

Table 589-1 Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β -cell destruction ultimately leading to complete insulin deficiency)	
A. Immune mediated	
B. Idiopathic	
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)	
A. Typical	
B. Atypical	
III. Genetic defects of β -cell function	
A. MODY (maturity-onset diabetes of the young) syndromes	
1. MODY 1 chromosome 20, HNF4 α	
2. MODY 2 chromosome 7, glucokinase	
3. MODY 3 chromosome 12, HNF1 α , TCF-1	
4. MODY 4 chromosome 13, IPF-1	
5. MODY 5 chromosome 17, HNF1 β , TCF-2	
6. MODY 6 chromosome 2q32, neuro-D $_1/\beta_2$	
B. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, diabetes mellitus, deafness)	
C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin—chromosome 4p	
1. Wolfram locus 2—chromosome 4q22-24	
2. Wolfram mitochondrial	
D. Thiamine responsive megaloblastic anemia and diabetes	
IV. Drug or chemical induced	
A. Antirejection—cyclosporine, sirolimus	
B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)	
C. L-Asparaginase	
D. β -Adrenergic blockers	
E. Vacor (rodenticide)	
F. Phenytoin (Dilantin)	
G. α -Interferon	
H. Diazoxide	
I. Nicotinic acid	
J. Pentamidine	
V. Diseases of exocrine pancreas	
A. Cystic fibrosis-related diabetes	
B. Trauma—pancreatectomy	
C. Pancreatitis—ionizing radiation	
D. Others	
VI. Infections	
A. Congenital rubella	
B. Cytomegalovirus	
C. Hemolytic-uremic syndrome	
VII. Variants of type 2 diabetes	
A. Genetic defects of insulin action	
1. Rabson-Mendenhall syndrome	
2. Leprechaunism	
3. Lipoatrophic diabetes syndromes	
4. Type A insulin resistance—acanthosis	
B. Acquired defects of insulin action	
1. Endocrine tumors—rare in childhood	
C. Pheochromocytoma	
D. Cushing	
E. Others	
1. Antiinsulin receptor antibodies	
VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency	
A. Prader-Willi syndrome, chromosome 15	
B. Down syndrome, chromosome 21	
C. Turner syndrome	
D. Klinefelter syndrome	
E. Others	
1. Bardet-Biedl	
2. Alström	
3. Werner	
F. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)	
G. Celiac disease	
H. Autoimmune polyendocrinopathy	
IX. Gestational diabetes	
X. Neonatal diabetes	
A. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1 β , others	
B. Permanent—agenesis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others	

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)	—	\pm	\pm	+	+
Uterus present*	+	+	Usually	—	—
Increased skin pigmentation	\pm	—	—	—	—
Sick baby	\pm	—	—	—	\pm
Dysmorphic features	—	\pm	—	—	—
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with \pm Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture For AR assay Or DNA screening for AR mutations in blood cells	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.

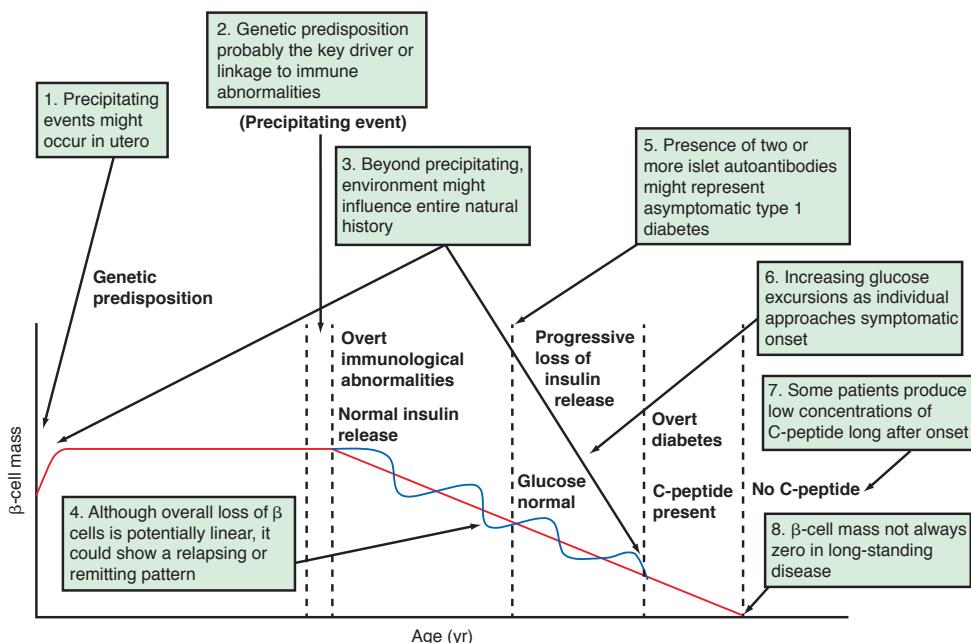


Figure 589-3 The natural history of type 1 diabetes—a 25 yr old concept revisited. A recreation of the model of type 1 diabetes, originally proposed in 1986, is shown in black. Additions and conjectures based on recent knowledge gains are shown in green. (From Atkinson MA, Eisenbarth GS, Michels AW: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

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

*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.

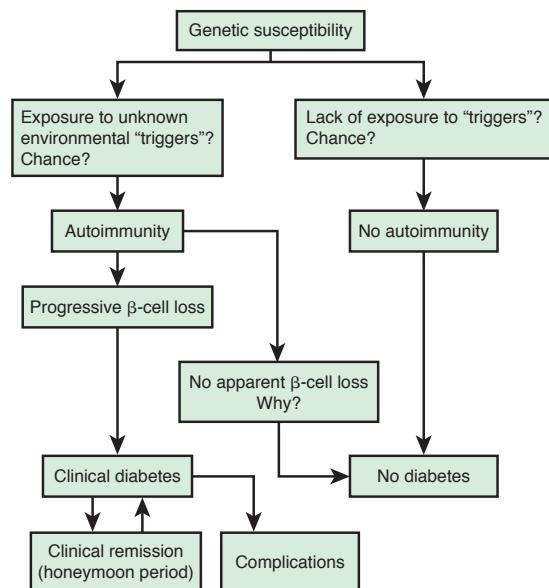


Figure 589-4 Schematic of the natural history of type 1 diabetes mellitus. Unknown triggers act upon a genetically susceptible host to trigger autoimmunity. Some proportion of those with autoimmunity develop progressive β-cell loss that eventually leads to clinical diabetes. This is followed by temporary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

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	

2770 Part XXVI ◇ The Endocrine System

Table 589-4 Classification of Diabetic Ketoacidosis

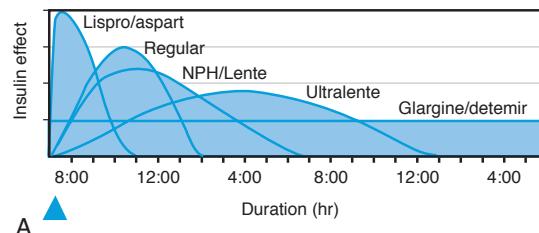
	NORMAL	MILD	MODERATE	SEVERE*
CO ₂ (mEq/L, venous) [†]	20-28	16-20	10-15	<10
pH (venous) [†]	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

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

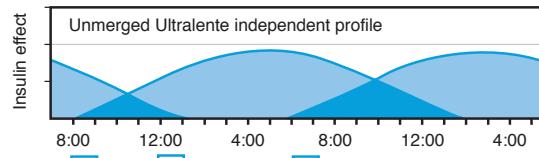
[†]CO₂ and pH measurement are method dependent; normal ranges may vary.

Table 589-5 Starting Doses of Insulin (units/kg/day)

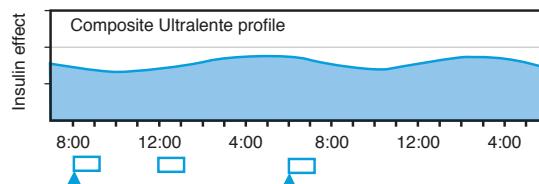
	NO DIABETIC KETOACIDOSIS	DIABETIC KETOACIDOSIS
Prepubertal	0.25-0.50	0.75-1.0
Pubertal	0.50-0.75	1.0-1.2
Postpubertal	0.25-0.50	0.8-1.0



A



B



C

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 15 for 7 hr; neutral protamine Hagedorn/Lente, peak 12 for 12 hr; Ultralente, peak 9 for 18 hr; glargin, 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 cumulative 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.

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 = $\frac{85 \text{ mL/kg} + \text{maintenance} - \text{bolus}}{23 \text{ hr}}$ 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; CO ₂ ≥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 = $\frac{(85 \text{ mL} \times 30) + 1750 \text{ mL} - 300 \text{ mL}}{23 \text{ hr}} = \frac{175 \text{ mL}}{\text{hr}}$ (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.

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		
NUTRIENT	(%) OF CALORIES	RECOMMENDED DAILY 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		
<i>Energy:</i> If using measured diet, reevaluate prescribed energy level at least every 3 mo.		
<i>Protein:</i> 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.		
<i>Alcohol:</i> Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.		
<i>Snacks:</i> Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).		
<i>Alternative sweeteners:</i> Use of a variety of sweeteners is suggested.		
<i>Educational techniques:</i> 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.		
<i>Eating disorders:</i> Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.		
<i>Exercise:</i> Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.		

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.

*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.

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.

Table 589-9 Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for Each Age Group

AGE GROUP (yr)	TARGET PREMEAL BG RANGE (mg/dL)	30-DAY AVERAGE BG RANGE (mg/dL)	TARGET HbA _{1c} (%)
<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 HbA_{1c} is 4.5-5.7% (95% confidence interval).

BG, blood glucose; HbA_{1c}, hemoglobin A_{1c}.

Table 589-13 Testing for Type 2 Diabetes in Children

- 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

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

Table 589-10 Guidelines for Sick Day Management
GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN

URINE KETONE STATUS	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.

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	Insulin sensitizer				Gastrointestinal disturbance, lactic acidosis	Avoid in hepatic or renal impairment
Metformin			1500-2500	2-3		
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		
Glyburide		20-24+	XL: 5-10	1		
Glimepiride		24+	2.5-10 2-4	1 or divided 1		
Glitinides	Promote insulin secretion					Titrate carefully in renal or hepatic dysfunction
Repaglinide		≤24	2-16	3		
Nateglinide		4	360	3		
α-Glucosidase inhibitors	Slow hydrolysis and absorption of complex carbohydrates		150-300	3 (with meals)	Transient gastrointestinal disturbances	
Acarbose			150-300	3 (with meals)		
Miglitol						
Thiazolidinedione	Peripheral insulin sensitizer				Upper respiratory tract infection, headache, edema, weight gain	
Rosiglitazone			4-8	1 or divided		
Pioglitazone			15-45	1		
Sitagliptin	GLP-1 receptor agonist	24	50-100	1	Upper respiratory tract infection, sore throat, diarrhea	No data in children or adolescents

Table 589-16 Summary of MODY Types and Special Clinical Characteristics

	GENE MUTATED	FUNCTION	SPECIAL FEATURE
MODY1	HNF4 α	Transcription factor	Decreased levels of triglycerides, apolipoproteins AI 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	HNF1 α	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	HNF1 β	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.**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 1 α /4 α ; 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.

Table 589-18 Clinical and Biochemical Features of Inherited Lipodystrophies

Subtype	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
	BSCL1	BSCL2	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 skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid features common	Acromegaloid features common	Frequent muscle hypertrophy; some have overlap features of muscular dystrophy	Nil specific
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe associated with pancreatitis	Severe associated with 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		

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

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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The Nervous System

Table 590-3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK	HEADACHE
CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions	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)
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	HEAD TRAUMA
Obtain an MRV if the infarct does not follow an arterial distribution	CT without contrast initially
CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation	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	EPILEPSY
CT if <24 hr; MRI if >24 hr	MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected
MRI and MRA to assess for underlying vascular malformation, tumor, etc.	PET
Catheter angiography if MRA is nondiagnostic	Interictal SPECT
ARTERIOVENOUS MALFORMATION	BRAIN TUMOR
CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible	MRI with and without gadolinium
Catheter angiography if noninvasive imaging is nondiagnostic	MRS
	PET
CEREBRAL ANEURYSM	MULTIPLE SCLEROSIS
CT without contrast for acute subarachnoid hemorrhage	MRI with and without gadolinium
MRA or CTA to identify the aneurysm	Obtain sagittal FLAIR images
Catheter angiography may be necessary in some cases	
TCD to detect vasospasm	MENINGITIS OR ENCEPHALITIS
	CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination
HYPOXIC-ISCHEMIC BRAIN INJURY	MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis
Ultrasound in infants	
If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI	BRAIN ABSCESS
In older children, CT if unstable; otherwise, MRI	MRI with and without gadolinium
MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes	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	MOVEMENT DISORDERS
MRI, particularly T2-weighted and FLAIR images	MRI with and without gadolinium
Diffusion-weighted images may be useful in distinguishing acute and chronic changes	PET
MRS, SPECT, and PET may be useful in certain disorders	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.

Table 591-5 Commonly Used Clinical Genetic Classifications of Craniosynostosis

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 FGFR2 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 syndrome	Mutation in FGFR3
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 syndrome	Mutation in FBXO1

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

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

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 craniostenosis, 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 or 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 paraparesia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.

From Sheri 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.

Table 591-3 Causes of Microcephaly

CAUSES	CHARACTERISTIC FINDINGS
PRIMARY (GENETIC)	
Familial (autosomal recessive)	Incidence 1 in 40,000 live births 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
<i>Syndromes</i>	
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)	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 Incidence 1 in 6,500 live births
Cri-du-chat (5 p-)	Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry Incidence 1 in 50,000 live births
Cornelia de Lange	No specific neuropathology Prenatal and postnatal growth delay; synophrys; thin, downturned upper lip
Rubinstein-Taybi	Proximally placed thumb 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)	
<i>Congenital Infections</i>	
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
Toxoplasmosis	Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification
<i>Drugs</i>	
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
<i>Other Causes</i>	
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
Hypoxic-ischemic encephalopathy	Further studies show no abnormalities with maternal fever Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI

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, hypertelorism
Multiple		Oxycephaly	Tower skull with undeveloped sinuses and shallow orbits, and elevated intracranial pressure

CSO, craniosynostosis; OFC, occipital-frontal circumference.

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

Table 592-2 Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly		
	DEFORMATIONAL	SYNOSTOTIC
Birth history	<ul style="list-style-type: none"> Intrauterine compression Firstborn child 	<ul style="list-style-type: none"> Typically no complications
Head shape at birth	<ul style="list-style-type: none"> Typically normal 	<ul style="list-style-type: none"> Can be irregular
Age first noticed shape irregularity	<ul style="list-style-type: none"> Usually in 1st few mo of life 	<ul style="list-style-type: none"> Can be at birth
How patient prefers to sleep	<ul style="list-style-type: none"> Same side, same position Same even during naps 	<ul style="list-style-type: none"> Variable
Bald spot	<ul style="list-style-type: none"> Yes 	<ul style="list-style-type: none"> No
Motor development for age	<ul style="list-style-type: none"> If age atypical for deformational plagiocephaly, typically slow motor development for age Torticollis present History of limited activity or mobility 	<ul style="list-style-type: none"> Varies depending on presence of concomitant syndrome
Tummy time	<ul style="list-style-type: none"> Decreased 	<ul style="list-style-type: none"> Suggested time
Signs/symptoms of increasing intracranial pressure	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> Possible

Table 592-3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly		
	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	<p>External forces applied to the skull</p> <ul style="list-style-type: none"> Prenatal: uterine compression, intrauterine constrained Postnatal: congenital torticollis, sleeping position 	Premature fusion of 1 or more cranial sutures
Common types	<ul style="list-style-type: none"> Lateral Posterior 	<ul style="list-style-type: none"> Bilateral coronal Sagittal Metopic
Common distinguishing features	<ul style="list-style-type: none"> Normal round head shape at birth Parallelogram shape to head Ipsilateral ear anteriorly displaced No palpable bony ridges 	<ul style="list-style-type: none"> Can have abnormal head shape at birth Trapezoid shape to head Ipsilateral ear posteriorly displaced Palpable bony ridges
Management	<ul style="list-style-type: none"> Repositioning Physical therapy Helmet in some cases 	<ul style="list-style-type: none"> 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.

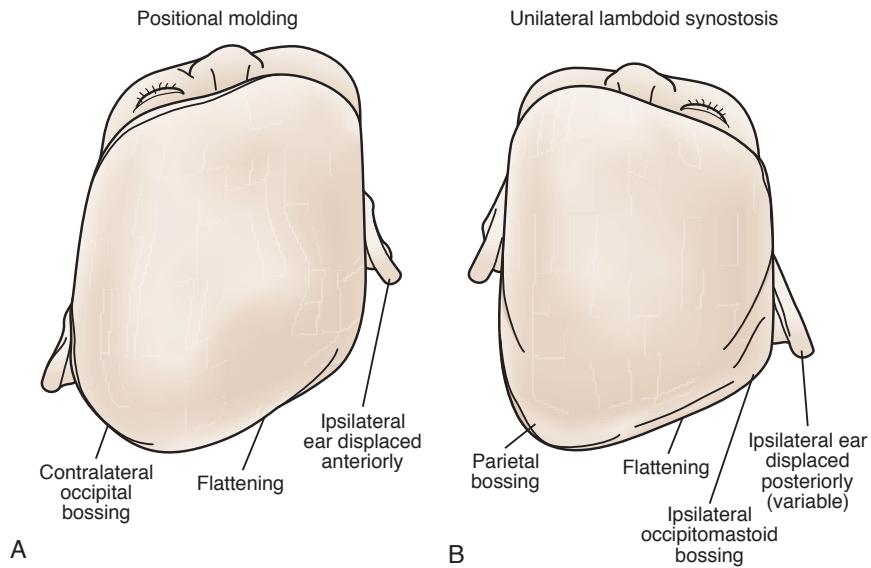


Figure 592-1 Differentiating physical findings between deformational plagiocephaly and craniosynostosis. Vertex views. **A**, Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B**, Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape.

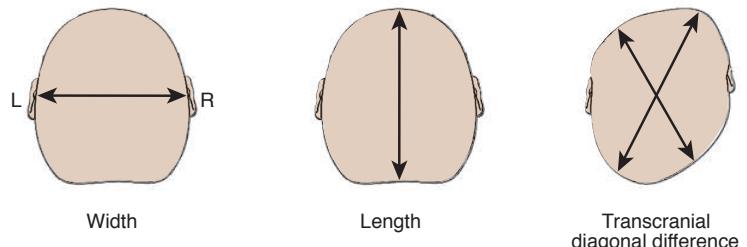


Table 591-4 Causes of Hydrocephalus

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

*Toxoplasmosis, neurocysticercosis, mumps.

Figure 592-2 Cranial measurements.

Table 592-4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

TYPE		LATERAL DEFORMATIONAL PLAGIOCEPHALY		POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)	
CLINICAL FINDINGS					
Occiput (vertex view)		Ipsilateral occipital flattening; contralateral occipital bossing		Uniform occipital flattening	
Ear position (vertex view)		Ipsilateral ear may be anteriorly displaced		Normal	
Face, forehead (anterior, lateral, and vertex views)		May be normal; more-severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced		Temporal bossing, increase in vertical height in severe cases	
Other		Torticollis, head position preference		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	CI: 0.82-0.9	Central posterior deformity ("ping-pong ball depression")
Moderate	TDD 10-12 mm	Type II Type III	Malposition of ear Forehead deformity	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
Severe	TDD >12 mm	Type IV Type V	Malar deformity Vertical or temporal skull growth	CI: >1.0	Vertical head, head growth, or temporal bossing

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

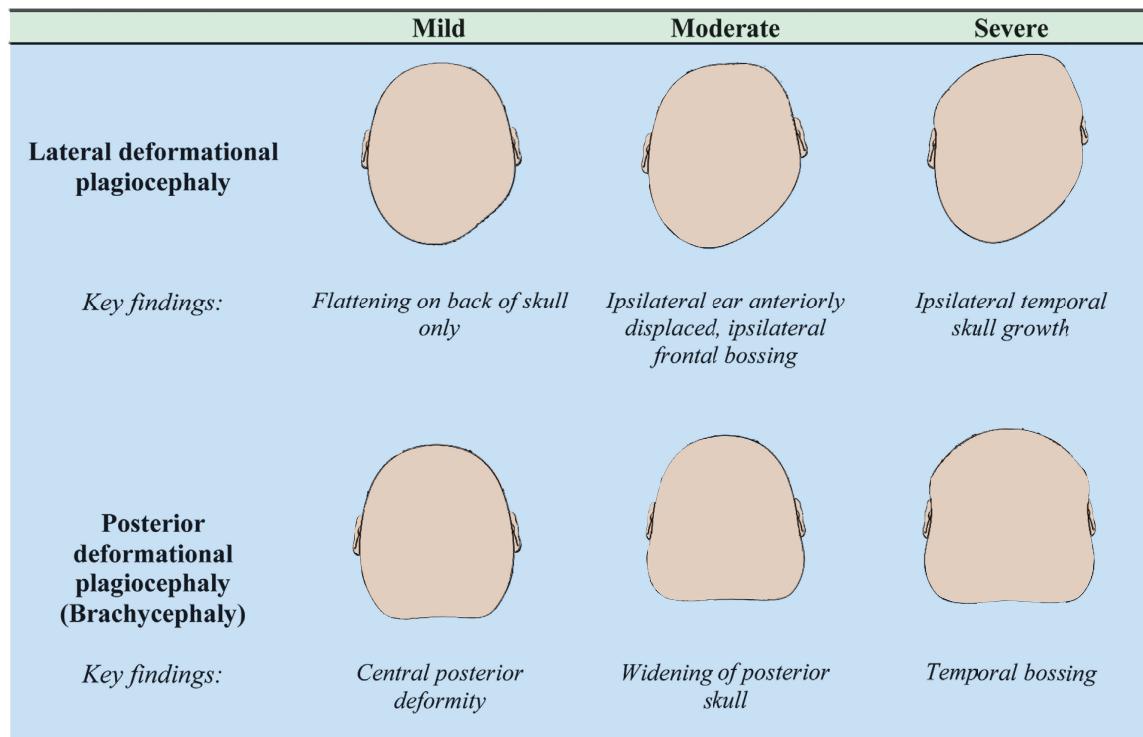


Figure 592-3 Types of deformational plagiocephaly.

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

Table 593-1 Types of Epileptic Seizures

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

Table 593-2

Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

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

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

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

Table 593-4 Identified Genes for Syndromic Epilepsy Syndromes*

SYNDROME	GENE	PROTEIN
Rett/atypical Rett syndromes	<i>MECP2</i> <i>CDKL5</i> <i>FOXP1</i> <i>MBD5</i> <i>MEF2C</i>	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	<i>UBE3A</i> <i>SLC9A6</i> <i>MBD5</i> <i>TCF4</i> <i>NRXN1</i> <i>CNTNAP2</i>	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	<i>ZEB2</i>	Zinc finger E-box-binding homeobox 2
Creatine deficiency syndromes	<i>GAMT</i> <i>GATM</i>	Guanidinoacetate N-methyltransferase Glycine amidinotransferase, mitochondrial
Neuronal ceroid lipofuscinosis (NCL)	<i>PPT1 (CLN1)</i> <i>TPP1 (CLN2)</i> <i>CLN3</i> <i>CLN5</i> <i>CLN6</i> <i>MFSD8 (CLN7)</i> <i>CLN8</i> <i>CTSD (CLN10)</i> <i>KCTD7 (CLN14)</i>	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	<i>ADSL</i>	Adenylosuccinate lyase
Cerebral folate deficiency	<i>FOLR1</i>	Folate receptor alpha
Epilepsy with variable learning and behavioral disorders	<i>GRIN2A</i> <i>SYN1</i>	Glutamate receptor ionotropic, N-methyl-D-aspartate (NMDA) 2A Synapsin-1
17q21.31 microdeletion syndrome	<i>KANSL1</i>	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	<i>PNKP</i>	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.

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.

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	

Table 593-9 Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

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.

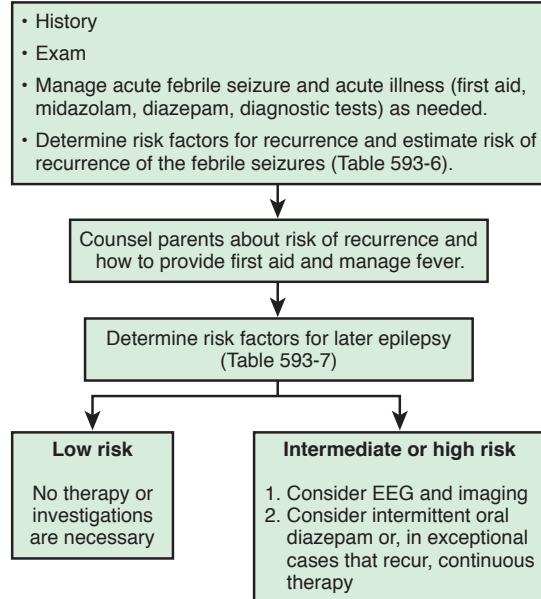


Figure 593-1 Management of febrile seizures.

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 593-7 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%

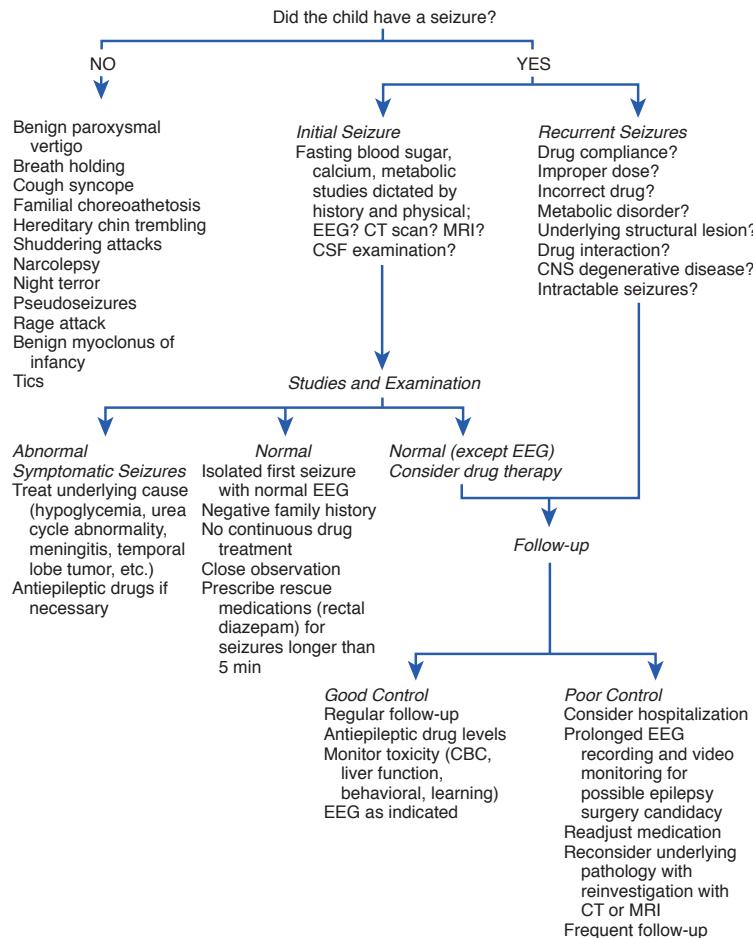


Figure 593-4 Approach to the child with a suspected convulsive disorder.

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.

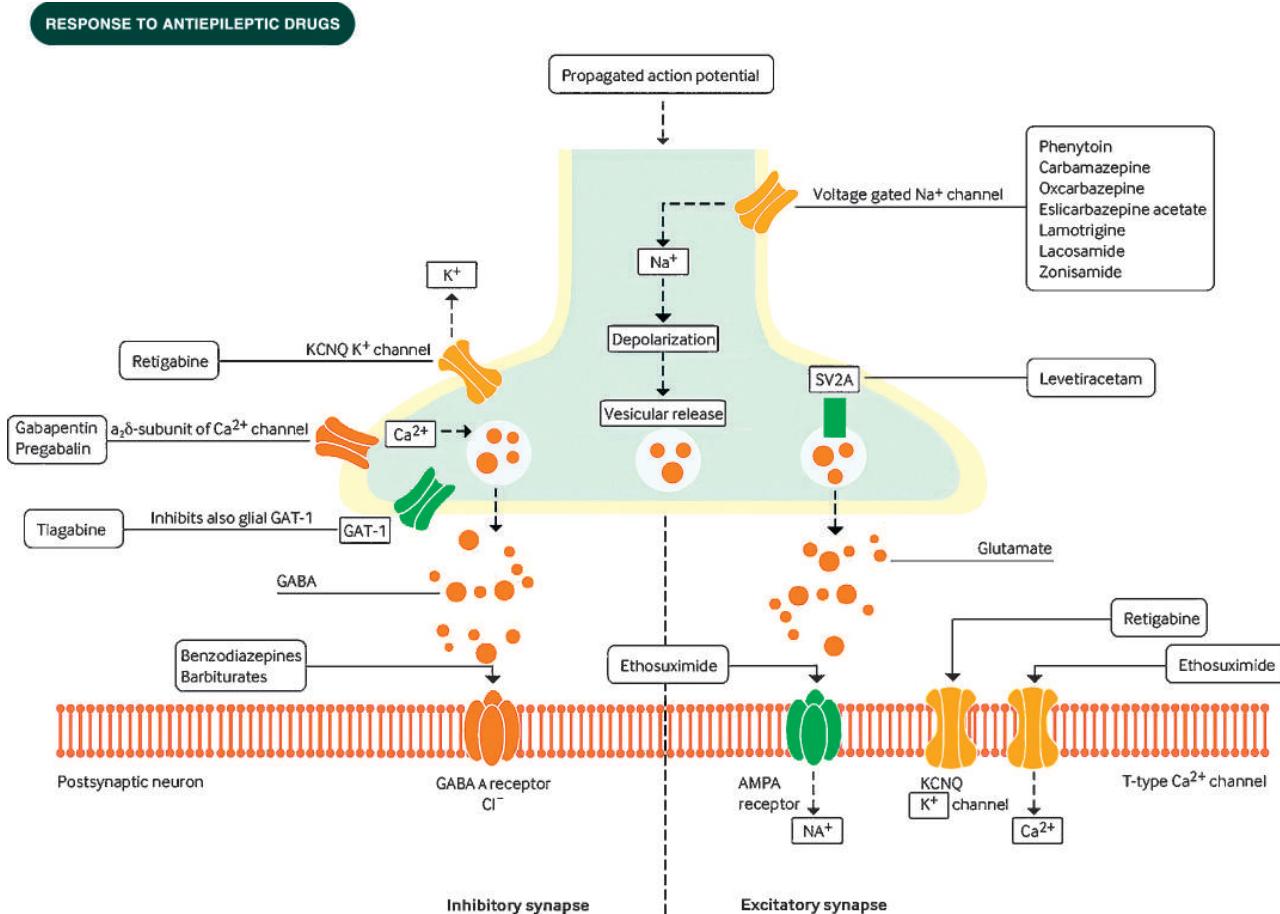


Figure 593-5 Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory (left hand side) and excitatory (right hand 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.)

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, adrenocorticotrophic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clonazepam; 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.

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.

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

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.

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 hyperchlremia (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.

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.

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
 - Hyponatremia
 - 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

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)
- Pallidoneuronal 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, cycloserpine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors

PERIPHERAL NEUROPATHIES**PSYCHOGENIC**

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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• Age of onset of nodding ranging from 3-18 yr Plus at least 1 of the following minor criteria: <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• 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 <ul style="list-style-type: none">• 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. 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.

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	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
Diazepam	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 1-1.5 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.

Table 593-3 Identified Genes for Epilepsy Syndromes*†

EPILEPSY TYPE	GENE	PROTEIN
INFANTILE ONSET		
Benign familial neonatal seizures	<i>KCNQ2</i>	Potassium voltage-gated channel
	<i>KCNQ3</i>	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	<i>SCN2A</i>	Sodium channel protein type 2 α
Early familial neonatal infantile seizures	<i>SCN2A</i>	Sodium channel protein type 2 α
Early infantile epileptic encephalopathy (EIEE)	<i>CDKL5 (EIEE2)</i> <i>ARX (EIEE1)</i> <i>TSC1</i> <i>TSC2</i> <i>SCN1A (EIEE6)</i> <i>PCDH19(EIEE9)</i> <i>KCNQ2 (EIEE7)</i> <i>STXBP1 (EIEE4)</i> <i>SLC2A1</i> <i>ALDH7A1</i> <i>POLG</i> <i>SCN2A (EIEE11)</i> <i>PLCβ1 (EIEE12)</i> <i>ATP6AP2</i> <i>SPTAN1 (EIEE5)</i> <i>SLC25A22 (EIEE3)</i> <i>PNPO</i> <i>SCN1A</i> <i>SCN1B</i> <i>GABRG2</i> <i>SCN2A</i>	Cyclin-dependent kinase-like 5 Aristaless-related homeobox Hamartin Tuberin Sodium channel protein type 1 α 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 2 α Phospholipase C β 1 Renin receptor α -Spectrin Mitochondrial glutamate carrier 1 Pyridoxine-5'-phosphate oxidase Sodium channel protein type 1 α Sodium channel protein type 1 β γ -Aminobutyric acid receptor subunit γ 2 Sodium channel protein type 1 α
Generalized epilepsy with febrile seizures plus (early onset)		
CHILDHOOD ONSET		
Childhood onset epileptic encephalopathies	<i>SCN1A</i> <i>PCDH19</i> <i>SLC2A1</i> <i>POLG</i> <i>SCN2A</i>	Sodium channel protein type 1 α Protocadherin-19 Solute carrier family 2, facilitated GTM1 DNA polymerase subunit γ 1 Sodium channel protein type 2 α
Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder		Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	<i>SCN1A</i> <i>SCN1B</i> <i>GABRG2</i> <i>SCN2A</i>	Sodium channel protein type 1 α Sodium channel protein type 1 β γ -Aminobutyric acid receptor subunit γ 2 Sodium channel protein type 1 α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	<i>EFHC1</i> <i>CACNB4</i> <i>GABRA1</i>	EF-hand domain-containing protein 1 Voltage-dependent L-type calcium channel γ -Aminobutyric acid receptor subunit α 1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	<i>EPM2A</i> <i>NHLRC1</i> <i>CSTB</i> <i>PRICKLE1</i> <i>PPT1, TPP1, CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8</i>	Laforin NHL repeat-containing protein 1 (Malin) Cystatin-B Prickle-like protein 1 Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	<i>CHRNA4</i> <i>CHRN B2</i> <i>CHRNA2</i>	Neuronal acetylcholine receptor α 4 Neuronal acetylcholine receptor β 2 Neuronal acetylcholine receptor α 2
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)	See Childhood Onset AD-LTLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	<i>LGI1</i>	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>).

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	POSTICHTAL 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	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing	Blurring of vision, tinnitus, dizziness	Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Syncope with reflex anoxic seizures	Minor bump to head, upsetting surprises	Crying in breath-holding spells		
Syncope: trigeminal vagal	Cold water on face			
Syncope: orthostatic	Standing up, bathing, awakening			
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.**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.

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)

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

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)—cont'd

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

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

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 components 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

Table 595-2 Migraine Without Aura

- A. At least 5 attacks fulfilling criteria B to D
- B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
- C. 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)
- D. During headache at least 1 of the following:
 - 1. Nausea and/or vomiting
 - 2. Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

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

Table 595-3 Migraine with Typical Aura

- A. At least 2 attacks fulfilling criteria B and C
- B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
- C. 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
- D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

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

Table 595-4 Migraine with Brainstem Aura

- A. At least 2 attacks fulfilling criteria B to D
- B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
- C. 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
- D. 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
- E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

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

Table 595-5 Vestibular Migraine with Vertigo

- A. At least 5 episodes fulfilling criteria C and D
- B. A current or past history of 1.1 *Migraine without aura* or 1.2 *Migraine with aura*
- C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
- D. 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:
 - a. Unilateral location
 - b. Pulsating quality
 - c. Moderate or severe intensity
 - d. Aggravation by routine physical activity
 - 2. Photophobia and phonophobia
 - 3. Visual aura
- E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

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

Table 595-6 Chronic Migraine

- A. 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
- B. 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*
- C. 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
- D. Not better accounted for by another ICHD-3 diagnosis

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

Table 595-9	Infrequent Episodic Tension-Type Headache
A.	At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D
B.	Lasting from 30 min to 7 days
C.	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
D.	Both of the following:
1.	No nausea or vomiting
2.	No more than 1 of photophobia or phonophobia
E.	Not better accounted for by another ICHD-3 beta diagnosis

Table 595-7 Indications for Neuroimaging in a Child with Headaches

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 cephalgias 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

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children

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

Continued

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

*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.

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 596-3 Major Features of TSC

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

Table 596-4 Minor Features of TSC

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

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, megalecephaly, 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

Table 597-2 Selected Causes of Ataxia in Childhood

CONGENITAL	
<ul style="list-style-type: none"> • Agenesis of vermis of the cerebellum • Aplasia or dysplasia of the cerebellum • Basilar impression • Cerebellar dysplasia with microgyria, macrogryria, 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 	
DEGENERATIVE AND/OR GENETIC	
<ul style="list-style-type: none"> • 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 	
ENDOCRINOLOGIC	
<ul style="list-style-type: none"> • Acquired hypothyroidism • Cretinism 	
INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY	
<ul style="list-style-type: none"> • Acute cerebellar ataxia • Acute disseminated encephalomyelitis • Autoimmune (anti-glutamic acid decarboxylase, anti-γ-aminobutyric acid receptor antibodies) • Cerebellar abscess • Cerebellitis • Coxsackievirus • Diphtheria • Echo virus • 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 	
METABOLIC	
	<ul style="list-style-type: none"> • 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
NEOPLASTIC	
	<ul style="list-style-type: none"> • Frontal lobe tumors • Hemispheric cerebellar tumors • Midline cerebellar tumors • Neuroblastoma • Pontine tumors (primarily gliomas) • Spinal cord tumors
PRIMARY PSYCHOGENIC	
	<ul style="list-style-type: none"> • Conversion reaction
TOXIC	
	<ul style="list-style-type: none"> • Alcohol • Benzodiazepines • Carbamazepine • Clonazepam • Lead encephalopathy • Neuroblastoma • Phenobarbital • Phenytoin • Primidone • Tic paralysis poisoning
TRAUMATIC	
	<ul style="list-style-type: none"> • Acute cerebellar edema • Acute frontal lobe edema
VASCULAR	
	<ul style="list-style-type: none"> • Angioblastoma of cerebellum • Basilar migraine • Cerebellar embolism • Cerebellar hemorrhage • Cerebellar thrombosis • Posterior cerebellar artery disease • Vasculitis • von Hippel-Lindau disease

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 α_{1A} 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	Encephalomyopathy	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.

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

2886 Part XXVII ◆ The Nervous System

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.

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								
SCA8	13q21	SCA8	SCA8 RNA	CTG repeat in 3' UTR	18-72	2-91*	110-155*	
SCA10	22q13	SCA10	Ataxin-10	ATTCT repeat in intron 9	14-45	10-29	750-4500	
SCA12	5q31-q33	SCA12	P2R2B	CAG repeat in 5' UTR	8-55	7-32	55-78	
SCA31	16q22.1	BEAN/TK2	BEAN/TK2	TGGAA repeat insertion in intron of BEAN and TK	45-72	Rarely (0.23%) 1.5-2.0 kb	2.5-3.8 kb	
OTHER MUTATIONS								
SCA14	19q13.4	PKC-γ	PKC-γ	Missense mutation	10-69			
SCA27	13q34	FGF14	FGF14	Fibroblast growth factor deficiency	15-20			
SCA5	11p11-q11	SPTBN2	β-3 spectrin	Deletion, missense mutations	10-68			
SCA11	15q14-q21.3	TTBK2	TTBK2	Truncation mutation	15-43			
SCA13	19q13.3-q13.4	KCNC3	KCNC3	Missense mutations	<1-60			
SCA15	3p24.2-3pter	ITPR1	ITPR1	Deletion, missense mutation	Child-adult			
SCA28	18p11.22-q11.2	AFG3L2	AFG3L2	Missense mutations	12-36			

Table 597-8 Drugs That Can Induce Chorea

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

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
 Dentatorubropallidolusian atrophy
 Neuroacanthocytosis
 Leigh syndrome and other mitochondrial disorders
 Ataxia telangiectasia
 Benign hereditary chorea
 Wilson disease
 Spinocerebellar atrophy (types 2, 3, or 17)
 Pantothetic 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)**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.

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

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 muscle 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

Table 597-7 Genetic Choresas

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
HDL2*	AD [†]	<i>JPH3</i> , 16q	Junctophilin-3	20-40	Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity
SCA17	AD [†]	<i>TBP</i> , 6q	TBP	10-30	Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline
DRPLA	AD [†]	<i>DRPLA</i> , 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 [†]	<i>MJD</i> , 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	<i>VPS13A</i> (formerly <i>CHAC</i>), 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	<i>FTL</i> , 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	<i>ATM</i> , 11q (AT) <i>MRE11</i> , 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	<i>APTX</i> , 9p (AOA 1) <i>SETX</i> , 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	<i>PANK2</i> , 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

2890 Part XXVII ◆ The Nervous System

Table 597-7 Genetic Choresas—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.

¹Disorders 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, Seppe K, Mair KJ, et al: Seminar on choreas, Lancet Neurol 5:589-602, 2006.

Table 601-2 Classification of Cerebral Vasculitis

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

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.

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 597-10 Causes of Dystonia in Childhood

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

Table 597-11

Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES	DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental 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
Alternating hemiplegia of childhood	Episodic hemiplegia/quadruplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells	Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia	Myoclonus dystonia	Myoclonus Head, upper limb involvement
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation	Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine	Neuroacanthocytosis	Oromandibular and lingual dystonia
Complex regional pain syndrome	Lower limb involvement Prominent pain	Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Dopa-responsive dystonia (DRD)	Diurnal variation	Rapid onset dystonia parkinsonism (DYT12)	Acute onset 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 neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence	Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
DYT1 dystonia	Lower limb onset followed by generalization	Tics	Stereotyped movements Premonitory urge, suppressible
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis	Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD
GM ₁ gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity		
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		

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: scarring globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia Kernicterus Mitochondrial Genetic/metabolic

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.

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	Hypospadica
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.

Table 598-4 Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

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 thalamus. 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.
 - A. 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.
 - B. Differential diagnosis from radiologic viewpoints. Leigh encephalopathy and related mitochondrial cytopathies; glutaric aciduria, methylmalonic aciduria, 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

Table 600-1 Differential Diagnosis of Demyelinating Disorders

- 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
- Griselli syndrome type 2

Table 598-5 Autoimmune Encephalitis in Children

	MECHANISMS	TUMOR ASSOCIATION	SYNDROME	ANCILLARY TEST	TREATMENT/ PROGNOSIS
DEMONSTRATED IMMUNE MECHANISMS					
Anti-NMDAR encephalitis	Antibodies against NR1 subunit of NMDAR, disrupt function by crosslinking and internalization of receptors	Age and gender related: 41% in females older than 12 yr; <6% in girls younger than 12 yr. No 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%	80% complete recovery after immunotherapy and tumor removal (if appropriate). Frequently second-line drug* immunotherapy is required. Relapses in ~15% of patients
Limbic encephalitis	Antibodies against intraneuronal antigens: Hu, Ma2, amphiphysin, GAD Antibodies against synaptic antigens: GABA _A R, mGluR5	Extremely rare in children (see text)	Severe short-term memory loss, seizures	EEG: temporal lobe epileptic activity, focal or generalized slowing MRI: increased T2 and FLAIR signal in limbic region CSF: pleocytosis and increased proteins	If autoantigens are intracellular, poor response to immunotherapy If autoantigens are on the cell surface, ~80% are responsive to immunotherapy
STRONGLY SUSPECTED IMMUNE MECHANISMS					
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable antibodies (a few patients have Hu antibodies)	Neuroblastoma occurs in 50% of children <2 year old; teratoma in teenagers and young adults	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	CSF abnormalities suggesting B-cell activation MRI: in some cases cerebellar atrophy	Partial response to immunotherapy in neuroblastoma-related opsoclonus High response to immunotherapy in teratoma-associated opsoclonus
Bickerstaff encephalitis	GQ1b antibodies	No tumor association	Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome	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)	Often good outcome with steroids, IVIG and/or plasma exchange
Hashimoto encephalitis	TPO antibodies	No tumor association	Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia	48% hypothyroidism, MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	No tumor association	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. Patients may need functional hemispherectomy
Basal ganglia encephalitis	Antibodies to D2R in some cases	No tumor association	Abnormal movement and behavior disorder	Variable basal ganglia T2/FLAIR abnormalities	Mostly monophasic, can relapse
POSSIBLE IMMUNE MECHANISMS					
CLIPPERS	No antibodies	No tumor association	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	Steroid-responsive but may require chronic steroid or other immunosuppressive therapy
ROHHAD	Unknown. Autoimmune and genetic origin postulated.	Neural crest tumor in ~50% of cases ^t	Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic; in some patients limited response to immunotherapy

*Includes rituximab and cyclophosphamide.

^tExact 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; GABA_AR, 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.

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.

Table 599-1

AGE AT ONSET (yr)	CONDITIONS	COMMENTS
<2 with hepatomegaly	Fructose intolerance Galactosemia Glycogenosis (glycogen storage disease) types I-IV Mucopolysaccharidoses 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, opisthotonus 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, quadriplegia
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

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.

^{||}Verhey 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.

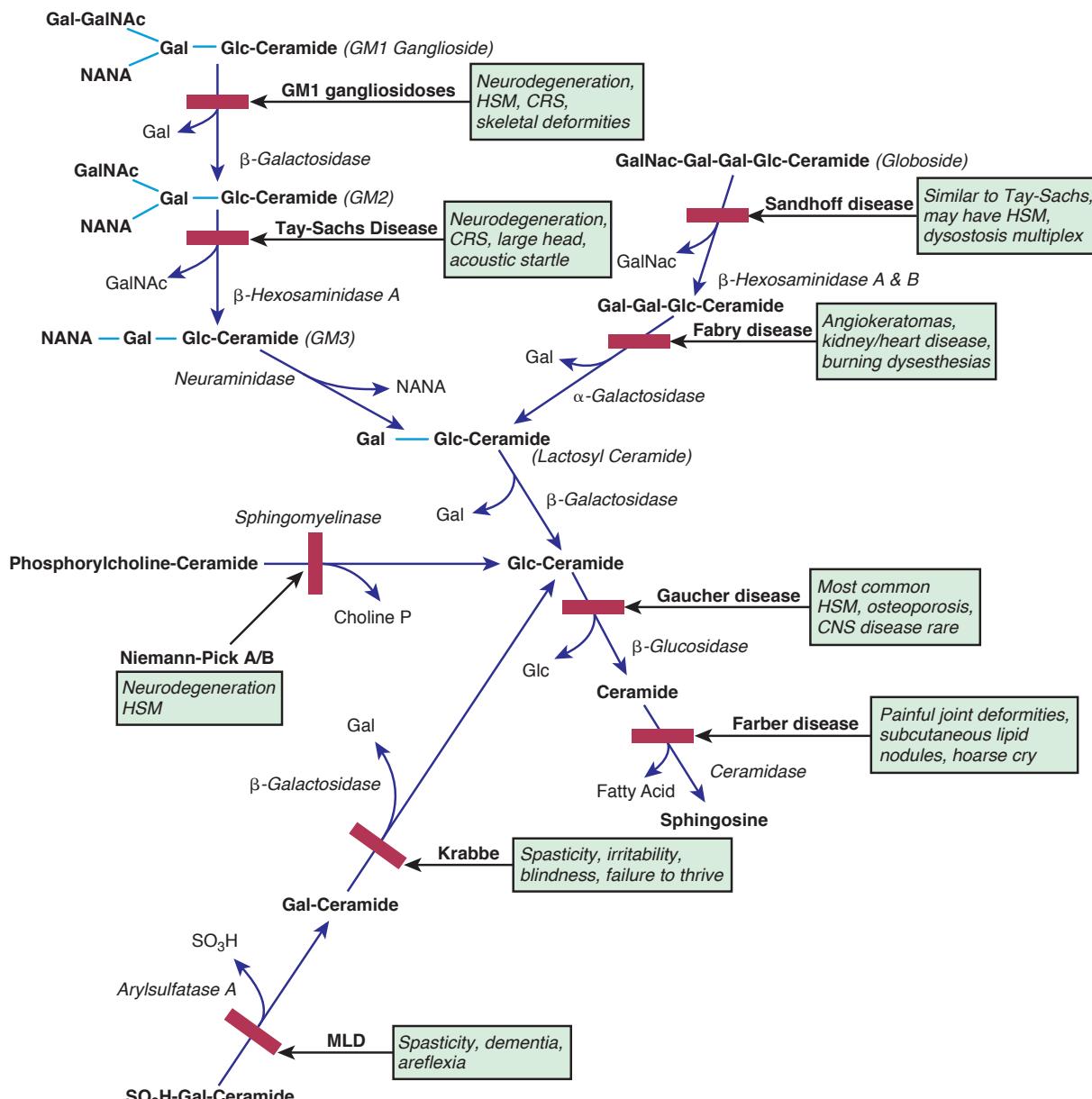


Figure 599-1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM,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

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	CLN1	Palmitoyl-protein thioesterase-1 (PPT1) [†]	6-24 months	Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss
Variant infantile	CLN1		3 yr to adulthood	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

Table 600-2 | IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System

DISORDER	IPMSSG 2012
CIS	<ul style="list-style-type: none"> A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, unless caused by fever
Monophasic ADEM	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> See multiphasic ADEM
Multiphasic ADEM	<ul style="list-style-type: none"> 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	<p>Any of the following:</p> <ul style="list-style-type: none"> 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	<p>All are required:</p> <ul style="list-style-type: none"> Optic neuritis Acute myelitis <p>At least 2 of 3 supportive criteria</p> <ul style="list-style-type: none"> 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 new T2 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	<p>Cognitive impairment</p> <p>Hemisensory and motor</p> <p>Affective (mainly depression)</p> <p>Epilepsy (rare)</p> <p>Focal cortical deficits (rare)</p>	<p>Deficits in attention, reasoning, and executive function (early); dementia (late)</p> <p>Upper motor neuron signs</p>
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect
Cerebellum and cerebellar pathways	<p>Tremor</p> <p>Clumsiness and poor balance</p>	<p>Postural and action tremor, dysarthria</p> <p>Limb incoordination and gait ataxia</p>
Brainstem	<p>Diplopia, oscillopsia</p> <p>Vertigo</p> <p>Impaired swallowing</p> <p>Impaired speech and emotional lability</p> <p>Paroxysmal symptoms</p>	<p>Nystagmus, internuclear and other complex ophthalmoplegias</p> <p>Dysarthria</p> <p>Pseudobulbar palsy</p>
Spinal cord	<p>Weakness</p> <p>Stiffness and painful spasms</p> <p>Bladder dysfunction</p> <p>Erectile impotence</p> <p>Constipation</p>	<p>Upper motor neuron signs</p> <p>Spasticity</p>
Other	<p>Pain</p> <p>Fatigue</p> <p>Temperature sensitivity and exercise intolerance</p>	

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

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)	Retrospective Prospective multicenter
Glatiramer acetate*	Immunomodulator	Modulates T cells and reduces antigen presentation	Flushing, lipodystrophy at injection sites	Prospective single center Prospective multicenter
SECOND-LINE THERAPIES				
Natalizumab*	Monoclonal antibody	Targets α_4 -integrin; prevents T-cell migration into CNS and other tissues	Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)	Retrospective Prospective multicenter
Cyclophosphamide	Chemotherapeutic	DNA alkylation; effects include cytotoxic immune cell depletion	Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility	Retrospective multicenter
Mitoxantrone*	Chemotherapeutic	Disrupts DNA synthesis; effects include cytotoxic immune cell depletion	Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections	Retrospective single center
Daclizumab	Monoclonal antibody	Targets/inactivates interleukin-2 receptor; inhibits activated T cells	Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions	Retrospective multicenter
Rituximab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	PML (rate undefined); infusion-related side effects	No efficacy assessments available in pediatric MS
Azathioprine	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	Transaminitis; leukopenia; lymphoma	No efficacy assessments available in pediatric MS
Fingolimod*†	Immunomodulator	Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments	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
Teriflunomide*†	Immunomodulator	Impairs immune cell proliferation via pyrimidine synthesis inhibition	Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity	FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date
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	Prospective trials in pediatric and adult MS are currently underway
Ocrelizumab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretical risk of PML (undefined)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Dimethyl fumarate [†]	Immunomodulator	Neuroprotectant; antioxidant	Flushing reaction; gastrointestinal upset; headache	FDA approved for adult MS in March 2013; no use in pediatric MS to date
Alemtuzumab	Monoclonal antibody	Anti-CD52 antibody target; depletes mature T cells	Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Laquinimod [†]	Immunomodulator	Modulates T cell and cytokine production	Transaminitis	Recently completed phase III trial in adult MS; no use in pediatric MS to date

*FDA approved for the treatment of adult MS.

†Orally administered therapy.

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

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 encephalomyopathy (Leigh disease) Sulfite oxidase deficiency 11 β -Ketoreductase deficiency 17 α -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 (cystathione 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.

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/puerperum 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 head 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 601-4 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 601-4 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

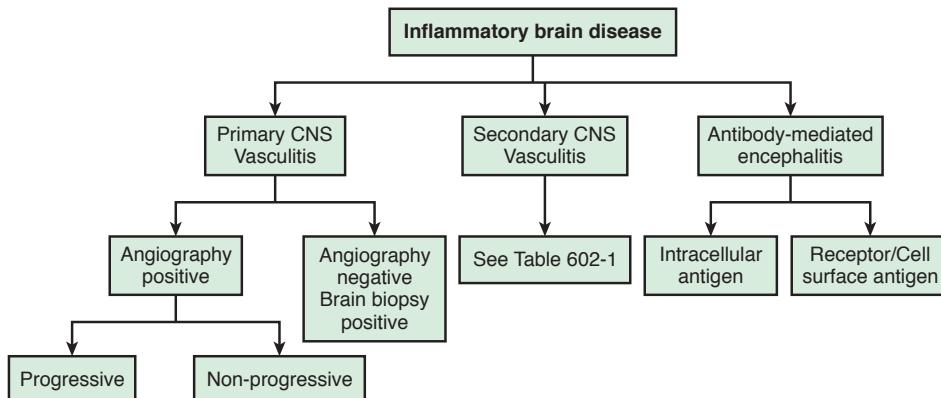
MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperum 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 head 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 601-3 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 head 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

**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, Behcet 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)

Table 602-2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

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
2. 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
3. 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
4. Brain biopsy

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.

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (mm H ₂ O)	LEUKOCYTES (mm ³)	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 meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain Pretreatment may render CSF sterile. Antigen may be detected by agglutination test
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	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 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	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 meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. <i>Mycobacterium tuberculosis</i> may be detected by PCR of CSF
Fungal meningitis	Usually elevated	5-500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (<i>Naegleria</i>) meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature
BRAIN ABSCESES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated (100-300)	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated (100-300)	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids

Continued

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (mm H ₂ O)	LEUKOCYTES (mm ³)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal or elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	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.

Table 603-4 Antibiotics Used for the Treatment of Bacterial Meningitis*

DRUGS	Neonates		INFANTS AND CHILDREN
	0-7 DAYS	8-28 DAYS	
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	SPINAL CORD DISORDERS
<ol style="list-style-type: none"> Vertebral spine disorders <ol style="list-style-type: none"> Trauma <ol style="list-style-type: none"> Blunt Penetrating Surfing Atlantoaxial subluxation <ol style="list-style-type: none"> Trisomy 21 Mucopolysaccharidosis type IV Grisel syndrome Destructive lesions <ol style="list-style-type: none"> Tuberculosis Lymphoma Langerhans cell histiocytosis Scheuermann disease Epidural disease <ol style="list-style-type: none"> Tumor <ol style="list-style-type: none"> Neuroblastoma Wilms tumor Ewing sarcoma Abscess <ol style="list-style-type: none"> Associated dermal sinus, vertebral body infection Hematoma Arachnoiditis <ol style="list-style-type: none"> Tuberculosis Cryptococcosis Carcinomatous infiltration Spinal nerve root inflammation <ol style="list-style-type: none"> Guillain-Barré syndrome 	<ol style="list-style-type: none"> Congenital malformation <ol style="list-style-type: none"> Neurenteric cysts Spinal cord tethering Infection <ol style="list-style-type: none"> Nonpolio enteroviruses West Nile virus Human T-lymphocyte virus 1 Neurocysticercosis Vascular disorders <ol style="list-style-type: none"> Arteriovenous malformation Cavernomas Cobb syndrome Fibrocartilaginous embolization Spinal cord infarction Vasculitis <ol style="list-style-type: none"> Systemic lupus erythematosus Behcet disease Nutritional disorders <ol style="list-style-type: none"> Vitamin B₁₂ deficiency (Subacute combined degeneration) Toxic injury <ol style="list-style-type: none"> Chemotherapy (e.g., methotrexate) Radiation Immune mediated <ol style="list-style-type: none"> Acute disseminated encephalomyelitis Neuromyelitis optica Multiple sclerosis

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

Table 603-2 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

VIRUSES	PARASITES (NONEOSINOPHILIC)
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	<i>Toxoplasma gondii</i> (toxoplasmosis) <i>Acanthamoeba</i> spp. <i>Naegleria fowleri</i> Malaria
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	POSTINFECTIOUS Vaccines: rabies, influenza, measles, poliovirus Demyelinating or allergic encephalitis
BACTERIA	SYSTEMIC OR IMMUNOLOGICALLY MEDIATED
<i>Mycobacterium tuberculosis</i> (early and late) <i>Leptospira</i> species (leptospirosis) <i>Treponema pallidum</i> (syphilis) <i>Borrelia</i> species (relapsing fever) <i>Borrelia burgdorferi</i> (Lyme disease) <i>Nocardia</i> species (nocardiosis) <i>Brucella</i> species <i>Bartonella</i> species (cat-scratch disease) <i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever) <i>Rickettsia prowazekii</i> (typhus) <i>Ehrlichia canis</i> <i>Coxiella burnetii</i> <i>Mycoplasma pneumoniae</i> <i>Mycoplasma hominis</i> <i>Chlamydia trachomatis</i> <i>Chlamydia psittaci</i> <i>Chlamydia pneumoniae</i> Partially treated bacterial meningitis	<i>Acute Disseminated Encephalomyelitis (ADEM)</i> <i>Autoimmune Encephalitis</i> Bacterial endocarditis Kawasaki disease Systemic lupus erythematosus Vasculitis, including polyarteritis nodosa Sjögren syndrome Mixed connective tissue disease Rheumatoid arthritis Behcet syndrome Wegener granulomatosis Lymphomatoid granulomatosis Granulomatous arteritis Sarcoidosis Familial Mediterranean fever Vogt-Koyanagi-Harada syndrome
BACTERIAL PARAMENINGEAL FOCUS	MALIGNANCY
Sinusitis Mastoiditis Brain abscess Subdural-epidural empyema Cranial osteomyelitis	Leukemia Lymphoma Metastatic carcinoma Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)
FUNGI	DRUGS
<i>Coccidioides immitis</i> (coccidioidomycosis) <i>Blastomyces dermatitidis</i> (blastomycosis) <i>Cryptococcus neoformans</i> (cryptococcosis) <i>Histoplasma capsulatum</i> (histoplasmosis) <i>Candida</i> species Other fungi (<i>Alternaria</i> , <i>Aspergillus</i> , <i>Cephalosporium</i> , <i>Cladosporium</i> , <i>Drechslera hawaiiensis</i> , <i>Paracoccidioides brasiliensis</i> , <i>Petriellidium boydii</i> , <i>Sporotrichum schenckii</i> , <i>Ustilago</i> spp., <i>Zygomycetes</i>)	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)
PARASITES (EOSINOPHILIC)	MISCELLANEOUS
<i>Angiostrongylus cantonensis</i> <i>Gnathostoma spinigerum</i> <i>Baylisascaris procyonis</i> <i>Strongyloides stercoralis</i> <i>Trichinella spiralis</i> <i>Toxocara canis</i> <i>Taenia solium</i> (cysticercosis) <i>Paragonimus westermani</i> <i>Schistosoma</i> spp. <i>Fasciola</i> spp.	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])

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.

Table 603-3 Classification of Encephalitis by Cause and Source

I. INFECTIONS: VIRAL	III. PARAINFECTIOUS: POSTINFECTIOUS, ALLERGIC, AUTOIMMUNE
A. Spread: person to person only	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. Mumps: frequent in an unimmunized population; often mild	A. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)
2. Measles: may have serious sequelae	Measles
3. Enteroviruses: frequent at all ages; more serious in newborns	Rickettsial infections
4. Parechovirus	Rubella
5. Rubella: uncommon; sequelae rare except in congenital rubella	Influenzas A and B
6. Herpesvirus group	Mumps
a. Herpes simplex (types 1 and 2, possibly 6): relatively common; sequelae frequent; devastating in newborns	Varicella-zoster
b. Varicella-zoster virus: uncommon; serious sequelae not rare	M. pneumoniae
c. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type	B. Associated with vaccines
d. Epstein-Barr virus (infectious mononucleosis): not common	Rabies
7. Pox group	Measles
a. Vaccinia and variola: uncommon, but serious CNS damage occurs	Vaccinia
8. Parvovirus (erythema infectiosum): not common	Yellow fever
9. Influenzas A and B	C. Autoimmune encephalitis
10. Adenovirus	D. Acute disseminated encephalomyelitis (ADEM)
11. Other: reoviruses, respiratory syncytial, parainfluenza, hepatitis B	Paraneoplastic
B. Arthropod-borne agents	Idiopathic
C. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:	IV. HUMAN SLOW-VIRUS DISEASES
Eastern equine	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)
Western equine	A. Subacute sclerosing panencephalitis; measles; rubella?
Venezuelan equine	B. Creutzfeldt-Jakob disease (spongiform encephalopathy)
St. Louis	C. Progressive multifocal leukoencephalopathy
West Nile	D. Kuru (Fore tribe in New Guinea only)
D. Spread by warm-blooded mammals	E. Human immunodeficiency virus
1. Rabies: saliva of many domestic and wild mammalian species	V. UNKNOWN: COMPLEX GROUP
2. Herpesvirus simiae ("B" virus): monkeys' saliva	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.
3. Lymphocytic choriomeningitis: rodents' excreta	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).
II. INFECTIONS: NONVIRAL	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.
A. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis	
B. <i>Mycoplasma pneumoniae</i> : interval of some days between respiratory and CNS symptoms	
C. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component	
D. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease	
E. Cat-scratch disease	
F. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis	
G. Protozoal: <i>Plasmodium</i> , <i>Trypanosoma</i> , <i>Naegleria</i> , and <i>Acanthamoeba</i> spp.; <i>Toxoplasma gondii</i>	
H. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis	

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.

Table 605-1 Etiology of Childhood Pseudotumor Cerebri

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

Table 607-3 Differential Diagnosis of Infantile Hypotonia

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

Table 607-4 Differential Diagnosis of Acute Flaccid Paralysis

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)

Table 607-1 Distinguishing Features of Disorders of the Motor System

LOCUS OF LESION	WEAKNESS				DEEP TENDON REFLEXES	ELECTRO-MYOGRAPHY	MUSCLE BIOPSY	OTHER
	Face	Arms	Legs	Proximal-Distal				
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.

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.

Table 608-2 Clinical Signs of Muscular Dystrophy

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

Continued

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								
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	++	Not frequent	Progressive with substantial variability	++	None	
Limb-girdle muscular dystrophy with sarcoglycan deficiency (types 2C, 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the 2nd decade	Proximal > distal (pattern A)	++	++	Progression of motor, cardiac, and respiratory signs	++	None	
Limb-girdle muscular dystrophy with abnormal glycosylation of dystroglycan (types 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	++	+ (++)	Progressive	++	Mental retardation reported in some cases	
Limb-girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	-	-	Progressive in adulthood	++	None	
Limb-girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the 4th decade	Proximal > distal (pattern A); in some pattern B	-	+	Progressive in adulthood	+ (+)	None	
Limb-girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal > distal (pattern A) but also pattern E	-	-	Roughly half lose ambulation in adulthood	++	None	
Facioscapulohumeral dystrophy	Independent ambulation achieved, variable progression	Pattern D	-	-	Slowly progressive	N or +	Neurosensory hearing loss and retinal degeneration	
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	++	Not frequent	Progression of cardiac signs > motor signs	+ (+)	None	
ADULT-ONSET MUSCULAR DYSTROPHY								
Limb-girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8:1 ratio of men to women	Mainly lower limbs pattern A, rarely Pattern E	-	-	Slowly progressive in adulthood	++	None	
Limb-girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal > distal (pattern A)	-	-	Generally slowly progressive in adulthood	+	Dysarthria in some cases	
Limb-girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	-	-	Slowly progressive, variable	++	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.

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 Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the 2nd decade	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
Emery-Dreifuss muscular dystrophy 2 and limb-girdle muscular dystrophy 1B	Conduction disease and cardiac failure	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	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality
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)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy-like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 2I	Cardiac involvement reported in 29-62% of limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr	Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	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

Continued

2970 Part XXVIII ◆ Neuromuscular Disorders

Table 608-3 Cardiac Involvement in Muscular Dystrophies—cont'd

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

ECG, electrocardiogram.

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

Table 609-1 Channelopathies and Related Disorders

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

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.

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
ρ -Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

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.

Table 610-1 Toxic Myopathies

INFLAMMATORY
Cimetidine
D-Penicillamine
Procainamide
L-Tryptophan
L-DOPA
NONINFLAMMATORY NECROTIZING OR VACUOLAR
Cholesterol-lowering agents
Chloroquine
Colchicine
Emetine
ϵ -Aminocaproic acid
Labetalol
Cyclosporine and tacrolimus
Isoretinoic acid (vitamin A analog)
Vincristine
Alcohol
RHABDOMYOLYSIS AND MYOGLOBINURIA
Cholesterol-lowering drugs (especially statins)
Alcohol
Heroin
Amphetamine
Toluene
Cocaine
ϵ -Aminocaproic acid
Pentazocine
Phencyclidine
MALIGNANT HYPERTHERMIA
Halothane
Ethylene
Diethyl ether
Methoxyflurane
Ethyl chloride
Trichloroethylene
Gallamine
Succinylcholine
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

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

2992 Part XXVIII ◆ Neuromuscular Disorders

	Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes								
	Presynaptic	Synaptic	Postsynaptic						
	CHOLINE ACETYLTRANSFERASE DEFICIENCY	LEMS-LIKE FORM	AChE DEFICIENCY	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 Muppudi 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.

2996 Part XXVIII ◆ Neuromuscular Disorders

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 β ₂	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 Eyemade B, Hantaï D, Estouenet B: Congenital myasthenic syndromes, *Handb Clin Neurol* 113:1469-1480, 2013.

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				

Table 612-5 Spinal 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.

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. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common	Delayed motor and sensory conduction studies. Motor studies typically <38 m/s	
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, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss		LITAF
1D (607678)	Possible cranial nerve involvement. Late onset in childhood or early adulthood		EGR2
1E (118300)	Associated with deafness (29-45%)		PMP22
1F (607734)			NEFL
Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500)	Autosomal dominant. Recurrent mononeuropathy simplex or multiplex frequently related to trauma	Significant slowing of motor and sensory conduction velocities in clinically affected nerves but also in unaffected nerves	PMP 22 deletion
Slowed NCVs	Often a miscellaneous group. Incidentally detected with no clinical symptoms.	Moderately slowed conduction velocities	
Asymptomatic	Autosomal dominant		ARHGEF10
CMT2 (AXONAL)			
CMT2 A-L (HMSN type II)	Autosomal dominant (A, B, D, E, F, G, I) Autosomal recessive (B1, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness	Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally	
2A1 (118210)	CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to <i>MFN2</i> mutations		2A1: <i>KIF1B</i> (one family)
2A2 (609260)			2A2: <i>MFN2</i>
2B (600882)	CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness		2B: <i>RAB7</i>
2B1 (605588)	Average onset 34 yr (Costa Rican family)		2B1: <i>LMNA</i>
2B2 (605589)	Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405)		? <i>MED25</i>
2C (606071)	Upper limb predominance		<i>TRP4</i> 12q23-q24 <i>TRP4</i>
2D (601472) (allelic to dSMA)			<i>GARS</i>
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	<i>NEFL</i>

Continued

3000 Part XXVIII ◆ Neuromuscular Disorders

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

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

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	<5 m/s	PRX
4G (605285) 4H (609311)	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	30-35 m/s <10 m/s or absent	10q22 FDG4
4J (611228)	Onset by 5 yr. Severe disorder. Similarities to motor neuron disease	2-7 m/s; some cases higher	FIG4
CCFDN (604168)	Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy	19-33 m/s	CTDP1
MIXED PATHOLOGY (AXONAL AND DEMYELINATING)			
CMT X	X-linked dominant. Onset 1st-2nd decade.	Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced	GJB1
X-linked CMT X1 (302800)	Progressive wasting and weakness of distal limb musculature, especially hands, more marked in affected males than carrier females	Mixed demyelinating/axonal	
X2 (302801)	X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected	Mixed demyelinating/axonal	Xp22.2
X3 (302802)	X-linked recessive. ± Spasticity. Females unaffected	Mixed demyelinating/axonal	Xq26
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	Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation	Xq24-26.1
X5 (311070)	X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes	Axonal neuropathy—mild demyelinating changes	Xq21.32-q24 PRPS1
Intermediate forms of CMT	Patients have neurophysiologic results that fall between axonal and demyelinating ranges	"Intermediate values" 30-40 m/s—most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB)	
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 <i>GADP1</i> 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 paraparesia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)	Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with 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	Small/absent SNAPs. Motor studies axonal in type	SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1 CMT with pyramidal signs: MFN2
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	No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated	MFN2
HMSN VII	HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset		

Continued

3002 Part XXVIII ◆ Neuromuscular Disorders

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	<i>HSPB1</i> 7q34-q36
dHMNII (608634)	Autosomal dominant. Adult onset, distal weakness and wasting		<i>HSPB8, HSPB3</i>
dHMNIIjuv (158590)	(Allelic CMT2F, CMT2L)		<i>HSPB1</i>
dHMNIII	Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis		11q13.3
dHMNIV (607088)	Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis		11q13
Distal SMA type 3			
dHMNV (600794)	(Allelic CMT2D) Autosomal dominant. Upper limb predominance, occasional pyramidal features		<i>GARS</i>
dHMN type V (Silver syndrome) (270685)	Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs		<i>BSCL2</i>
dHMNVI (604320)	(Allelic SMARD1) Autosomal recessive. Severe infantile form with respiratory distress		<i>IGHMBP2</i>
dHMN VIIA (158580)	Autosomal dominant. Onset with vocal cord paralysis		<i>DCTN1</i>
dHMN VIIIB (607641)	Autosomal dominant. Onset with vocal cord paralysis and facial weakness		2q14 Xq13-q21
X-linked dHMN			
dHMN/ALS4 (602433)	X-linked recessive. Juvenile onset with distal wasting and weakness		<i>SETX</i>
dHMN-J (Jerash)	Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs		9p21.1-p12
Congenital distal SMA (600175)	Autosomal recessive. Onset from 6-10 yr with pyramidal features in 1 Jordanian family		12q23-q24
Peripheral neuropathy with agenesis of corpus callosum (Charlevoix disease or Andermann syndrome) (218000)	Autosomal dominant congenital nonprogressive distal HMN with contractures Autosomal recessive. Increased in French Canadian populations. Progressive axonal neuropathy. CNS malformations—absence/hypoplasia of corpus callosum in most, early onset, developmental delay, areflexia, dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade	EMG: denervation. Axonal neuropathy	<i>SLC12A6 (KCC3)</i>
Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)	Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood 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	Normal or mildly prolonged MNCVs distal to affected brachial plexus	<i>SEPT9</i>
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	<i>SPTLC1</i> <i>RAB7</i> 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	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	<i>WNK1</i>
HSN (HSAN) 2B (223900)	Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood		<i>FAM134B</i>

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)	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	Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased	<i>IKBAP</i>
HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)	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	Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)	<i>NTRK1</i>
HSN (HSAN) 5 (608654)	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	Normal motor and sensory nerve conduction studies	<i>NGFβ</i>

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

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 paroxysms	
Dermatomyositis	
Critical illness myopathy/polyneuropathy	

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

Table 617-1 Etiologies of Acute Peripheral Facial Palsy

COMMON	OTHER LESS-COMMON CONDITIONS
Idiopathic	
Herpes simplex virus type 1*	
Varicella-zoster virus*	
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.	

Table 614-1 Toxic and Metabolic Neuropathies

METALS
Arsenic (insecticide, herbicide)
Lead (paint, batteries, pottery)
Mercury (metallic, vapor)
Thallium (rodenticides)
Gold
OCCUPATIONAL OR INDUSTRIAL CHEMICALS
Acrylamide (grouting, flocculation)
Carbon disulfide (solvent)
Cyanide
Dichlorophenoxyacetate
Dimethylaminopropionitrile
Ethylene oxide (gas sterilization)
Hexacarbons (glue, solvents)
Organophosphates (insecticides, petroleum additive)
Polychlorinated biphenyls
Tetrachlorobiphenyl
Trichloroethylene
DRUGS
Amiodarone
Chloramphenicol
Chloroquine
Cisplatin
Colchicine
Dapsone
Ethambutol
Ethanol
Fluoroquinolones
Gold
Hydralazine
Isoniazid
Metronidazole
METABOLIC DISORDERS
Fabry disease
Krabbe disease
Leukodystrophies
Porphyria
Tangier disease
Tyrosinemia
Uremia
BIOLOGIC AND INFECTIOUS NEUROPATHIES
Diphtheria
Herpesviruses
HIV
Leprosy
Lyme disease
Rabies
West Nile virus

Table 616-2 Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies By Pathology

DISORDER	ANTIBODIES
Acute inflammatory demyelinating polyradiculoneuropathy	Unknown
Acute motor and sensory axonal neuropathy	GM ₁ , GM _{1b} , GD _{1a}
Acute motor axonal neuropathy	GM ₁ , GM _{1b} , GD _{1a} , GaINac-GD _{1a}
Acute sensory neuropathy	GD _{1b}
ACUTE PANDYSAUTONOMIA	
Regional Variants	
Fisher syndrome	GQ _{1b} , GT _{1a}
Oropharyngeal Overlap	GT _{1a}
Fisher/Guillain-Barré overlap syndrome	GQ _{1b} , GM ₁ , GM _{1b} , GD _{1a} , GaINac-GD _{1a}

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

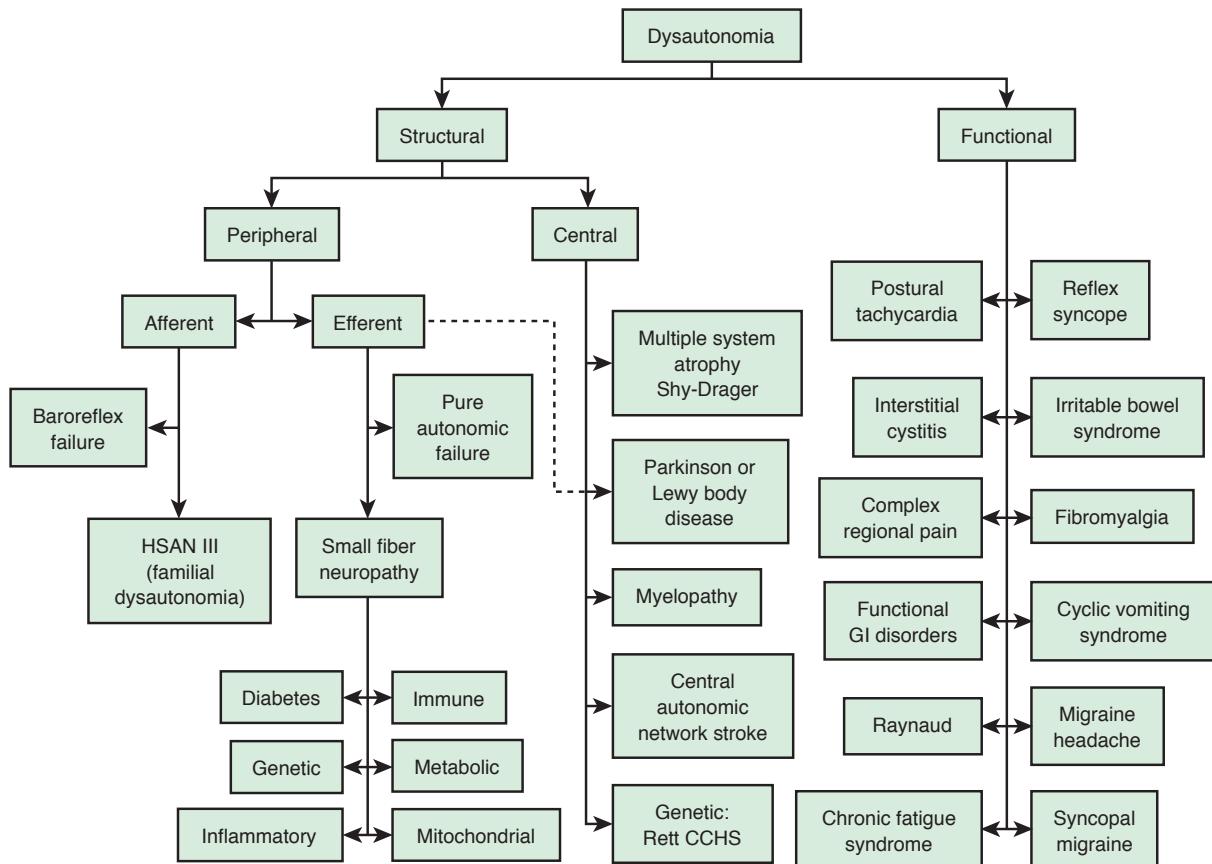


Figure 615-1 Classification of autonomic disorders or dysautonomias. The first conceptual division is between a structural and functional disorder. The word "functional" is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word "functional" in functional gastrointestinal disorders, and without implication of a psychiatric 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 function. 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.)

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)

3008 Part XXVIII ◆ Neuromuscular Disorders

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	Frequent (71%)	Almost consistent (99%)	Infrequent (9%)
Pain perception	Absent	Mild to moderate decrease	Absent
Temperature perception	Severe decrease	Mild to moderate decrease	Absent
Vibration sense	Normal	Normal	Normal to moderate decrease
Autonomic			
Gastroesophageal reflux	Frequent (71%)	Frequent (67%)	Uncommon (24%)
Postural hypotension	Uncommon (25%)	Almost consistent (99%)	Uncommon (29%)
Episodic hypertension	Rare	Frequent	Rare
Ectodermal features			
Dry skin	No	No	Consistent
Fractures	29%	40%	71%
Scoliosis	59%	85%	23%
Intelligence			
IQ <65	Common (38%)	Uncommon (10%)	Common (33%)
Hyperactivity	Common (41%)	Uncommon	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.

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

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 botulinum toxin

Disorders of the Eye

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 Picture tests -Allen figures -Lea symbols	<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. 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 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 (Brückner 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

Table 621-1 Causes of Childhood Severe Visual Impairment or Blindness

CONGENITAL	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
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	
Glucoma	
Cataracts	
Persistent hyperplastic primary vitreous	
PHAKOMATOSES	
Tuberous sclerosis	
Neurofibromatosis (special association with optic glioma)	
Sturge-Weber syndrome	
von Hippel-Lindau disease	
TUMORS	
Retinoblastoma	
Optic glioma	
Perioptic meningioma	
Craniopharyngioma	
Cerebral glioma	
Astrocytoma	
Posterior and intraventricular tumors when complicated by hydrocephalus	
Pseudotumor cerebri	
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	
INFECTIOUS/INFLAMMATORY PROCESSES	
Encephalitis, especially in the prenatal infection syndromes caused by <i>Toxoplasma gondii</i> , cytomegalovirus, rubella virus, <i>Treponema pallidum</i> , herpes simplex virus	
Meningitis; arachnoiditis	
Chorioretinitis	
Endophthalmitis	
Trachoma	
Keratitis	
Uveitis	
HEMATOLOGIC DISORDERS	
Leukemia with central nervous system involvement	
VASCULAR AND CIRCULATORY DISORDERS	
Collagen vascular diseases	
Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage	
Central retinal occlusion	
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	
OTHER	
Retinopathy of prematurity	
Sclerocornea	
Conversion reaction	
Optic neuritis	
Osteopetrosis	

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

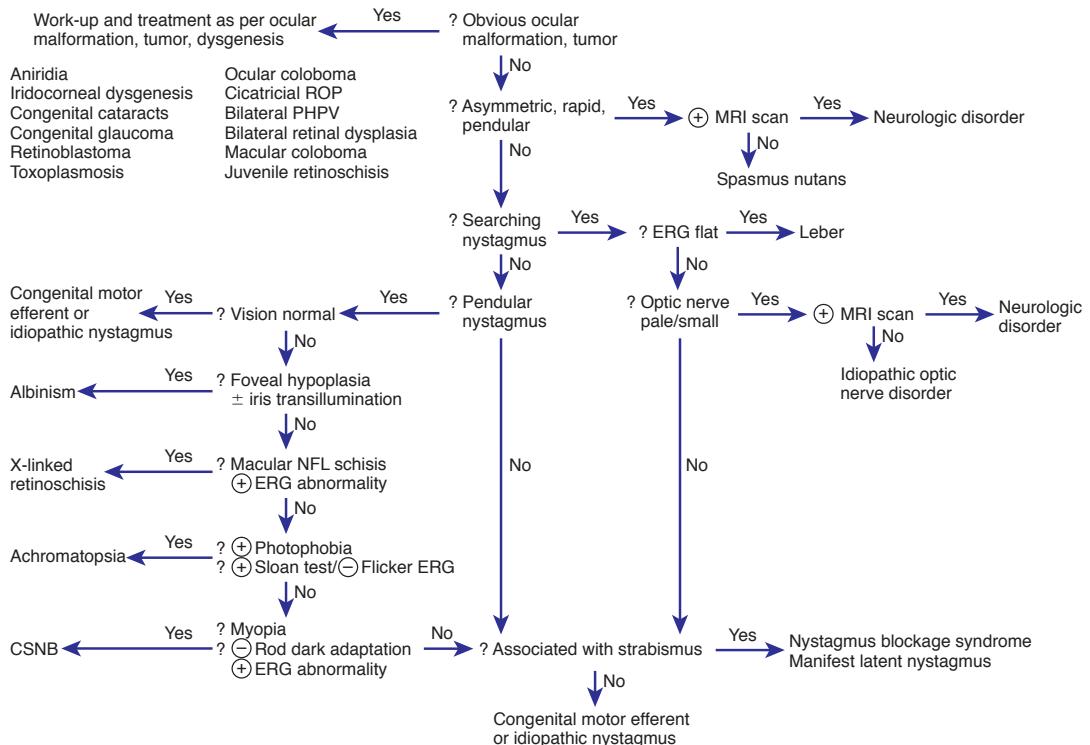


Figure 623-7 Algorithm for the work-up of an infant with nystagmus. ⊕, positive; ⊖, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. (From Nelson LB: Harley's pediatric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

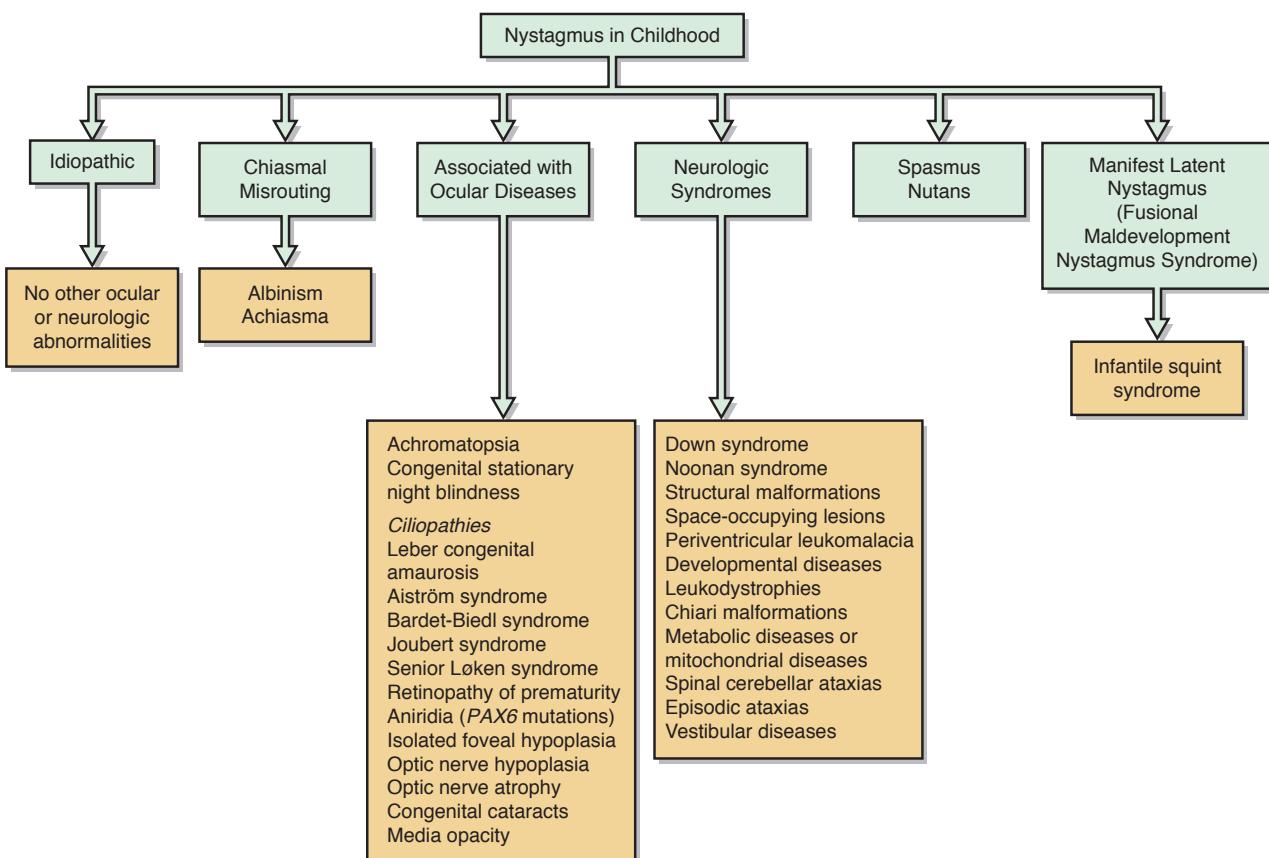


Figure 623-8 Classification of nystagmus based on associated diseases. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)

Table 626-1 The Red Eye

CONDITION	ETIOLOGY	SIGNS AND SYMPTOMS	TREATMENT
Bacterial conjunctivitis	<i>Haemophilus influenzae</i> , <i>Haemophilus aegyptius</i> , <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Moraxella catarrhalis</i>	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia	Topical antibiotics, parenteral ceftriaxone for gonococcus, <i>H. influenzae</i>
Hyperacute bacterial conjunctivitis	<i>Neisseria gonorrhoeae</i> , <i>Neisseria meningitidis</i>	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	<i>Chlamydia trachomatis</i> , gonococcus, chemical (silver nitrate), <i>S. aureus</i>	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and erythromycin for <i>C. trachomatis</i>
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, <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>Pseudomonas</i> , <i>Acanthamoeba</i> , 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	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Candida albicans</i> , associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iritis)	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, <i>Toxocara canis</i>	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	<i>S. aureus</i> , <i>Staphylococcus epidermidis</i> , seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, <i>Phthirus pubis</i> , <i>Pediculus capitis</i>	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses, lid hygiene
Dacryocystitis	Obstructed lacrimal sac: <i>S. aureus</i> , <i>H. influenzae</i> , 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	<i>S. aureus</i> , <i>Streptococcus</i> , 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: <i>H. influenzae</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , streptococci Trauma: <i>S. aureus</i> Fungi: <i>Aspergillus</i> , <i>Mucor</i> 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: <i>S. aureus</i> , streptococci Bacteremia: pneumococcus, streptococci, <i>H. influenzae</i> , <i>S. aureus</i>	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.

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, Gentesol) 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

*

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

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.

Table 628-1 Differential Diagnosis of Cataracts

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

3048 Part XXIX ♦ Disorders of the Eye

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 (uveoocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)
- Behçet syndrome
- Lyme disease

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.

Table 629-2 Examination Schedule for Children with JIA Without Known Iridocyclitis

JIA SUBTYPE	AGE OF ONSET	
	≤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 of duration	Annually regardless of duration

Table 632-1 Primary and Secondary Childhood Glaucomas

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

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

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.

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	Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies
	GJB3	Symmetric high-frequency sensorineural loss beginning in the 3rd decade
DFNA3	GJB2	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
	GJB6	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

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.

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.
Waardenburg (WS2)	MITF, others	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.
Branchiootorenal	EYA1	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.
CHARGE syndrome	CHD7	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.
Goldenhar syndrome	Unknown	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.
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.
Alport syndrome	COL4A3, COL4A4, and COL4A5	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.
Usher syndrome type 1 (USH1)	USH1A, MYO7A, USH1C, CDH23, USH1E, PCDH15, USH1G	Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nystagmus become severe enough to be noticeable).
Usher syndrome type 2 (USH2)	USH2A, USH2B, USH2C, others	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.
Usher syndrome type 3 (USH3)	USH3	Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function.

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

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.

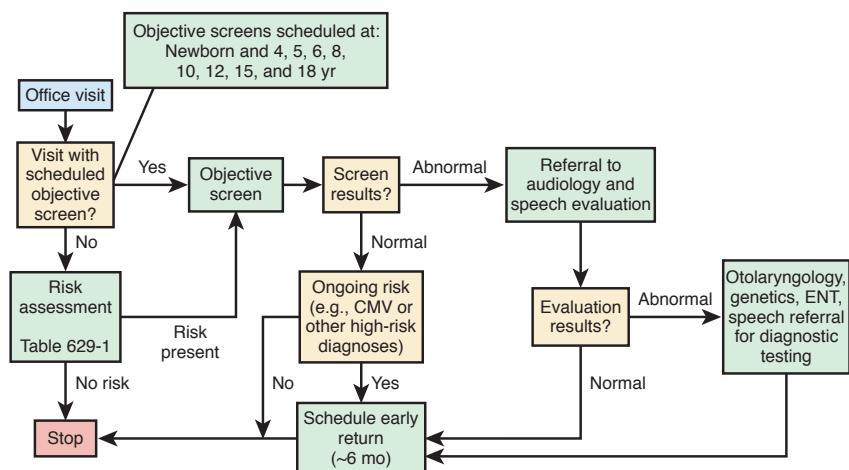


Figure 637-2 Hearing-assessment algorithm within an office visit. CMV, cytomegalovirus; ENT, ear, nose, and throat. (From Harlor AD Jr, Bower C: Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening, Pediatrics 124:1252–1263, 2009, Fig. 1, p. 1254.)

Table 637-6 Criteria for Referral for Audiologic Assessment

REFERRAL GUIDELINES FOR CHILDREN WITH "SPEECH" DELAY	
AGE (mo)	
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, 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)

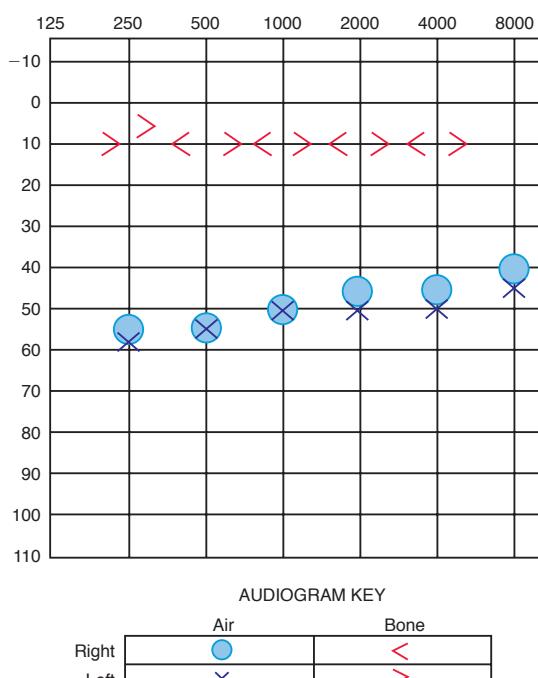


Figure 637-3 Audiogram showing bilateral conductive hearing loss.

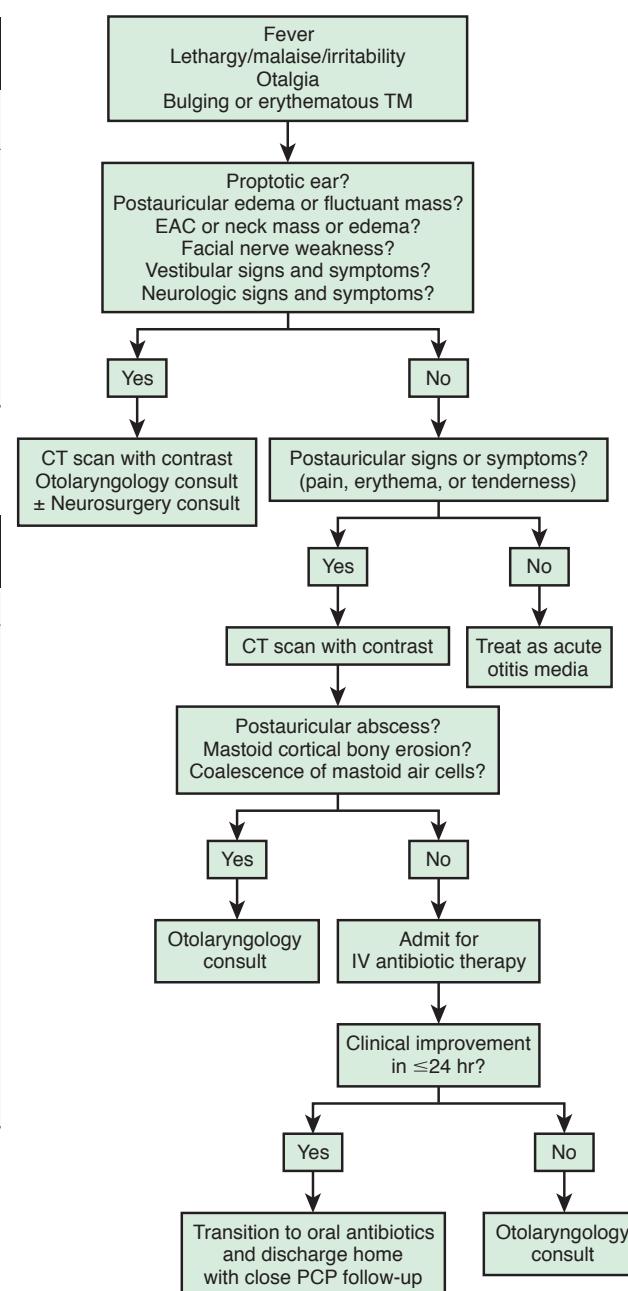


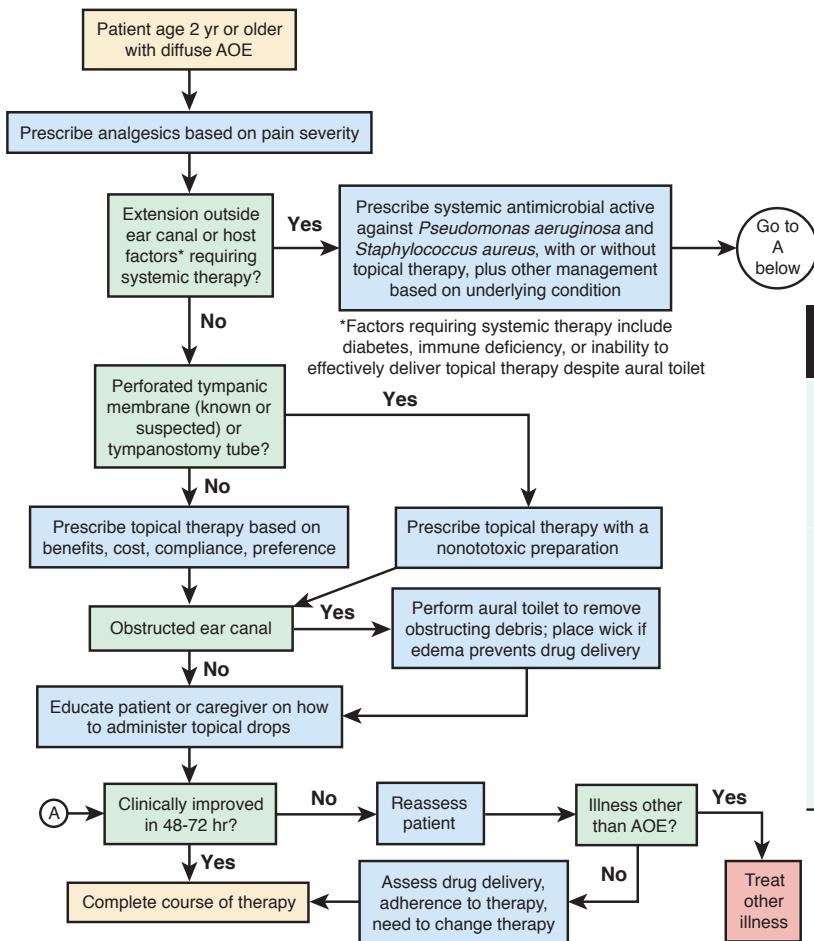
Figure 640-7 Diagnosis and treatment algorithm for cases of suspected acute mastoiditis.

3084 Part XXX ◇ The Ear

Table 640-1 Treatments for Otolgia 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.

**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 Foundation, Inc.)

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.

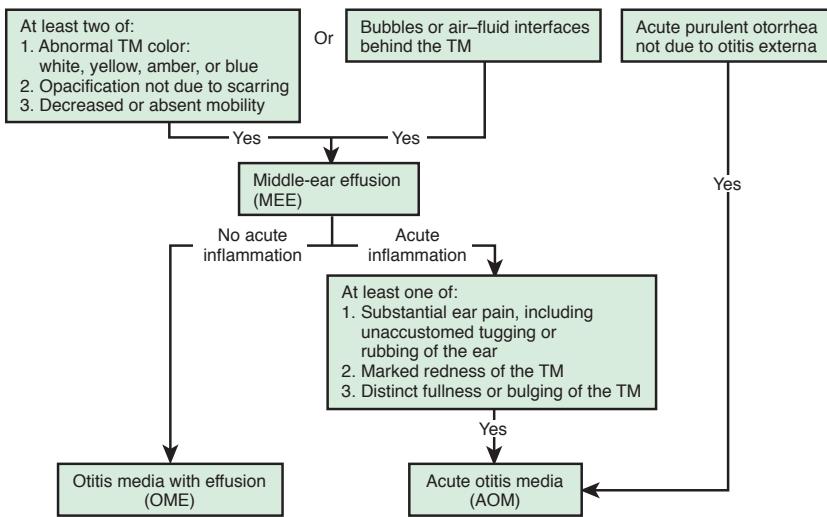


Figure 640-1 Algorithm for distinguishing between acute otitis media and otitis media with effusion. TM, tympanic membrane.

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.

Table 640-5 Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess

DISEASE	Postauricular Signs and Symptoms				EXTERNAL CANAL INFECTION	MIDDLE-EAR EFFUSION
	CREASE*	ERYTHEMA	MASS	TENDERNESS		
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.

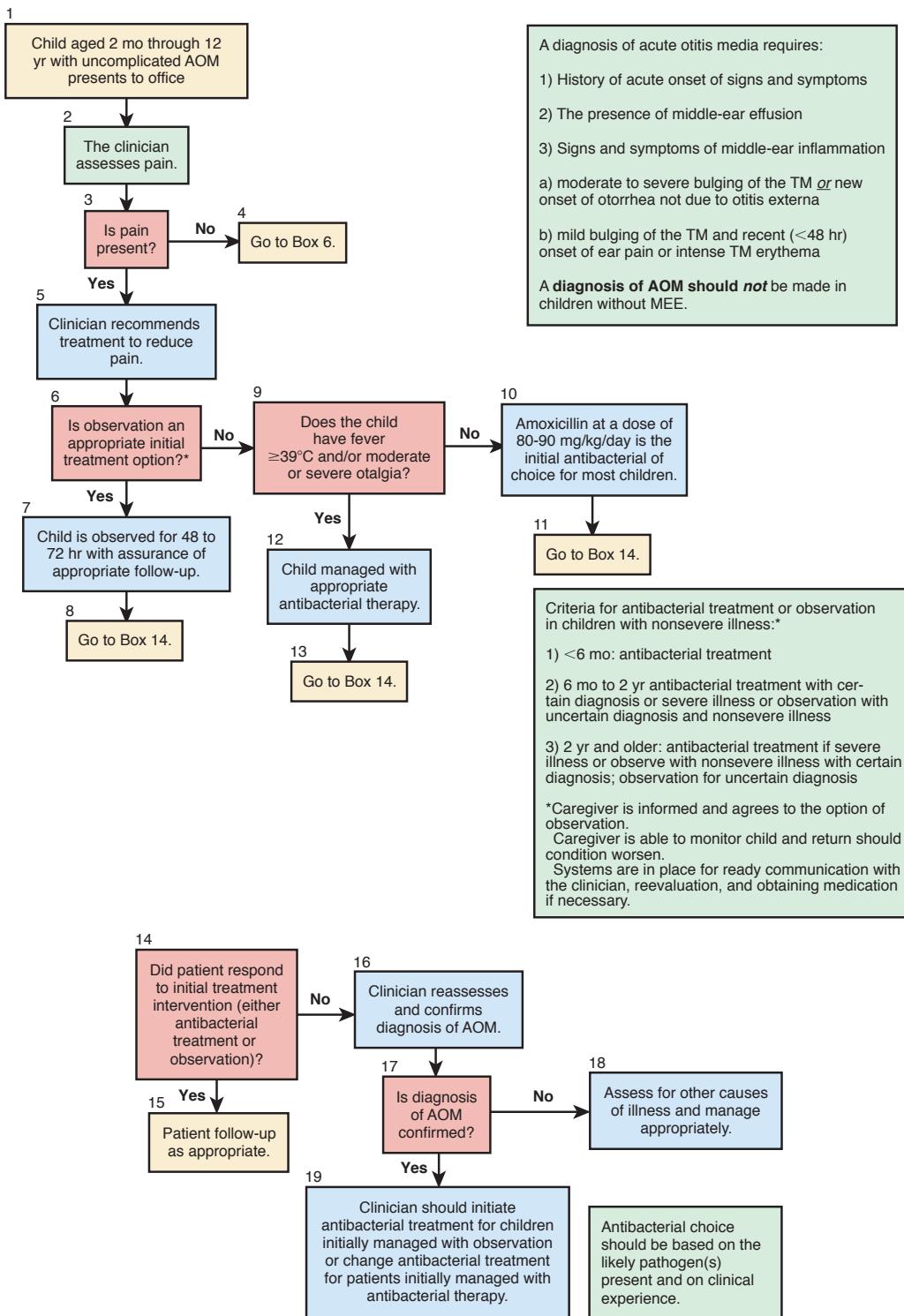


Figure 640-6 Management of acute otitis media. (From Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media, Pediatrics 113:1451-1465, 2004.)

The Skin

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	Seborheic dermatitis Atopic dermatitis Juvenile dermatomyositis
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring	Subacute cutaneous lupus erythematosus 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 Seborheic dermatitis
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly, macules; discrete papules overlying knuckles	Periorcular 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	Behcet syndrome Vasculitis <i>Yersinia</i> colitis
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Diffuse	Skin biopsy Leukocytosis ESR	Fever Flu-like illness Conjunctivitis	Infection Urticaria Erythema multiforme Urticular 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.

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
Exanthematosus	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 exanthematosus 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		

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.