Type 1B: Autosomal dominant. Predominantly sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcers. More often adult onset. Hearing often abnormal  Normal MNCVs; SNAPs are absent | *SPTLC1 RAB7* 3p24–p22 |
| HSN (HSAN) 2(A) (201300) Autosomal recessive. Onset in infancy/early  childhood–1st 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs  HSN (HSAN) 2B (223900) Autosomal recessive. Impaired sensation,  ulcers, and arthropathy develop in childhood | *WNK1*  *FAM134B* |

**Chapter 613** ◆ Hereditary Motor-Sensory Neuropathies **3003**

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| **Table 613-1** Hereditary | Peripheral Neuropathies—cont’d | | |
| **DISORDER (OMIM NO.)** | **CLINICAL FEATURES** | **NERVE CONDUCTION STUDIES** | **GENE OR LOCUS** |
| HSN (HSAN) 3 (Riley-Day syndrome, familial dysautonomia) (223900)  HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)  HSN (HSAN) 5 (608654) | Autosomal recessive. History of neurologic abnormality and of difficult feeding from birth. Failure to produce tears regularly. Absent or reduced DTRs. Absent corneal reflexes, postural hypotension, emotional lability. Relative indifference to pain, absence of fungiform papillae on tongue, absence of flare with intradermal histamine. Normal intelligence  Autosomal recessive. Onset from infancy, often high fevers due to truncal anhidrosis during hot weather. Painless injuries of extremities and oral structures, often self-mutilation. Lack of pain sensation, both peripheral and visceral, inability to distinguish hot and cold. Preservation of DTRs. Mild mental retardation. Hyperactivity and emotional lability common  Autosomal recessive. Onset in early life. Rare disorder. Painless injuries of the extremities. Lack of pain and thermal sensitivity in the limbs but preservation of response to tactile and mechanical stimuli. Preservation of muscle strength and DTRs. Distal anhidrosis. Bone and joint fractures; arthropathy. Normal intelligence | Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased  Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)  Normal motor and sensory nerve conduction studies | *IKBAP*  *NTRK1*  *NGF*β |

\*The term CMT3 should be reserved for hereditary neuropathies in which hypomyelination is the dominant feature. This would include congenital hypomyelinating neuropathy, Dejerine-Sottas disease, and congenital amyelinating neuropathy.

CCFDN, congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound motor unit action potential; CMT, Charcot-Marie-Tooth disease; CP, common peroneal; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuronopathy; DI, dominant intermediate; dSMA, distal spinal muscular atrophy; DTR, deep tendon reflex; EMG, electromyography;

EOHMSN, early-onset HMSN; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.

*From Wilmshurst JM, Ouvrier R: Hereditary peripheral neuropathies of childhood: an overview for clinicians,* Neuromuscul Disord *21(11):763–775, 2011.*

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| **Table 616-1** | Differential Diagnosis of Childhood Guillain-Barré Syndrome |
| SPINAL CORD LESIONS  Acute transverse myelitis Epidural abscess  Tumors  Poliomyelitis (natural or live virus) Enteroviruses  Hopkins syndrome Vascular malformations Cord infarction  Fibrocartilaginous embolism  Cord compression from vertebral subluxation related to congenital abnormalities or trauma  Acute disseminated encephalomyelitis  Bickerstaff brainstem encephalitis for Miller-Fisher syndrome | |
| PERIPHERAL NEUROPATHIES  Toxic   * Vincristine * Glue sniffing * Heavy metal: gold, arsenic, lead, thallium * Organophosphate pesticides * Fluoroquinolones Infections * HIV * Diphtheria * Lyme disease   Inborn errors of metabolism   * Leigh disease * Tangier disease * Porphyria   Critical illness: polyneuropathy/myopathy Vasculitis syndromes  Porphyria  Mitochondrial neurogastrointestinal encephalomyopathy CD59 deficiency | |
| NEUROMUSCULAR JUNCTION DISORDERS  Tick paralysis Myasthenia gravis Botulism Hypercalcemia Myopathies Periodic paralyses Dermatomyositis  Critical illness myopathy/polyneuropathy | |

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| **Table 614-1** | Toxic and Metabolic Neuropathies | |
| METALS  Arsenic (insecticide, herbicide) Lead (paint, batteries, pottery) Mercury (metallic, vapor) Thallium (rodenticides)  Gold | | Nitrofurantoin Nitrous oxide  Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddI], d4T, others)  Penicillamine Pentamidine Phenytoin  Pyridoxine (excessive) Statins  Stilbamidine Suramin Tacrolimus  Taxanes (paclitaxel, docetaxel) Thalidomide  Tryptophan (eosinophilia- myalgia syndrome)  Vincristine |
| OCCUPATIONAL OR INDUSTRIAL CHEMICALS  Acrylamide (grouting, flocculation)  Carbon disulfide (solvent) Cyanide Dichlorophenoxyacetate Dimethylaminopropionitrite Ethylene oxide (gas sterilization) Hexacarbons (glue, solvents) Organophosphates (insecticides,  petroleum additive) Polychlorinated biphenyls Tetrachlorbiphenyl Trichloroethylene | |
| METABOLIC DISORDERS  Fabry disease Krabbe disease Leukodystrophies Porphyria Tangier disease Tyrosinemia Uremia |
| DRUGS  Amiodarone Chloramphenicol Chloroquine Cisplatin Colchicine Dapsone Ethambutol Ethanol Fluoroquinolones Gold  Hydralazine Isoniazid Metronidazole | |
| BIOLOGIC AND INFECTIOUS NEUROPATHIES  Diphtheria Herpesviruses HIV  Leprosy Lyme disease Rabies  West Nile virus |

*From Agrawal S, Peake D, Whitehouse WP: Management of children with Guillain Barré syndrome,* Arch Dis Child Educ Pract Ed *92:161–168, 2007.*

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| --- | --- | --- |
| **Table 617-1** | Etiologies of Acute Peripheral Facial Palsy | |
| COMMON  Idiopathic  Herpes simplex virus type 1\* Varicella-zoster virus\* | | OTHER LESS-COMMON CONDITIONS  Trauma  Schwannoma of facial nerve Infiltrative tumor  Aneurysm or vascular malformation  Anomalous narrowing of facial canal  Hypertension Sjögren syndrome  Diabetes mellitus, type 1 Guillain-Barré syndrome Sarcoidosis  Melkersson-Rosenthal syndrome† Ribavirin  Interferon |
| LESS-COMMON INFECTIONS  Otitis media ± cholesteatoma Lyme disease  Epstein-Barr virus Cytomegalovirus Mumps  Human herpesvirus 6 Intranasal influenza vaccine *Mycoplasma*  *Toxocara Rickettsia* AIDS/HIV | |

\*Implicated in idiopathic Bell palsy.

†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

*From Hughes RAC: Treatment of Guillain-Barré syndrome with corticosteroids: lack of benefit?* Lancet *363:181–182, 2004.*

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| --- | --- | --- |
| **Table 616-2** | Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies By Pathology | |
| **DISORDER** | | **ANTIBODIES** |
| Acute inflammatory demyelinating polyradiculoneuropathy  Acute motor and sensory axonal neuropathy  Acute motor axonal neuropathy  Acute sensory neuronopathy | | Unknown  GM1, GM1b, GD1a GM1, GM1b, GD1a,  GalNac-GD1a GD1b |
| ACUTE PANDYSAUTONOMIA  *Regional Variants* Fisher syndrome Oropharyngeal *Overlap*  Fisher/Guillain-Barré overlap syndrome | | GQ1b, GT1a GT1a  GQ1b, GM1, GM1b, GD1a,  GalNac-GD1a |

**Chapter 615** ◆ Autonomic Neuropathies **3007**



Structural

Functional

Peripheral

Central

Afferent

Baroreflex

failure

HSAN III

(familial dysautonomia)

Small fiber

neuropathy

Efferent

Dysautonomia

Mitochondrial

Inflammatory

Syncopal migraine

Chronic fatigue syndrome

Genetic: Rett CCHS

Genetic

Raynaud

Migraine headache

Diabetes

Central autonomic network stroke

Cyclic vomiting syndrome

Functional GI disorders

Myelopathy

Fibromyalgia

Complex regional pain

Parkinson or Lewy body disease

Irritable bowel syndrome

Interstitial cystitis

Multiple system atrophy

Shy-Drager

Reflex syncope

Postural tachycardia

Metabolic

Immune

Pure autonomic failure

###### **Figure 615-1** Classification of autonomic disorders or dysautonomias. The first conceptual division is between a structural and functional disorder. The word “functional” is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word “functional” in functional gastrointestinal disorders, and without implication of a psy- chiatric etiology. In the absence of any evidence of consistent structural abnormalities functional disorders clearly cannot be localized in the nervous system. In contrast, structural disorders can be further divided into those localized in the central and peripheral nervous systems, with the division point usually taken at the sympathetic ganglion. Finally, peripheral nervous system disorders can be further classified based on whether they primarily involve afferent or efferent nerves. It should be emphasized that there is overlap between these groups, for example, diabetes will often involve afferent nerve fibers, but this classification emphasizes the predominant fiber involvement. A *dotted line* links Parkinson disease to a peripheral efferent group as Lewy bodies are present in the both parasympathetic and sympathetic ganglia, impairing peripheral autonomic func- tion. See below for discussion of specific disorders. *CCHS*, Congenital central hypoventilation syndrome; *HSAN*, hereditary sensory autonomic neuropathy. *(From Chelimsky T, Robertson D, Chelimsky G: Disorders of the autonomic nervous system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors*: Bradley’s neurology in clinical practice*, ed 6, Philadelphia, 2012, WB Saunders, Fig. 77-1, p. 2018.)*

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| **Table 615-1** | Autonomic Neuropathies | |
| Guillain-Barré syndrome (see Chapter 608) Non–Guillain-Barré syndrome autoimmunity   * Paraneoplastic (type I antineuronal nuclear antibody) * Lambert-Eaton syndrome * Antibodies to neuronal nicotinic acetylcholine receptors * Antibodies to P/Q-type calcium channels * Other autoantibodies * Systemic lupus erythematosus   Hereditary sensory and autonomic neuropathies   * Type I autosomal dominant * Type II autosomal recessive (Morvan disease) * Type III autosomal recessive (Riley-Day) * Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis) * Type V absence of pain | | Metabolic   * Fabry disease * Diabetes mellitus * Tangier disease * Porphyria Infectious * HIV * Chagas disease * Botulism * Leprosy * Diphtheria Other * Triple A (Allgrove) syndrome * Navajo Indian neuropathy * Multiple endocrine neoplasia type 2b Toxins (see Table 614-1 in Chapter 614) |
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**3008 Part XXVIII** ◆ Neuromuscular Disorders

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| **Table 615-2** | Major Clinical Features of Hereditary Sensory-Autonomic Neuropathy Types II, III, and IV | | | |
| **CLINICAL FEATURES** | | **HSAN TYPE II** | **HSAN TYPE III** | **HSAN TYPE IV** |
| Onset | | Birth | Birth | Birth |
| Initial symptoms (from birth to age 3 yr) | | Swallowing problems  Self-mutilation (65%) Delayed development | Swallowing problems  Aspiration pneumonia Breech presentation (37%) Hypothermia  Delayed development | Fevers  Self-mutilation (88%) |
| Unique features | | No axon flare  Lack of fungiform papilla Hearing loss (30%) | No axon flare  Lack of fungiform papilla Alacrima | No axon flare Anhidrosis Consanguinity 50% |
| Sensory dysfunction  Depressed deep tendon reflexes Pain perception  Temperature perception Vibration sense | | Frequent (71%) Absent  Severe decrease Normal | Almost consistent (99%) Mild to moderate decrease Mild to moderate decrease Normal | Infrequent (9%) Absent  Absent  Normal to moderate decrease |
| Autonomic Gastroesophageal reflux Postural hypotension Episodic hypertension | | Frequent (71%)  Uncommon (25%) Rare | Frequent (67%)  Almost consistent (99%) Frequent | Uncommon (24%)  Uncommon (29%) Rare |
| Ectodermal features Dry skin  Fractures Scoliosis | | No 29%  59% | No 40%  85% | Consistent 71%  23% |
| Intelligence IQ <65  Hyperactivity | | Common (38%)  Common (41%) | Uncommon (10%) Uncommon | Common (33%)  Common (54%) |

Frequency definitions: rare = <1%; infrequent = <10%; uncommon = <30%; common = 30-65%; frequent = >65%.

*From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV,* Orphanet J Rare Dis *2:39, 2007, Table 2.*

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| **Table 615-3** | Autonomic Function Testing |
| Sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function | |
| CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION  Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments  Heart rate response to Valsalva maneuver Heart rate response to standing | |
| SYMPATHETIC ADRENERGIC FUNCTION  Blood pressure response to upright posture (standing or tilt table) Blood pressure response to Valsalva maneuver  Microneurography | |
| SYMPATHETIC CHOLINERGIC FUNCTION  Thermoregulatory sweat testing Quantitative sudomotor-axon reflex test Sweat imprint methods  Sympathetic skin response | |

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| **Table 615-4** | Management of Autonomic Neuropathies | |
| **PROBLEM** | | **TREATMENT** |
| Orthostatic hypotension | | Volume and salt supplements Fluorohydrocortisone (mineralocorticoid) Midodrine (α agonist) |
| Gastroparesis | | Prokinetic agents (metoclopramide, domperidone, erythromycin) |
| Hypomotility | | Fiber, laxatives |
| Urinary dysfunction | | Timed voiding; bladder catheterization |
| Hyperhidrosis | | Anticholinergic agents (glycopyrrolate, propantheline)  Intracutaneous botulism toxin |

# Disorders of the Eye

**Chapter 619** ◆ Examination of the Eye **3017**

|  |  |  |  |
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| **Table 619-1** Vision Screening Guidelines | | | |
| **FUNCTION** | **RECOMMENDED TESTS** | **REFERRAL CRITERIA** | **COMMENTS** |
| AGES 3-5 YR  Distance visual acuity | Snellen letters Snellen numbers Tumbling E test HOTV test | <4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., <10/20 or 20/40), or  Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40) | Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages  6 yr and older. |
|  | Picture tests | Testing distance of 3 m (10 ft) is recommended for all visual acuity tests. |
|  | -Allen figures  -Lea symbols | A line of figures is preferred over a single figure.  The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to eye; the examiner must ensure that it is not possible to peek with the nontested eye. |
| Ocular alignment | Cross cover test at 3 m (10 ft) or  Random dot E stereo test at 40 cm (630 sec of arc)  Simultaneous red reflex test (Bruckner test) | Any eye movement  <4 of 6 correct  Any asymmetry of pupil color, size, brightness | Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well. |
| Ocular media clarity (cataracts, tumors, etc.) | Red reflex | White pupil, dark spots, absent reflex | Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma. |
| AGES 6 YR AND OLDER  Distance visual acuity | Snellen letters Snellen numbers Tumbling E test HOTV test  Picture tests  -Allen figures  -Lea symbols | <4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e.,  <10/15 or 20/30)  Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30) | Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages  6 yr and older.  Testing distance of 3 m (10 ft) is recommended for all visual acuity tests.  A line of figures is preferred over a single figure.  The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye. |
| Ocular alignment | Cross cover test at 3 m (10 ft) or  Random dot E stereo test at 40 cm (630 sec of arc) | Any eye movement  <4 of 6 correct |  |

**3022 Part XXIX** ◆ Disorders of the Eye

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| **Table 621-1** | Causes of Childhood Severe Visual Impairment or Blindness | |
| CONGENITAL  Optic nerve hypoplasia or aplasia Septooptic dysplasia  Optic coloboma Congenital hydrocephalus Hydranencephaly Porencephaly Micrencephaly  Encephalocele, particularly occipital Morning glory disc  Aniridia Microphthalmia/anophthalmia Peters anomaly  Rieger anomaly  Persistent pupillary membrane Glaucoma  Cataracts  Persistent hyperplastic primary vitreous | | Special types: Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease  Retinal degenerations: retinitis pigmentosa and its variants and Leber congenital type  Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown |
| INFECTIOUS/INFLAMMATORY PROCESSES  Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii*, cytomegalovirus, rubella virus, *Treponema pallidum*, herpes simplex virus  Meningitis; arachnoiditis Chorioretinitis Endophthalmitis Trachoma  Keratitis Uveitis |
| PHAKOMATOSES  Tuberous sclerosis  Neurofibromatosis (special association with optic glioma)  Sturge-Weber syndrome von Hippel-Lindau disease | | HEMATOLOGIC DISORDERS  Leukemia with central nervous system involvement |
| VASCULAR AND CIRCULATORY DISORDERS  Collagen vascular diseases  Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage  Central retinal occlusion |
| TUMORS  Retinoblastoma Optic glioma  Perioptic meningioma Craniopharyngioma Cerebral glioma Astrocytoma  Posterior and intraventricular tumors when complicated by hydrocephalus  Pseudotumor cerebri | |
| TRAUMA  Contusion or avulsion of optic nerves, chiasm, globe, cornea Cerebral contusion or laceration  Intracerebral, subarachnoid, or subdural hemorrhage Retinal detachment  Laser injury |
| DRUGS AND TOXINS  Quinine Ethambutol Methanol Many others |
| NEURODEGENERATIVE DISEASES  Cerebral storage disease  Gangliosidoses, particularly Tay-Sachs disease, Sandhoff variant, generalized gangliosidosis  Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten- Mayou-Spielmeyer-Vogt  Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome  Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease  Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica | |
| OTHER  Retinopathy of prematurity Sclerocornea  Conversion reaction Optic neuritis Osteopetrosis |

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| --- | --- | --- | --- | --- |
| **Table 623-1** | Specific Patterns | of | Nystagmus | |
| **PATTERN** | | **DESCRIPTION** | | **ASSOCIATED CONDITIONS** |
| Latent nystagmus | | Conjugate jerk nystagmus toward viewing eye | | Congenital vision defects, occurs with occlusion of eye |
| Manifest latent nystagmus | | Fast jerk to viewing eye | | Strabismus, congenital idiopathic nystagmus |
| Periodic alternating | | Cycles of horizontal or horizontal-rotary that change direction | | Caused by both visual and neurologic conditions |
| Seesaw nystagmus | | One eye rises and intorts as other eye falls and extorts | | Usually associated with optic chiasm defects |
| Nystagmus retractorius | | Eyes jerk back into orbit or toward each other | | Caused by pressure on mesencephalic tegmentum (Parinaud syndrome) |
| Gaze-evoked nystagmus | | Jerk nystagmus in direction of gaze | | Caused by medications, brainstem lesion, or labyrinthine dysfunction |
| Gaze-paretic nystagmus | | Eyes jerk back to maintain eccentric gaze | | Cerebellar disease |
| Downbeat nystagmus | | Fast phase beating downward | | Posterior fossa disease, drugs |
| Upbeat nystagmus | | Fast phase beating upward | | Brainstem and cerebellar disease; some visual conditions |
| Vestibular nystagmus | | Horizontal-torsional or horizontal jerks | | Vestibular system dysfunction |
| Asymmetric or monocular nystagmus | | Pendular vertical nystagmus | | Disease of retina and visual pathways |
| Spasmus nutans | | Fine, rapid, pendular nystagmus | | Torticollis, head nodding; idiopathic or gliomas of visual pathways |

**3032 Part XXIX** ◆ Disorders of the Eye

Work-up and treatment as per ocular malformation, tumor, dysgenesis

Yes

? Obvious ocular malformation, tumor

Aniridia

Iridocorneal dysgenesis Congenital cataracts

Ocular coloboma Cicatricial ROP Bilateral PHPV

No

? Asymmetric, rapid, Yes



+

pendular MRI scan

Yes

Neurologic disorder

Congenital glaucoma

Retinoblastoma Toxoplasmosis

Bilateral retinal dysplasia

Macular coloboma No Juvenile retinoschisis

No Spasmus nutans

Congenital motor

Yes

Yes

? Searching nystagmus

No

? Pendular

Yes

? ERG flat

No

? Optic nerve

Yes

Yes



+

Leber

Yes

Neurologic

efferent or

idiopathic nystagmus

? Vision normal

No

nystagmus

pale/small MRI scan No

disorder

Albinism

X-linked retinoschisis

Achromatopsia

Yes ? Foveal hypoplasia

± iris transillumination

No

Yes ? Macular NFL schisis No

+ ERG abnormality

No

Yes

? Photophobia

+

+

? Sloan test/ – Flicker ERG

No

Idiopathic optic nerve disorder

No

CSNB

Yes ? Myopia No

? Rod dark adaptation



–

+

ERG abnormality

? Associated with strabismus

No

Yes

Nystagmus blockage syndrome Manifest latent nystagmus

Congenital motor efferent or idiopathic nystagmus

**Figure 623-7** Algorithm for the work-up of an infant with nystagmus. 8, positive; Θ, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. *(From Nelson LB:* Harley’s pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 470.)*

Nystagmus in Childhood

Idiopathic

Chiasmal

Misrouting

Associated with

Ocular Diseases

Neurologic

Syndromes

Manifest Latent

Nystagmus (Fusional Maldevelopment

Nystagmus Syndrome)

Achromatopsia

Congenital stationary night blindness

*Ciliopathies* Leber congenital amaurosis

Aiström syndrome Bardet-Biedl syndrome Joubert syndrome Senior Løken syndrome

Retinopathy of prematurity Aniridia (*PAX6* mutations) Isolated foveal hypoplasia Optic nerve hypoplasia Optic nerve atrophy Congenital cataracts Media opacity

Down syndrome Noonan syndrome Structural malformations

Space-occupying lesions Periventricular leukomalacia Developmental diseases Leukodystrophies

Chiari malformations Metabolic diseases or mitochondrial diseases Spinal cerebellar ataxias Episodic ataxias Vestibular diseases

Infantile squint syndrome

Albinism Achiasma

No other ocular or neurologic abnormalities

Spasmus Nutans

**Figure 623-8** Classification of nystagmus based on associated diseases. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabis- mus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)*

**Chapter 626** ◆ Disorders of the Conjunctiva **3037**

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| --- | --- | --- | --- |
| **Table 626-1** The | Red Eye | | |
| **CONDITION** | **ETIOLOGY** | **SIGNS AND SYMPTOMS** | **TREATMENT** |
| Bacterial conjunctivitis | *Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis* | Mucopurulent unilateral or bilateral discharge, normal vision, photophobia | Topical antibiotics, parenteral ceftriaxone for gonococcus,  *H. influenzae* |
| Hyperacute bacterial conjunctivitis | *Neisseria gonorrhoeae, Neisseria meningitides* | Conjunctival injection and edema (chemosis); gritty sensation |  |
| Viral conjunctivitis | Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus | As above; may be hemorrhagic, unilateral | Self-limited |
| Neonatal conjunctivitis | *Chlamydia trachomatis*, gonococcus, chemical (silver nitrate), *S. aureus* | Palpebral conjunctival follicle or papillae; as above | Ceftriaxone for gonococcus and erythromycin for *C. trachomatis* |
| Allergic conjunctivitis | Seasonal pollens or allergen exposure | Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae | Antihistamines, topical mast cell stabilizers or prostaglandin inhibitors, steroids |
| Keratitis | Herpes simplex virus, adenovirus,  *S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba*, chemicals | Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection | Specific antibiotics for bacterial/ fungal infections; keratoplasty, acyclovir for herpes |
| Endophthalmitis | *S. aureus, S. pneumoniae, Candida albicans*, associated surgery or trauma | Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze | Antibiotics |
| Anterior uveitis (iridocyclitis) | JIA, postinfectious with arthritis and rash, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease | Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision | Topical steroids, plus therapy for primary disease |
| Posterior uveitis (choroiditis) | Toxoplasmosis, histoplasmosis,  *Toxocara canis* | No signs of erythema, decreased vision | Specific therapy for pathogen |
| Episcleritis/scleritis | Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura) | Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation | Episcleritis is self-limiting; topical steroids for fast relief |
| Foreign body | Occupational exposure | Unilateral, red, gritty feeling; visible or microscopic size | Irrigation, removal; check for ulceration |
| Blepharitis | *S. aureus, Staphylococcus epidermidis*, seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, *Phthirus pubis, Pediculus capitis* | Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins | Topical antibiotics, warm compresses, lid hygiene |
| Dacryocystitis | Obstructed lacrimal sac: *S. aureus,*  *H. influenzae,* pneumococcus | Pain, tenderness, erythema, and exudates in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis | Systemic, topical antibiotics; surgical drainage |
| Dacryoadenitis | *S. aureus, Streptococcus*, CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia | Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis | Systemic antibiotics; drainage of orbital abscesses |
| Orbital cellulitis (postseptal cellulitis) | Paranasal sinusitis: *H. influenzae,*  *S. aureus, S. pneumoniae*, streptococci  Trauma: *S. aureus*  Fungi: *Aspergillus, Mucor* spp. if immunodeficient | Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis | Systemic antibiotics, drainage of orbital abscesses |
| Periorbital cellulitis (preseptal cellulitis) | Trauma: *S. aureus,* streptococci Bacteremia: pneumococcus,  streptococci, *H. influenzae,*  *S. aureus* | Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance | Systemic antibiotics |

CMV, cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

*From Behrman R, Kliegman R:* Nelson’s essentials of pediatrics, *ed 3, Philadelphia, 1998, WB Saunders.*

**Chapter 626** ◆ Disorders of the Conjunctiva **3039**

|  |  |  |
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| **Table 626-2** | Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages | |
| **DRUG** | | **DOSAGE** |
| Bacitracin (AK-Tracin, Bacticin) ointment | | Apply 0.5 inch in eye q3-4h |
| Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution | | 1-2 gtt in eye q15min × 6h, then q30min × 18h, then q1h × 1 day, then q4h × 12 days\* |
| Gatifloxacin (Zymar) 0.3% ophthalmic solution | | 1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days |
| Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment | | Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h |
| Levofloxacin (Quixin) 0.5% ophthalmic solution | | 1-2 gtt in eye q2h × 2 days while awake, then q4h × 5 days while awake |
| Moxifloxacin (Vigamox) 0.5% ophthalmic solution | | 1 gt in eye tid × 7 days |
| Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution | | 1-2 gtt in eye q4h × 7-10 days |
| Ofloxacin (Ocuflox) 0.3% ophthalmic solution | | 1-2 gtt in eye q2-4h × 2 days, then 1-2 gtt in eye qid × 5 days |
| Polymyxin B and trimethoprim (Polytrim) ophthalmic solution | | 1 gt in eye q3h × 7-10 days |
| Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment | | Ointment: 0.5-inch ribbon in eye q3-4h and qhs × 7 days Solution: 1-2 gtt in eye q2-3h × 7-10 days |
| Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution | | 1-2 gtt in eye q4h |

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| --- | --- | --- | --- |
| **Table 623-2** | Specific Patterns of Nonnystagmus Eye Movements | | |
| **PATTERN** | | **DESCRIPTION** | **ASSOCIATED CONDITIONS** |
| Opsoclonus | | Multidirectional conjugate movements of varying rate and amplitude | Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome |
| Ocular dysmetria | | Overshoot of eyes on rapid fixation | Cerebellar dysfunction |
| Ocular flutter | | Horizontal oscillations with forward gaze and sometimes with blinking | Cerebellar disease, hydrocephalus, or central nervous system neoplasm |
| Ocular bobbing | | Downward jerk from primary gaze, remains for a few sec, then drifts back | Pontine disease |
| Ocular myoclonus | | Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement | Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus |

**3042 Part XXIX** ◆ Disorders of the Eye

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| **Table 627-1** STUMPED: Differential Diagnosis of Neonatal Corneal Opacities | | | | | | |
| **DIAGNOSIS** | **LATERALITY** | **OPACITY** | **OCULAR PRESSURE** | **OTHER OCULAR ABNORMALITIES** | **NATURAL HISTORY** | **INHERITANCE** |
| S—Sclerocornea | Unilateral or bilateral | Vascularized, blends with sclera, clearer centrally | Normal (or elevated) | Cornea plana | Nonprogressive | Sporadic |
| T—Tears in endothelium and Descemet membrane | | | | | | |
| Birth trauma | Unilateral | Diffuse edema | Normal | Possible hyphema, periorbital ecchymoses | Spontaneous improvement in 1 mo | Sporadic |
| Infantile glaucoma | Bilateral | Diffuse edema | Elevated | Megalocornea, photophobia and tearing, abnormal angle | Progressive unless treated | Autosomal recessive |
| U—Ulcers | | | | | | |
| Herpes simplex keratitis | Unilateral | Diffuse with geographic epithelial defect | Normal | None | Progressive | Sporadic |
| Congenital rubella | Bilateral | Disciform or diffuse edema, no frank ulceration | Normal or elevated | Microphthalmos, cataract, pigment epithelial mottling | Stable, may clear | Sporadic |
| Neurotrophic exposure | Unilateral or bilateral | Central ulcer | Normal | Lid anomalies, congenital sensory neuropathy | Progressive | Sporadic |
| M—Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidosis type IV)\* | Bilateral | Diffuse haze, denser peripherally | Normal | Few | Progressive | Autosomal dominant |
| P—Posterior corneal defect | Unilateral or bilateral | Central, diffuse haze or vascularized leukoma | Normal or elevated | Anterior chamber cleavage syndrome | Stable, sometimes early clearing or vascularization | Sporadic, autosomal recessive |
| E—Endothelial dystrophy | | | | | | |
| Congenital hereditary endothelial dystrophy | Bilateral | Diffuse corneal edema, marked corneal thickening | Normal | None | Stable | Autosomal dominant or recessive |
| Posterior polymorphous dystrophy | Bilateral | Diffuse haze, normal corneal thickness | Normal | Occasional peripheral anterior synechiae | Slowly progressive | Autosomal dominant |
| Congenital hereditary stromal dystrophy | Bilateral | Flaky, feathery stromal opacities; normal corneal thickness | Normal | None | Stable | Autosomal dominant |
| D—Dermoid | Unilateral or bilateral | White vascularized mass, hair, lipid arc | Normal | None | Stable | Sporadic |

\*Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).

*From Nelson LB, Calhoun JH, Harley RD:* Pediatric ophthalmology, *ed 3, Philadelphia, 1991, WB Saunders, p. 210.*

**Chapter 628** ◆ Abnormalities of the Lens **3045**

|  |  |
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| **Table 628-1** Differential Diagnosis of Cataracts | |
| DEVELOPMENTAL VARIANTS | *Inborn Errors of Metabolism*  Abetalipoproteinemia (absent chylomicrons, retinal degeneration) Fabry disease (α-galactosidase A deficiency)  Galactokinase deficiency  Galactosemia (galactose-1-phosphate uridyltransferase deficiency) Homocystinemia (subluxation of lens, mental retardation)  Infantile neuronal ceroid lipofuscinosis Mannosidosis (acid α-mannosidase deficiency) Niemann-Pick disease (sphingomyelinase deficiency)  Refsum disease (phytanic acid α-hydrolase deficiency)  Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)  Zellweger syndrome |
| Prematurity (Y-suture vacuoles) with or without retinopathy of |
| prematurity |
| Mittendorf dot (remnant of hyaloid artery) |
| Persistent pupillary membrane (remnant of embryonic lens |
| vasculature) |
| GENETIC DISORDERS |
| *Simple Mendelian Inheritance* |
| Autosomal dominant (most common) |
| Autosomal recessive |
| X-linked |
| *Major Chromosomal Defects* |
| Trisomy disorders (13, 18, 21)  Turner syndrome (45X) |
| ENDOCRINOPATHIES |
| Hypocalcemia (hypoparathyroidism) |
| Deletion syndromes (11p13, 18p, 18q) |
| Hypoglycemia  Diabetes mellitus |
| Duplication syndromes (3q, 20p, 10q)  *Multisystem Genetic Disorders* |
| Alport syndrome (hearing loss, renal disease) | CONGENITAL INFECTIONS  Toxoplasmosis Cytomegalovirus infection Syphilis  Rubella  Perinatal herpes simplex infection Measles (rubeola)  Poliomyelitis Influenza Varicella-zoster |
| Alström syndrome (nerve deafness, diabetes mellitus) |
| Apert disease (craniosynostosis, syndactyly) |
| Cerebrooculofacial syndrome |
| Cockayne syndrome (premature senility, skin photosensitivity) |
| Conradi disease (chondrodysplasia punctata) |
| Crouzon disease (dysostosis craniofacialis) |
| Ectodermal dysplasia |
| Hallermann-Streiff syndrome (microphthalmia, small pinched nose, |
| skin atrophy, and hypotrichosis) |
| Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis) |
| OCULAR ANOMALIES |
| Microphthalmia |
| Ichthyosis (keratinizing disorder with thick, scaly skin) |
| Coloboma |
| Incontinentia pigmenti (dental anomalies, mental retardation, |
| Aniridia |
| cutaneous lesions) |
| Mesodermal dysgenesis |
| Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal |
| Persistent pupillary membrane |
| disease) |
| Posterior lenticonus |
| Marfan syndrome |
| Persistent fetal vasculature |
| Meckel-Gruber syndrome (renal dysplasia, encephalocele) |
| Primitive hyaloid vascular system |
| Myotonic dystrophy |
| Retinitis pigmentosa |
| Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic |
| patella) |
| MISCELLANEOUS DISORDERS  Atopic dermatitis Drugs (corticosteroids) Radiation  Trauma  Juvenile idiopathic arthritis Retinopathy of prematurity |
| Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia) |
| Nevoid basal cell carcinoma syndrome (autosomal dominant, basal |
| cell carcinoma erupts in childhood) |
| Peters anomaly (corneal opacifications with iris-corneal dysgenesis) |
| Progeria |
| Rieger syndrome (iris dysplasia, myotonic dystrophy) |
| Rothmund-Thomson syndrome (poikiloderma: skin atrophy) |
|  |
| Rubinstein-Taybi syndrome (broad great toe, mental retardation) | IDIOPATHIC |
| Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental |  |
| retardation) |  |
| Sotos syndrome (cerebral gigantism) |  |
| Spondyloepiphyseal dysplasia (dwarfism, short trunk) |  |
| Werner syndrome (premature aging in 2nd decade of life) |  |

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| **Table 634-1** | Chandler Classification of Orbital Complications of Sinusitis, a Clinical Description | |
| **CHANDLER CLASS** | **STAGE** | **CLINICAL DESCRIPTION AND DEFINITION** |
| I | Inflammatory edema | Eyelid edema and erythema Normal extraocular movement Normal visual acuity |
| II | Orbital cellulitis | Diffuse edema of orbital contents without discrete abscess formation |
| III | Subperiosteal abscess | Collection of purulent exudate\* beneath periosteum of lamina papyracea  Displacement of globe downward/laterally |
| IV | Orbital abscess | Purulent collection within orbit\* Proptosis  Chemosis Ophthalmoplegia Decreased vision |
| V | Cavernous sinus thrombosis | Bilateral eye findings Prostration Meningismus |

\*The radiographic correlation of a subperiosteal or orbital abscess seen with CT is a contrast-enhancing mass in the extraconal or intraconal space, possibly with areas of cavitation, because purulence cannot be determined with CT scanning.

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| **Table 629-1** | Uveitis in Childhood |
| ANTERIOR UVEITIS  Juvenile idiopathic arthritis (pauciarticular) Sarcoidosis  Trauma Tuberculosis Kawasaki disease Ulcerative colitis Crohn syndrome  Postinfectious (enteric or genital) with arthritis and rash Spirochetal (syphilis, leptospiral)  Brucellosis  Heterochromic iridocyclitis (Fuchs) Viral (herpes simplex, herpes zoster) Ankylosing spondylitis  Stevens-Johnson syndrome  Chronic infantile neurologic cutaneous arthritis syndrome (CINCA) Familial Mediterranean fever  Hyperimmunoglobulin D syndrome  Tumor necrosis factor receptor–associated periodic syndrome Muckle-Wells syndrome  Blau syndrome Psoriasis Multiple sclerosis  Cyclic neutropenia  Chronic granulomatous disease  X-linked lymphoproliferative disease Hypocomplementemic vasculitis Idiopathic  Drugs | |
| POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)  Toxoplasmosis Toxocariasis  Parasites (toxocariasis) Sarcoidosis  Cat-scratch disease Tuberculosis  Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile) Subacute sclerosing panencephalitis  Tubulointestinal nephritis and uveitis syndrome Idiopathic | |
| ANTERIOR AND/OR POSTERIOR UVEITIS  Sympathetic ophthalmia (trauma to other eye)  Vogt-Koyanagi-Harada syndrome (uveootocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)  Behçet syndrome Lyme disease | |

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| --- | --- | --- |
| **Table 629-2** | Examination Schedule for Children with JIA Without Known Iridocyclitis | |
|  | | **AGE OF ONSET** |
| **JIA SUBTYPE ≤6 yr >6 yr** | | |
| OLIGOARTHRITIS OR POLYARTHRITIS  *Positive ANA*  Less than 4 yr duration Every 3 mo Every 6 mo 4-7 yr duration Every 6 mo Annually More than 7 yr duration Annually Annually *Negative ANA*  Less than 4 yr duration Every 6 mo Annually 4-7 yr duration Annually Annually  More than 7 yr duration Annually Annually  *Systemic* Annually regardless Annually regardless of duration of duration | | |

**3060 Part XXIX** ◆ Disorders of the Eye

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| --- | --- | --- |
| **Table 632-1** | Primary and Secondary Childhood Glaucomas | |
| 1. PRIMARY GLAUCOMAS    1. Congenital open-angle glaucoma       1. Congenital       2. Infantile       3. Late recognized    2. Autosomal dominant juvenile glaucoma    3. Primary angle-closure glaucoma    4. Associated with systemic abnormalities       1. Sturge-Weber syndrome       2. Neurofibromatosis type 1 (NF-1)       3. Stickler syndrome       4. Oculocerebrorenal (Lowe) syndrome       5. Rieger syndrome       6. Hepatocerebrorenal syndrome       7. Marfan syndrome       8. Rubinstein-Taybi syndrome       9. Infantile glaucoma associated with mental retardation and paralysis       10. Oculodentodigital dysplasia       11. Open-angle glaucoma associated with microcornea and absence of frontal sinuses       12. Mucopolysaccharidosis       13. Trisomy 13       14. Cutis marmorata telangiectasia congenita       15. Warburg syndrome       16. Kniest syndrome (skeletal dysplasia)       17. Michel syndrome       18. Nonprogressive hemiatrophy    5. Associated with ocular abnormalities       1. Congenital glaucoma with iris and pupillary abnormalities       2. Aniridia          1. Congenital glaucoma          2. Acquired glaucoma       3. Congenital ocular melanosis       4. Sclerocornea       5. Iridotrabecular dysgenesis       6. Peters syndrome       7. Iridotrabecular dysgenesis and ectropion uveae       8. Posterior polymorphous dystrophy       9. Idiopathic or familial elevated episcleral venous pressure       10. Anterior corneal staphyloma       11. Congenital microcornea with myopia       12. Congenital hereditary endothelial dystrophy       13. Congenital hereditary iris stromal hypoplasia | | 1. SECONDARY GLAUCOMAS    1. Traumatic glaucoma       1. Acute glaucoma          1. Angle concussion          2. Hyphema          3. Ghost cell glaucoma       2. Late-onset glaucoma with angle recession       3. Arteriovenous fistula    2. Secondary to intraocular neoplasm       1. Retinoblastoma       2. Juvenile xanthogranuloma       3. Leukemia       4. Melanoma       5. Melanocytoma       6. Iris rhabdomyosarcoma       7. Aggressive nevi of the iris    3. Secondary to uveitis       1. Open-angle glaucoma       2. Angle-blockage glaucoma          1. Synechial angle closure          2. Iris bombé with pupillary block 2. Lens-induced glaucoma    1. Subluxation–dislocation and pupillary block       1. Marfan syndrome       2. Homocystinuria    2. Spherophakia and pupillary block    3. Phacolytic glaucoma 3. Secondary to surgery for congenital cataract    1. Lens material blockage of the trabecular meshwork (acute or subacute)    2. Pupillary block    3. Chronic open-angle glaucoma associated with angle defects 4. Steroid-induced glaucoma 5. Secondary to rubeosis    1. Retinoblastoma    2. Coats disease    3. Medulloepithelioma    4. Familial exudative vitreoretinopathy 6. Secondary angle-closure glaucoma    1. Retinopathy of prematurity    2. Microphthalmos    3. Nanophthalmos    4. Retinoblastoma    5. Persistent hyperplastic primary vitreous    6. Congenital pupillary iris–lens membrane 7. Glaucoma associated with increased venous pressure    1. Carotid or dural-venous fistula    2. Orbital disease 8. Secondary to maternal rubella 9. Secondary to intraocular infection    1. Acute recurrent toxoplasmosis    2. Acute herpetic iritis |

*From Nelson LB:* Harley’s pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 294.*

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| **Table 637-9** | Recommended Pneumococcal Vaccination Schedule for Persons with Cochlear Implants | | | |
| **AGE AT FIRST PCV13 DOSE (mo)\*** | | **PCV12 PRIMARY SERIES** | **PCV13 ADDITIONAL DOSE** | **PPV23 DOSE** |
| 2-6 | | 3 doses, 2 mo apart† | 1 dose at 12-15 mo of age‡ | Indicated at ≥24 mo of age§ |
| 7-11 | | 2 doses, 2 mo apart† | 1 dose at 12-15 mo of age‡ | Indicated at ≥24 mo of age§ |
| 12-23 | | 2 doses, 2 mo apart¶ | Not indicated | Indicated at ≥24 mo of age§ |
| 24-59 | | 2 doses, 2 mo apart¶ | Not indicated | Indicated§ |
| ≥60 | | Not indicated| | Not indicated| | Indicated |

\*A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 182).

†For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.

‡The additional dose should be administered 8 wk or more after the primary series has been completed.

§Children younger than age 5 yr should complete the PCV13 series first; 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 182). (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR Recomm Rep* 49[RR-9]:1–35, 2000, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP], 2010, *MMWR Morb Mortal Wkly Rep* 59(9);258–261, 2010.)

¶Minimum interval between doses is 8 wk.

|PCV13 is not recommended generally for children age 5 yr or older.

PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

*From Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices,* MMWR Morb Mortal Wkly Rep *52(31):739–740, 2003.*

# The Ear

**3072 Part XXX** ◆ The Ear

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| **Table 637-1** | Indicators Associated with Hearing Loss |
| INDICATORS ASSOCIATED WITH SENSORINEURAL AND/OR CONDUCTIVE HEARING LOSS  *Neonates (Birth-28 Days) When Universal Screening Is Not Available*  Family history of hereditary childhood sensorineural hearing loss  In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis  Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies  Birthweight <1500 g (3.3 lb)  Hyperbilirubinemia at a serum level requiring exchange transfusion  Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics Bacterial meningitis  Apgar scores of 0-4 at 1 min or 0-6 at 5 min  Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation  Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock  *Infants and Toddlers (Age 29 Days-2 Yr) When Certain Health Conditions Develop That Require Rescreening*  Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay Bacterial meningitis and other infections associated with sensorineural hearing loss  Head trauma associated with loss of consciousness or skull fracture  Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or Jervell and Lange-Nielsen syndrome  Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics  Recurrent or persistent otitis media with effusion for 3 mo or longer Skeletal dysplasia  *Infants and Toddlers (Age 29 Days-3 Yr) Who Require Periodic Monitoring of Hearing*  Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr, and at appropriate intervals thereafter | |
| INDICATORS ASSOCIATED WITH DELAYED-ONSET SENSORINEURAL HEARING LOSS  Family history of hereditary childhood hearing loss  In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis Neurofibromatosis type 2 and neurodegenerative disorders  Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, arthritis, dermatitis) | |
| INDICATORS ASSOCIATED WITH CONDUCTIVE HEARING LOSS  Recurrent or persistent otitis media with effusion  Anatomic deformities and other disorders that affect eustachian tube function Neurodegenerative disorders | |

*Note:* At all ages, parents’ concern about hearing loss must be taken seriously even in the absence of risk factors.

*Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing: Joint Committee on Infant Hearing 1994 position statement,* Pediatrics *95:152, 1995.*

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| **Table 637-2** | Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss | |
| **LOCUS** | **GENE** | **AUDIO PHENOTYPE** |
| DFN3 | *POU3F4* | Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL |
| DFNA1 | *DIAPH1* | Low-frequency loss beginning in the 1st decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range |
| DFNA2 | *KCNQ4*  *GJB3* | Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies  Symmetric high-frequency sensorineural loss beginning in the 3rd decade |
| DFNA3 | *GJB2 GJB6* | Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment |
| DFNA6, 14,  and 38 | *WFS1* | Early-onset low-frequency sensorineural loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin |
| DFNA8, and 12 | *TECTA* | Early-onset stable bilateral hearing loss, affecting mainly mid to high frequencies |
| DFNA10 | *EYA4* | Progressive loss beginning in the 2nd decade as a flat to gently sloping audio profile that becomes steeply sloping with age |
| DFNA11 | *MYO7A* | Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age |
| DFNA13 | *COL11A2* | Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range |
| DFNA15 | *POU4F3* | Bilateral progressive sensorineural loss beginning in the 2nd decade |

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| **Table 637-2** | Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss—cont’d | |
| **LOCUS** | **GENE** | **AUDIO PHENOTYPE** |
| DFNA20, and 26 | *ACTG1* | Bilateral progressive sensorineural loss beginning in the 2nd decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases |
| DFNA22 | *MYO6* | Postlingual, slowly progressive, moderate to severe hearing loss |
| DFNB1 | *GJB2, GJB6* | Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other *GJB2* SNHL-causing allele variant; in children carrying 2 *GJB2* SNHL-causing missense mutations, severe to profound deafness is not observed |
| DFNB3 | *MYO7A* | Severe to profound sensorineural hearing loss |
| DFNB4 | *SLC26A4* | DFNB4 and Pendred syndrome (see Table 637-3) are allelic. DFNB4 hearing loss is associated with dilation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common |
| DFNB7, and 11 | *TMC1* | Severe-to-profound prelingual hearing impairment |
| DFNB9 | *OTOF* | *OTOF*-related deafness is characterized by 2 phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy. The nonsyndromic hearing loss is bilateral severe-to-profound congenital deafness |
| DFNB12 | *CDH23* | Depending on the type of mutation, recessive mutations of *CDH23* can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa |
| DFNB16 | *STRC* | Early-onset nonsyndromic autosomal recessive sensorineural hearing loss |
| mtDNA 1555A > G | *12S rRNA* | Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy |

SNHL, sensorineural hearing loss.

*Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children,* Lancet *365:879–890, 2005.*

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| **Table 637-3** | Common Types of Syndromic Sensorineural Hearing Loss | | |
| **SYNDROME** | | **GENE** | **PHENOTYPE** |
| DOMINANT  Waardenburg (WS1) | | *PAX3* | Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.  Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.  Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree.  Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.  Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic. |
| Waardenburg (WS2) | | *MITF*, others |
| Branchiootorenal | | *EYA1* |
| CHARGE syndrome | | *CHD7* |
| Goldenhar syndrome | | Unknown |
| RECESSIVE  Pendred syndrome | | *SLC26A4* | Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter.  Nephritis, deafness, lens defects, retinitis. Can lead to bilateral sensorineural hearing loss in the 2,000-8,000 Hz range. The hearing loss develops gradually and is not generally present in early infancy.  Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nyctalopia become severe enough to be noticeable).  Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.  Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function. |
| Alport syndrome | | *COL4A3, COL4A4,* and  *COL4A5* |
| Usher syndrome type 1 (USH1)  Usher syndrome type 2 (USH2) | | *USH1A, MYO7A, USH1C, CDH23, USH1E, PCDH15, USH1G*  *USH2A, USH2B, USH2C,*  others |
| Usher syndrome type 3 (USH3) | | *USH3* |

*Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children,* Lancet *365:879–890, 2005.*

**3076 Part XXX** ◆ The Ear

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| **Table 637-5** | Hearing Handicap | as a Function of Average Hearing Threshold | | Level of the Better Ear | |
| **AVERAGE THRESHOLD LEVEL (dB) AT 500-2,000 Hz (ANSI)** | **DESCRIPTION** | **COMMON CAUSES** | **WHAT CAN BE HEARD WITHOUT AMPLIFICATION** | **DEGREE OF HANDICAP (IF NOT TREATED IN 1ST YR OF LIFE)** | **PROBABLE NEEDS** |
| 0-15 | Normal range | Conductive hearing loss | All speech sounds | None | None |
| 16-25 | Slight hearing loss | Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL | Vowel sounds heard clearly, may miss unvoiced consonant sounds | Mild auditory dysfunction in language learning  Difficulty in perceiving some speech sounds | Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating |
| 26-30 | Mild | Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL | Hears only some speech sounds, the louder voiced sounds | Auditory learning dysfunction  Mild language retardation  Mild speech problems Inattention | Hearing aid Lip reading  Auditory training Speech therapy Appropriate surgery |
| 31-50 | Moderate hearing loss | Chronic otitis, ear canal/middle ear anomaly, SNHL | Misses most speech sounds at normal conversational level | Speech problems Language retardation Learning dysfunction Inattention | All of the above, plus consideration of special classroom situation |
| 51-70 | Severe hearing loss | SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement | Hears no speech sound of normal conversations | Severe speech problems Language retardation Learning dysfunction Inattention | All of the above; probable assignment to special classes |
| 71+ | Profound hearing loss | SNHL or mixed | Hears no speech or other sounds | Severe speech problems Language retardation Learning dysfunction Inattention | All of the above; probable assignment to special classes or schools |

ANSI, American National Standards Institute; SNHL, sensorineural hearing loss; TM, tympanic membrane.

*Modified from Northern JL, Downs MP:* Hearing in children, *ed 4, Baltimore, 1991, Williams & Wilkins.*

Screen results?

Referral to audiology and speech evaluation

Objective screens scheduled at: Newborn and 4, 5, 6, 8,

10, 12, 15, and 18 yr

Office visit

Otolaryngology, genetics, ENT, speech referral for diagnostic testing

No risk No Yes Normal

Schedule early

Stop return

(~6 mo)

Evaluation Abnormal

results?

Ongoing risk

(e.g., CMV or other high-risk diagnoses)

Risk

present

Risk

assessment

Table 629-1

Normal

Abnormal

Objective

screen

Yes

Visit with

scheduled objective screen?

No

**Figure 637-2** Hearing-assessment algorithm within an office visit. CMV, cytomegalovirus; ENT, ear, nose, and throat. *(From Harlor AD Jr, Bower C: Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening,* Pediatrics *124:1252–1263, 2009, Fig. 1, p. 1254.)*

**Chapter 637** ◆ Hearing Loss **3077**

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| **Table 637-6** | | Criteria for Referral for Audiologic Assessment |
| **AGE (mo)** | **REFERRAL GUIDELINES FOR CHILDREN WITH “SPEECH” DELAY** | |
| 12 | No differentiated babbling or vocal imitation | |
| 18 | No use of single words | |
| 24 | Single-word vocabulary of ≤10 words | |
| 30 | <100 words; no evidence of 2 word combinations; unintelligible | |
| 36 | <200 words; no use of telegraphic sentences; clarity  <50% | |
| 48 | <600 words; no use of simple sentences; clarity ≤80% | |

*From Matkin ND: Early recognition and referral of hearing-impaired children,*

Fever Lethargy/malaise/irritability Otalgia

Bulging or erythematous TM

Otolaryngology Admit for

consult IV antibiotic therapy

No

Yes

CT scan with contrast Treat as acute

otitis media

Postauricular abscess?

Mastoid cortical bony erosion? Coalescence of mastoid air cells?

No

Yes

CT scan with contrast Postauricular signs or symptoms?

Otolaryngology consult (pain, erythema, or tenderness)

± Neurosurgery consult

No

Yes

Proptotic ear?

Postauricular edema or fluctuant mass?

EAC or neck mass or edema?

Facial nerve weakness?

Vestibular signs and symptoms? Neurologic signs and symptoms?

Yes

No

Transition to oral antibiotics

and discharge home with close PCP follow-up

Otolaryngology

consult

Clinical improvement in ≤24 hr?

Pediatr Rev *6:151–156, 1984. Reproduced by permission of Pediatrics.*

|  |  |  |
| --- | --- | --- |
| **Table 637-7** | | Guidelines for Referral of Children with Suspected Hearing Loss |
| **AGE (mo)** | **NORMAL DEVELOPMENT** | |
| 0-4 | Should startle to loud sounds, quiet to mother’s voice, momentarily cease activity when sound is presented at a conversational level | |
| 5-6 | Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult | |
| 7-12 | Should correctly localize to sound presented in any plane  Should respond to name, even when spoken quietly | |
| 13-15 | Should point toward an unexpected sound or to familiar objects or persons when asked | |
| 16-18 | Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented | |
| 19-24 | Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry | |

PURE-TONE AUDIOGRAM

Frequency (cycles/sec)

125

—10

0

10

20

250 500 1000 2000 4000 8000

### **Figure 640-7** Diagnosis and treatment algorithm for cases of sus-pected acute mastoiditis.

30

40

50

60

70

80

90

100

110

AUDIOGRAM KEY

Air Bone

|  |  |
| --- | --- |
|  |  |
|  |  |

Right  Left

###### **Figure 637-3** Audiogram showing bilateral conductive hearing loss.

**3084 Part XXX** ◆ The Ear

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| --- | --- | --- |
| **Table 640-1** | Treatments for Otalgia in Acute Otitis Media | |
| **TREATMENT MODALITY** | | **COMMENTS** |
| Acetaminophen, ibuprofen | | Effective analgesia for mild to moderate pain. Readily available. Mainstay of pain management for AOM |
| Home remedies (no controlled studies that directly address effectiveness)  Distraction  External application of heat or cold Oil drops in external auditory canal | | May have limited effectiveness |
| Benzocaine, procaine, lidocaine (topical) | | Additional, but brief, benefit over acetaminophen in patients older than 5 yr |
| Naturopathic agents | | Comparable to amethocaine/phenazone drops in patients older than 6 yr |
| Homeopathic agents | | No controlled studies that directly address pain |
| Narcotic analgesia with codeine or analogs | | Effective for moderate or severe pain. Requires prescription; risk of respiratory depression, altered mental status, gastrointestinal tract upset, and constipation |
| Tympanostomy/myringotomy | | Requires skill and entails potential risk |

*From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media.* Pediatrics *131:e964-e999, 2013, Table 3.*

Patient age 2 yr or older with diffuse AOE

Prescribe analgesics based on pain severity

**No**

**No**

\*Factors requiring systemic therapy include diabetes, immune deficiency, or inability to effectively deliver topical therapy despite aural toilet

**Yes**



Prescribe topical therapy with a nonototoxic preparation

Perform aural toilet to remove obstructing debris; place wick if edema prevents drug delivery

Treat other illness

Reassess patient

Illness other than AOE?

Complete course of therapy

Assess drug delivery, adherence to therapy, need to change therapy

Perforated tympanic membrane (known or suspected) or tympanostomy tube?

Prescribe topical therapy based on benefits, cost, compliance, preference

Educate patient or caregiver on how to administer topical drops

Obstructed ear canal

Clinically improved in 48-72 hr?

A

**No**

Prescribe systemic antimicrobial active against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, with or without topical therapy, plus other management based on underlying condition

Go to A

below

|  |  |  |
| --- | --- | --- |
| Extension outside ear canal or host factors\* requiring systemic therapy? | | **Yes** |
|  |
|  | **No** | |

**Yes**

**No**

**Yes**

**Yes**

|  |  |
| --- | --- |
| **Table 637-4** | Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children |
| CONGENITAL INFECTIONS  Cytomegalovirus  Lymphocytic choriomeningitis virus Rubella virus  *Toxoplasma gondii Treponema pallidum* | |
| ACQUIRED INFECTIONS  *Borrelia burgdorferi* Epstein-Barr virus *Haemophilus influenzae* Lassa virus  Measles virus Mumps virus  *Neisseria meningitidis* Nonpolio enteroviruses *Plasmodium falciparum Streptococcus pneumoniae* Varicella-zoster virus | |

**Figure 639-1** Flow chart for managing acute otitis externa (AOE). *(From Rosenfeld RM, Brown L, Cannon CR, et al: Clinical practice guideline: acute otitis externa,* Otolaryngol Head Neck Surg *134:S4– S23, 2006. Copyright 2006 American Academy of Otolaryngology-Head and Neck Surgery Founda- tion, Inc.)*

**3088 Part XXX** ◆ The Ear

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| **Table 640-2** | Recommendations for | Initial | Management for Uncomplicated Acute Otitis Media\* | | |
| **AGE** | **OTORRHEA WITH AOM\*** | **UNILATERAL OR BILATERAL AOM\* WITH SEVERE SYMPTOMS†** | | **BILATERAL AOM\* WITHOUT OTORRHEA** | **UNILATERAL AOM\* WITHOUT OTORRHEA** |
| 6 mo to 2 yr | Antibiotic therapy | Antibiotic therapy | | Antibiotic therapy | Antibiotic therapy or additional observation |
| ≥2 yr | Antibiotic therapy | Antibiotic therapy | | Antibiotic therapy or additional observation | Antibiotic therapy or additional observation‡ |

\*Applies only to children with well-documented AOM with high certainty of diagnosis.

†A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.

‡This plan of initial management provides an opportunity for shared decision making with the child’s family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.

NOTE: For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.

*From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media.* Pediatrics *131:e964–e999, 2013, Table 4.*

Or

te

inflammation

No

inflammation

Yes

Otitis media with effusion (OME)

Acute otitis media (AOM)

Acute purulent otorrhea not due to otitis externa

At least one of:

1. Substantial ear pain, including unaccustomed tugging or rubbing of the ear
2. Marked redness of the TM
3. Distinct fullness or bulging of the TM

Yes

At least two of:

1. Abnormal TM color:

white, yellow, amber, or blue

1. Opacification not due to scarring
2. Decreased or absent mobility

Bubbles or air–fluid interfaces behind the TM

Yes

Yes

|  |  |  |  |
| --- | --- | --- | --- |
| Middle-ear effusion (MEE) | | | |
| acute |  |  | Acu |

###### **Figure 640-1** Algorithm for distinguishing between acute otitis media and otitis media with effusion. TM, tympanic membrane.

**3092 Part XXX** ◆ The Ear

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| **Table 640-3** | Recommended Antibiotics for (Initial or Delayed) Treatment and for Patients Who Have Failed Initial Antibiotic Treatment | | | |
| **Initial Immediate or Delayed Antibiotic Treatment** | | | **Antibiotic Treatment After 48-72 hr of Failure of Initial Antibiotic Treatment** | |
| **RECOMMENDED**  **FIRST-LINE TREATMENT** | | **ALTERNATIVE TREATMENT**  **(IF PENICILLIN ALLERGY)** | **RECOMMENDED FIRST-LINE**  **TREATMENT ALTERNATIVE TREATMENT** | |
| Amoxicillin (80-90 mg/kg/day in 2 divided doses) | | Cefdinir‡ (14 mg/kg/day in 1 or 2 doses) | Amoxicillin-clavulanate\* (90 mg/kg/day of amoxicillin, with  6.4 mg/kg/day of  clavulanate in 2 divided doses) | Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement; max 3 doses)  Clindamycin (30-40 mg/kg/day in 3 divided doses), with or without third-generation cephalosporin |
| or | | Cefuroxime‡ (30 mg/kg/day in 2 divided doses) | or | Failure of second antibiotic |
| Amoxicillin-clavulanate\* (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate [amoxicillin : clavulanate ratio, 14 : 1] in 2 divided doses) or Ceftriaxone (50 mg IM or IV for 3 days, every other day until improvement; max 3 doses) | | Cefpodoxime‡  (10 mg/kg/day in 2 divided doses)  Ceftriaxone‡ (50 mg IM or IV per day for 1 or 3 days) | Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement or for a maximum of 3 doses) | Clindamycin (30-40 mg/kg/day in 3 divided doses) with or without third-generation cephalosporin  Tympanocentesis† Consult specialist† |

IM, intramuscular; IV, intravenous.

\*May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis–conjunctivitis syndrome.

†Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious disease specialist consultation.

‡Cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross reactivity with penicillin allergy on the basis of their distinct chemical structures.

*From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media.* Pediatrics *131:e964–e999, 2013, Table 5.*

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 640-5** | Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess | | | | | | |
| **DISEASE** | | **CREASE\*** | **Postauricular Signs and Symptoms**  **ERYTHEMA MASS** | | **TENDERNESS** | **EXTERNAL CANAL INFECTION** | **MIDDLE-EAR EFFUSION** |
| Acute mastoiditis with periosteitis | | May be absent | Yes | No | Usually | No | Usually |
| Acute mastoiditis with subperiosteal abscess | | Absent | Maybe | Yes | Yes | No | Usually |
| Periosteitis of pinna with postauricular extension | | Intact | Yes | No | Usually | No | No |
| External otitis with postauricular extension | | Intact | Yes | No | Usually | Yes | No |
| Postauricular lymphadenitis | | Intact | No | Yes (circumscribed) | Maybe | No | No |

\*Postauricular crease (fold) between pinna and postauricular area.

*From Bluestone CD, Klein JO, editors:* Otitis media in infants and children*, ed 3, Philadelphia, 2001, WB Saunders, p. 333.*

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1

Child aged 2 mo through 12 yr with uncomplicated AOM presents to office

2

Is pain present?

The clinician assesses pain.

Clinician recommends treatment to reduce pain.

Go to Box 6.

A diagnosis of acute otitis media requires:

1. History of acute onset of signs and symptoms
2. The presence of middle-ear effusion
3. Signs and symptoms of middle-ear inflammation
   1. moderate to severe bulging of the TM *or* new onset of otorrhea not due to otitis externa
   2. mild bulging of the TM and recent (<48 hr) onset of ear pain or intense TM erythema

A **diagnosis of AOM should *not*** be made in children without MEE.

3

4

No

**Yes**

5

6 9 10

Go to Box 14.

Amoxicillin at a dose of 80-90 mg/kg/day is the initial antibacterial of choice for most children.

|  |  |  |
| --- | --- | --- |
| Does the child have fever  ≥39°C and/or moderate or severe otalgia? | | **No** |
|  |
| **Yes** |  | |

7

Child is observed for 48 to 72 hr with assurance of appropriate follow-up.

Go to Box 14.

|  |  |  |
| --- | --- | --- |
| Is observation an appropriate initial treatment option?\* | | **No** |
|  |
| **Yes** |  | |

11

12

Child managed with appropriate antibacterial therapy.

Go to Box 14.

8

Criteria for antibacterial treatment or observation in children with nonsevere illness:\*

1. <6 mo: antibacterial treatment
2. 6 mo to 2 yr antibacterial treatment with cer- tain diagnosis or severe illness or observation with uncertain diagnosis and nonsevere illness
3. 2 yr and older: antibacterial treatment if severe illness or observe with nonsevere illness with certain diagnosis; observation for uncertain diagnosis

\*Caregiver is informed and agrees to the option of observation.

Caregiver is able to monitor child and return should condition worsen.

Systems are in place for ready communication with the clinician, reevaluation, and obtaining medication if necessary.

13

14

|  |  |  |
| --- | --- | --- |
| Did patient respond to initial treatment intervention (either antibacterial treatment or observation)? | | **No** |
|  |
| 15 **Yes** |  | |

16

Clinician should initiate antibacterial treatment for children initially managed with observation or change antibacterial treatment for patients initially managed with antibacterial therapy.

Is diagnosis of AOM confirmed?

Clinician reassesses and confirms diagnosis of AOM.

Assess for other causes of illness and manage appropriately.

17 18

No

Patient follow-up as appropriate.

19 **Yes**

Antibacterial choice should be based on the likely pathogen(s) present and on clinical experience.

**Figure 640-6** Management of acute otitis media. *(From Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media,* Pediatrics *113:1451–1465, 2004.)*

# The Skin

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| **Table 645-2** Characteristics of Cutaneous Signs of Systemic Diseases | | | | | | |
| **DISEASE** | **AGE OF ONSET** | **SKIN LESIONS** | **DISTRIBUTION** | **DIAGNOSTIC EVALUATION(S) AND FINDINGS** | **ASSOCIATED SYMPTOMS/SIGNS** | **DIFFERENTIAL DIAGNOSIS** |
| Systemic lupus erythematosus | Any | Erythematous patches; palpable purpura; livedo reticularis; Raynaud phenomenon; thrombocytopenic and nonthrombocytopenic purpura | Photodistribution; “malar” face | ANA panel Anti–dsDNA  Leukopenia/lymphopenia Thrombocytopenia Complement levels Urinalysis | Arthritis Nephritis Cerebritis Serositis | Seborrheic dermatitis Atopic dermatitis Juvenile dermatomyositis |
| Discoid lupus erythematosus | Any | Annular, scaly plaques; atrophy; dyspigmentation | Photodistribution | ANA | Scarring | Subacute cutaneous lupus Polymorphous light  eruption  Juvenile dermatomyositis |
| Neonatal lupus erythematosus | Newborn | Annular, erythematous, scaly plaques | Head/neck | ANA  Anti-Ro (SSA), anti-La (SSB) | Heart block Thrombocytopenia | Tinea capitis Atopic dermatitis  Seborrheic dermatitis |
| Juvenile dermatomyositis | Any | Erythematous to violaceous scaly, macules; discrete papules overlying knuckles | Periocular face; shoulder girdle; extensor extremities; knuckles; palms | ANA AST ALT  Aldolase Creatine kinase  Lactate dehydrogenase | Proximal muscle weakness  Calcifications Vasculopathy | Atopic dermatitis  Allergic contact dermatitis Lupus erythematosus |
| Henoch-Schönlein purpura | Childhood and adolescence | Purpuric papules and plaques | Buttocks; lower extremities | Urinalysis  Blood urea nitrogen/creatinine ratio  Skin biopsy | Abdominal pain Arthritis | Vasculitis Drug eruption  Infantile hemorrhagic edema  Viral exanthem |
| Kawasaki disease | Infancy, childhood | Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation | Diffuse | Leukocytosis ESR  C-reactive protein Thrombocytosis | Strawberry tongue Conjunctivitis Lymphadenopathy Cardiovascular  complications | Viral syndrome Drug eruption Staphylococcal/  streptococcal illness |
| Inflammatory bowel disease | Childhood and adolescence | Aphthae; erythema nodosum; pyoderma gangrenosum; thrombophlebitis | Oral ulcers; perianal fissures | Skin biopsy | Abdominal pain Diarrhea Cramping Arthritis Conjunctivitis | Behçet syndrome Vasculitis  *Yersinia* colitis |
| Sweet syndrome | Any | Infiltrated erythematous, edematous plaques | Diffuse | Skin biopsy Leukocytosis ESR | Fever  Flu-like illness Conjunctivitis | Infection Urticaria  Erythema multiforme Urticarial vasculitis |
| Graft-versus-host disease | Any | Acute: erythema, papules, vesicles, bulla | Head and neck; palms/soles; diffuse | Skin biopsy Liver function | Fever Mucositis Hepatitis | Drug eruption Infectious exanthem |
| Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) | Any | Erythema; urticarial macules and plaques | Diffuse | Liver function Eosinophilia  Atypical lymphocytosis | Perioral edema Lymphadenopathy Fever  Hepatitis | Stevens-Johnson syndrome  Infectious exanthem |
| Serum sickness–like reaction (SSLR) | Any | Edematous, urticarial plaques | Acral; diffuse | None | Fever Lymphadenopathy Arthritis, nephritis | Kawasaki disease Urticaria |

ANA, antinuclear antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren’s syndrome A/B.

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**3112 Part XXXI** ◆ The Skin

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| **Table 645-3** | Drug Eruptions in Pediatric Patients | | | |
| **ERUPTION** | | **KEY DRUGS** | **LESIONAL PATTERN** | **MUCOSAL CHANGES** |
| Urticaria | | Penicillins, cephalosporins, sulfonamides, aspirin/ NSAIDs, radiocontrast media, TNF inhibitors | Pruritic erythematous wheals | None |
| Angioedema | | Aspirin/NSAIDs, angiotensin-converting enzyme inhibitors | Swelling of subcutaneous and deep dermal tissues | May be present |
| Serum sickness–like reaction | | Cephalosporins, penicillins, minocycline, bupropion, sulfonamides | Annular urticarial plaques | None |
| Exanthematous | | Any drug | Erythematous macules and/or papules | None |
| Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) | | Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline | Edema; erythematous macules and/or papules; sometimes vesicles or bullae | May be present |
| Lichenoid | | Captopril, enalapril, β-blockers, gold salts, hydrochlorothiazide, hydroxychloroquine, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs | Discrete flat-topped, reddish purple papules and plaques | May be present |
| Fixed drug | | Sulfonamides, ibuprofen, acetaminophen, tetracyclines, pseudoephedrine, barbiturates, lamotrigine, metronidazole, penicillin | Solitary to few erythematous, hyperpigmented plaques | Unusual |
| Pustular (acute generalized exanthematous pustulosis) | | β-Lactam antibiotics, macrolides, clindamycin, terbinafine, calcium channel blockers, antimalarials | Generalized small pustules and papules | Unusual |
| Acneiform | | Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, tetracycline, B vitamins, azathioprine | Follicle-based inflammatory papules and pustules predominate | None |
| Pseudoporphyria | | NSAIDs, cyclooxygenase-2 inhibitors, tetracyclines, furosemide | Photodistributed blistering and skin fragility | None |
| Vasculitis | | Penicillins, NSAIDs, sulfonamides, cephalosporins | Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers | Rarely |
| Stevens-Johnson/toxic epidermal necrolysis | | Sulfonamides, anticonvulsants, NSAIDs, allopurinol, dapsone | Target lesions, bullae, epidermal necrosis with detachment | Present |
| Drug-induced lupus | | Minocycline, procainamide, hydralazine, isoniazid, penicillamine, carbamazepine, chlorpromazine, infliximab | Rarely has skin manifestations but may be urticarial, vasculitic, erythematous | Rare |

NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

|  |  |
| --- | --- |
| **Table 646-1** | Potency of Topical Glucocorticosteroids |
| CLASS 1—SUPERPOTENT  Betamethasone dipropionate, 0.05% gel, ointment Clobetasol propionate cream, ointment, 0.05% Halobetasol propionate cream, ointment, 0.05% | |
| CLASS 2—POTENT  Betamethasone dipropionate cream 0.05% Desoximetasone cream, ointment, gel 0.05% and 0.25% Fluocinonide cream, ointment, gel, 0.05% | |
| CLASS 3—UPPER MID-STRENGTH  Betamethasone dipropionate cream, 0.05% Betamethasone valerate ointment, 0.1% Fluticasone propionate ointment, 0.005% Mometasone furoate ointment, 0.1% Triamcinolone acetonide cream, 0.5% | |
| CLASS 4—MID-STRENGTH  Desoximetasone cream, 0.05% Fluocinolone acetonide ointment, 0.025% Triamcinolone acetonide ointment, 0.1% | |
| CLASS 5—LOWER MID-STRENGTH  Betamethasone valerate cream/lotion, 0.1% Fluocinolone acetonide cream, 0.025% Fluticasone propionate cream, 0.05% Triamcinolone acetonide cream/lotion, 0.1% | |
| CLASS 6—MILD STRENGTH  Desonide cream, 0.05% | |
| CLASS 7—LEAST POTENT  Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone | |

|  |  |  |  |
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| **Table 648-1** | | Freiden’s Classification of Aplasia Cutis Congenita | |
| **GROUP** | **DEFINITION** | | **INHERITANCE** |
| 1 | Isolated scalp involvement; may be associated with single defects | | AD |
| 2 | Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele | | AD |
| 3 | Scalp ACC with epidermal nevus | | Sporadic |
| 4 | ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele | | Sporadic |
| 5 | ACC with placental infarcts, and/ or fetus papyraceus | | Sporadic |
| 6 | ACC with epidermolysis bullosa | | AD or AR |
| 7 | ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet | | AD or AR |
| 8 | ACC caused by teratogens (e.g., varicella, herpes, methimazole) | | Sporadic |
| 9 | ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p−, deletion Xp22.1, ectodermal dysplasia, Johanson- Blizzard syndrome, Adams- Oliver syndrome) | | Variable |

ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.