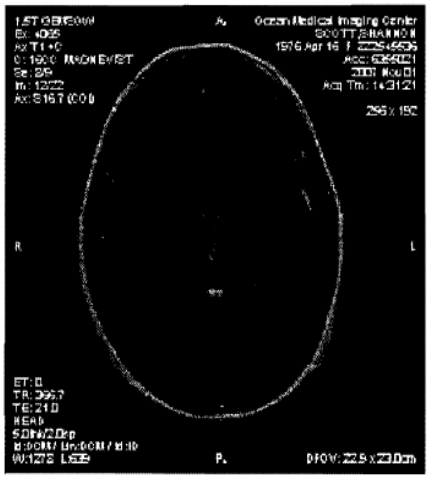
A Case of Acquired Hydrocephalus

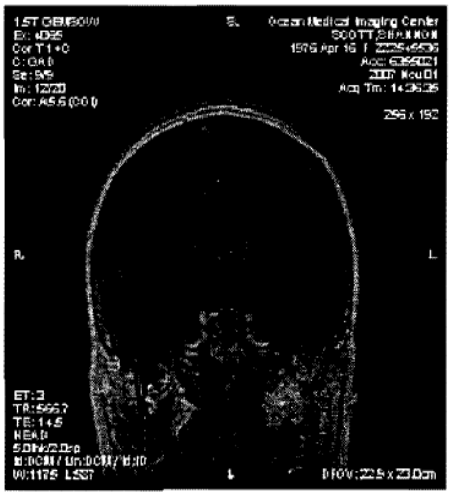
History: 31 year-old white female presenting with increasing "migraine" headaches.

Differential Diagnosis of Headache:

- *Tension-type*
- *Migraine*
- *Cluster*
- **Trigeminal neuralgia**
- Vascular causes (stroke, IPH, **SAH, SDH, AVM, unruptured aneurysm**, arterial hypertension, venous thrombosis)
- Infection (meningitis, encephalitis, **abscess**)
- **Brain tumor**
- **Hydrocephalus**
- Decreased CSF (s/p LP, etc.)
- Extracranial causes (sinusitis, TMJ, temporal arteritis)

Imaging:



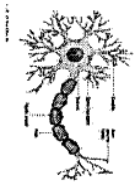


Differential Diagnosis of Hydrocephalus:

- Obstruction/Noncommunicating
  - *Congenital*: Neural tube defects, congenital aqueductal stenosis, X-linked hydrocephalus, Chiari malformation, Dandy-Walker malformation, Vein of Galen malformation, other congenital malformations, syndromic forms (with trisomies, etc.), intrauterine infection (TORCHS)
  - *Acquired*: CNS infection, tumor, post-hemorrhage (inflammation/scarring)
- Impaired CSF absorption—Inflammation of subarachnoid villi
- Excessive CSF production (rare)—Functional choroid plexus papilloma

Differential Diagnosis of Third Ventricle Lesion:

- Astrocytoma, GBM, oligodendroglioma, craniopharyngioma	- Ependymal tumor/cyst	- Choroid plexus papilloma
- Metastasis	- Colloid cyst	- Choroid plexus carcinoma
- Medulloblastoma, primitive neuroectodermal tumor, teratoma (kiddies)	- Epidermoid/dermoid cyst	- Central neurocytoma
- Intraventricular meningioma		- Primary CNS B-Cell lymphoma of the choroid plexus (!)



Neurology 200
September 2007

Amyotrophic Lateral Sclerosis (ALS)

1) Extreme physical activity is a risk factor for development of ALS. TRUE OR FALSE
2) There is a higher incidence of ALS in U.S. Gulf War veterans than in the general population. TRUE OR FALSE
3) What is the most common autonomic symptom patients with ALS experience? _____
4) What percentage of ALS patients had sensory abnormalities identified by NCS in one study?
a) 65% b) 4% c) 12% d) 23%
5) What laboratory tests do you need to monitor for patients on riluzole therapy? _____

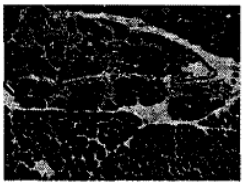
Case: A 62 year-old white male office worker with a history of HTN, hypothyroidism, and CAD s/p stent placement presents with left foot drop and hyperreflexia at the left ankle. Patient notes no other weakness and denies any sensory or autonomic symptoms. No other abnormalities are present on exam. Can this patient be diagnosed with ALS at this point? What is this patient's likely prognosis and disease course? How typical is this patient's history for ALS?

Epidemiology:

- Incidence in Europe/North America = 1.47-2.7 per 100,000 per year
- Prevalence in Europe/North America = 2.7-7.4 per 100,000
- 90% of cases are sporadic, 10% are familial
- Possible higher incidence in **Caucasians**
- 1.3-1.5 times more common in **males** than females
- Peak incidence is at age 74
- Only clear risk factors are age and family history
- Physical activity and trauma are probably not risk factors for developing the disease, but may contribute to younger age of onset and faster progression
- Environmental exposures (heavy metals, factory byproducts, DEET, etc.) have also been proposed as risk factors, but none have been confirmed thus far
- Survival motor neuron (SMN) gene mutations may be related to disease progression as well as risk of sporadic form
- Prevalence is high in Guam, West New Guinea, and parts of Japan—this may be related to consumption of cycad plants that are rich in an excitatory amino acid (BMMA)

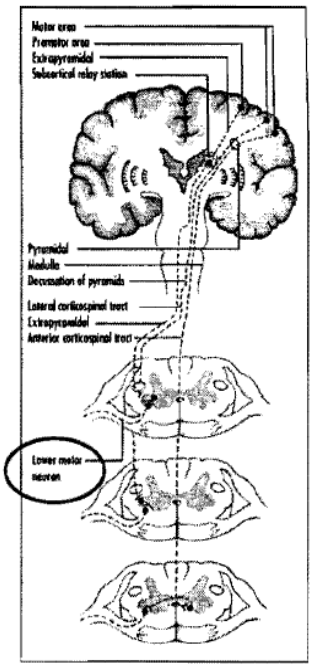
Pathophysiology:

- Degeneration and death of pyramidal and Betz cells in the cortex, leading to gliosis in the corticospinal tract



- Loss of large myelinated fibers in motor nerves, with denervation atrophy of muscles and fiber type grouping
- Loss of frontal or temporal cortical neurons, as well as loss of neurons in other locations, including the hippocampus (in some cases)
- Intracellular inclusions in degenerating neurons and glia—neurofilament inclusions in spinal motor neurons, Bunina bodies (cystatin C aggregates), and ubiquinated inclusions

- Etiology is unknown—some proposed mechanisms:
  - Superoxide dismutase type 1 mutations (toxic gain of function vs. abnormal protein aggregation)
  - Excitotoxicity (excessive glutamate)… riluzole is anti-glutaminergic!
  - Defective cytoskeleton (problems with axonal transport, etc.)
  - Mitochondrial dysfunction (possibly from oxidative stress)
  - Viral infection
  - Excessive apoptosis
  - Abnormalities in growth factors (VEGF of special recent interest)
  - Microglial activation/Inflammation

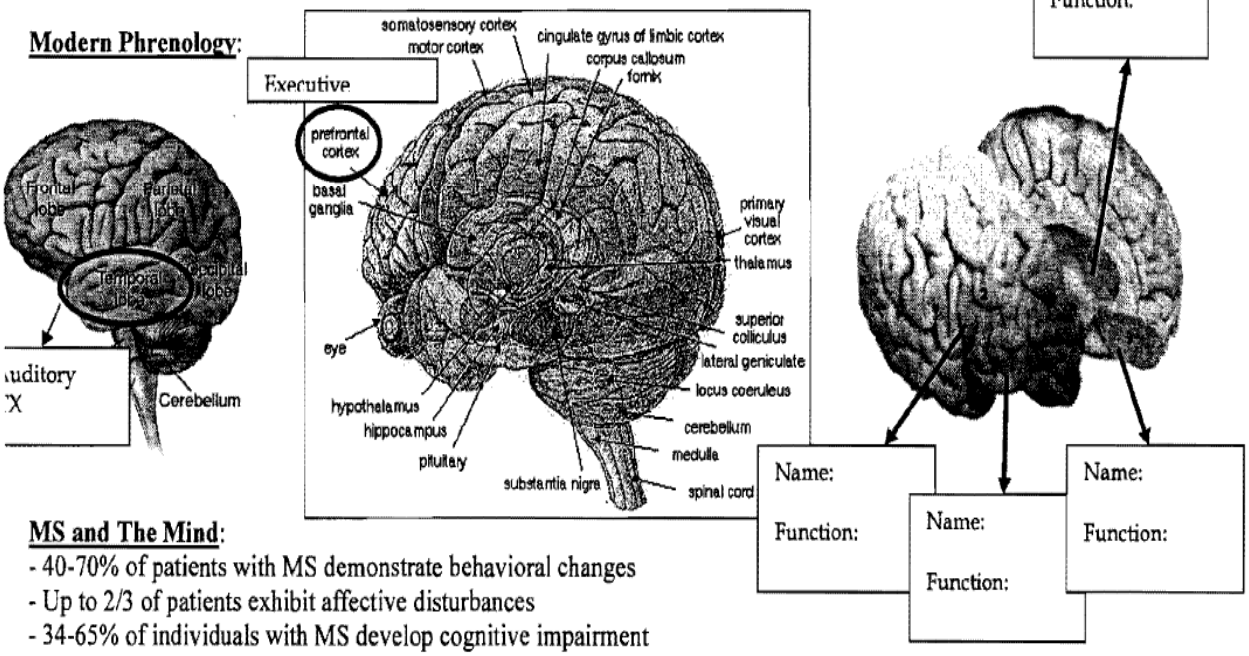


The Psychiatric Manifestations of Multiple Sclerosis (MS)

The Basics:

- MS is demyelinating disease of **unknown etiology**, with the predominant theory being that it results from **autoimmune IgG** production and alteration of lymphocytes in the CNS, causing inflammation, demyelination, and axonal disruption
- **Highest risk groups**: Females, Northern Europeans, smokers, patients with other autoimmune diseases
- Diagnosis based on **symptoms and lesions disseminated in space in time**, i.e. >1 attack + white matter lesions in >1 area of the brain, at >1 time
- Can present with a **wide variety of neurological manifestations**, including sensory symptoms (optic neuritis, numbness, tingling, pain), motor symptoms (weakness, internuclear ophthalmoplegia), fatigue, epilepsy, and bowel/bladder/sexual dysfunction
- **Course** of disease is variable and can be classified into four categories:
    1) Relapsing-remitting (66-90% at onset)
    2) Primary progressive (10-19% at onset)
    3) Progressive relapsing (15% at onset)
    4) Secondary progressive (~30% of relapsing eventually develop purely progressive disease)
- **Treatments** are generally aimed at either immunosuppression (corticosteroids, interferon, glatiramer acetate, cyclophosphamide, newer biologic immune modulators) or symptom relief (stimulants for fatigue, muscle relaxants for spasticity, etc.)
- **Progression of disability** is highly variable, but is slow in most patients
- Life expectancy is 83% of the general population's life expectancy, with mean age of death of 58

Modern Phrenology:



MS and The Mind:

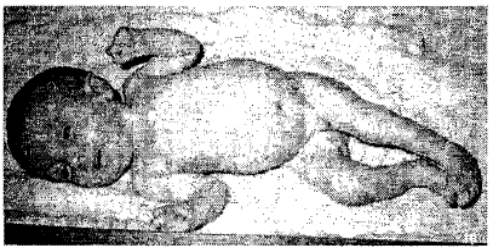
- 40-70% of patients with MS demonstrate behavioral changes
- Up to 2/3 of patients exhibit affective disturbances
- 34-65% of individuals with MS develop cognitive impairment
- MS can cause significant social dysfunction—divorce rates are twice the rate of the general population
- Diagnosis of psychiatric disorders in patients with MS can be difficult due to **overlap between neurological symptoms of MS and clinical criteria for psychiatric disorders** (such as fatigue, sleep disturbance, appetite changes, difficulties with concentration, etc.)
- The increased rates of psychiatric disorders in the MS population may result from a combination of the emotional impact of the disease and its resulting disability, the physical changes in the CNS, and/or the side effects of some medications used for treatment of the disease

Down Syndrome:
Clinical Features, Management, and Special Considerations

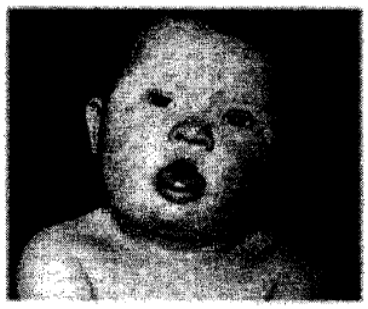
Epidemiology:
- 1/1000 live births
- Increasing risk with increasing maternal age
- Increasing risk with increasing paternal age???

Genetics:
Trisomy 21 can happen from 3 different cytogenetic abnormalities:
- Nondisjunction (94% of cases)
- Unbalanced Robertsonian translocation (3-4%)
- Mosaicism (2-3%)

Trisomy ____:
- Midline defects (face and forebrain): holoprosencephaly, microcephaly, seizures, severe MR, severe eye defects, cleft



Trisomy ____:
- MR, hypertonia (scissoring), delicate facial features, clenched hands with overlapping digits, rocker bottom feet



Trisomy _____:
- brachycephaly, epicanthal skin folds, Brushfield spots, upslanting palpebral fissures, protruding tongue, flat nasal bridge, folded/dysplastic ears, narrow palate, short neck, brachydactyly, clinodactyly, transverse palmar crease, space between first and second toes, MR

Health Supervision for Patients with Down Syndrome

Growth	- Measure at all health supervision visits - Watch for obesity or excessive weight gain (e.g. hypothyroidism) or loss (e.g. celiac disease) - Promote physical activity and caloric intake less than generally recommended for age
GI	- Evaluate for GI abnormalities at birth (duodenal atresia, imperforate anus, TE fistula) - Screen for celiac disease beginning at age 2 - Remain aware of increased risk of Hirschsprung's - Screen for feeding difficulties/aspiration risk
Pulmonary/Sleep	- Screen for obstructive sleep apnea at all visits after 1 year of age
Endocrine	- Thyroid function tests at birth, 6 months, 12 months, and then annually - Monitor for type 1 diabetes
ENT	- Hearing screen at neonatal visit (BAERs and otoacoustic emission if necessary) and evaluate every 6 mos. until age 3 and then annually
Ophthalmology	- Full assessment to monitor for strabismus, nystagmus, cataracts before 6 months - Assess acuity at least every 2 years until age 5 and then annually after age 5 - Screen for keratoconus and lens opacities yearly after age 5
Cardiology	- Echocardiogram at birth to monitor for CHD - Periodic evaluation for mitral valve prolapse and aortic regurgitation in adolescence/adulthood
Hematology	- CBC with differential at birth (myeloproliferative disorders/polycythemia) - CBC annually between 13 and 21 years to monitor for abnormalities
Orthopedics	- Monitor calcium and Vitamin D intake and supplement if necessary (osteopenia) - Spine radiographs to monitor atlantoaxial instability between 3 and 5 years OR Annual neurologic evaluation for evidence of spinal cord compression (Special Olympics requires neck radiographs) - Screen for other orthopedic disorders
Dental Hygiene	- Encourage good hygiene and dental visits every 6 months
Dermatology	- Screen for skin disorders, especially in adolescence (folliculitis is most common)
Education	- Screen to ensure appropriate services and supports are in place
Behavior/ Psychiatry	- Screen for psychiatric/behavioral disorders, especially ADHD, conduct disorder, depression, autism, and aggressive behavior
Sexuality	- Address puberty and sexuality in adolescent visits (including menstrual hygiene, PMS, etc. for females) - Provide information about contraceptive options to females - Screen for sexual abuse, particularly for females

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Nephrotic syndrome – chronic management

Definition: heavy proteinuria (albuminuria greater than 3 g/24 hours), hypoalbuminemia (less than 3.0 g/dL), and peripheral edema. (Normal urinary protein excretion is less than 150mg/day)

General pathogenesis: the normal glomerulus blocks protein filtration with physical and electric forces (GAGs repel anionic proteins). Albumin primarily blocked by the latter. The destruction of podocytes is a major cause of increased permeability. There is early evidence for an antibody-mediated mechanism.

Major causes: The majority (50-75%) are due to primary disease of the glomerulus. Certain systemic diseases can also cause this picture:

- Primary causes vary by age; in kids think Minimal Change until proven otherwise; in the elderly think membranous glomerulonephritis

Relative frequency of primary glomerular diseases causing nephrotic syndrome (%)			
	Children	**Adults <60 yrs**	**Adults >60 yrs**
Minimal Change	76%	20	20
Focal Segmental glomerulosclerosis	8	15	2
Membranous glomerulonephritis	7	40	39
Membranoproliferative glomerulonephritis	4	7	0
Other diseases	5	18	39

Lewis, EJ "Management of Nephrotic Syndrome in adults" as cited in NEJM volume 338, no 17.

- Secondary causes include diabetes (most common), lupus and amyloidosis
- Most glomerulopathies can be asst with malignancy, especially membranous glomerulonephritis; important to keep this in mind with elderly patients

Symptoms/presentation: Patients might be asymptomatic, or might present with classic edema (periorbital, b/l LE, ascites, even anasarca). Heavy proteinuria will result in "frothy urine." Patients might also have a severe hyperlipidemia on routine physical.

Diagnosis: 24-hour urine is the gold standard

- Easier way to diagnose is the **protein-to-creatinine** ratio (mg/mg) on a random urine specimen; the ratio is roughly equal to the g/24 hr
- Urinalysis will show protein and **maltese cross** under polarized light due to lipid
- Urine tests/serologies to determine cause: ANA, complement, protein electrophoresis, RPR, HBV/HCV, cryoglobulins, ASO
- **Renal biopsy** is indicated in adults to determine specific cause

Clinical implications:

Edema:

- Previously thought to be due to "underfill" – lose albumin → decreased oncotic pressure and loss of fluid from vasculature → activation of renin-angiotensin and aldo → fluid overload; but patients usually have a *normal plasma volume* and ANP is up (which occurs in hyper not hypovolemia)
- FSGS relapse patients show sodium retention before hypoalbuminemia, suggesting sodium retention is primary; appears to be mainly distal resorption
- Key danger of nephrotic edema is hypovolemia in early stages (when sodium resorption/albumin excretion is off balance)

- Treatment:
  - Low sodium diet (<3g per day)
  - Diuretics; furosemide and thiazide combination is effective; *need higher Lasix doses due to hypoalbuminuria*
  - Albumin infusion if symptomatic hypovolemia (concern re. pulmonary edema/HTN)

Hyperlipidemia

- ↑LDL/IDL/VLDL with or without ↑TG; HDL generally normal
- Over 80 percent of patients with the nephrotic syndrome also have LDL cholesterol levels greater than 130 mg/dL
- Elevated levels of apolipoprotein B due to overproduction (liver protein production increased) and decreased catabolism (unclear why – likely an enzyme lost in urine)
- Treatment: correction of nephrotic syndrome, also soy protein diet (25-30 percent reduction in lipids), statin (decreased total cholesterol by 31 to 33% with simvastatin); ACE inhibitors also shown to decrease cholesterol (9% in one small study)

Hypercoaguability

- 50% of patients have a thromboembolic complication
- Venous > arterial
- Due to low levels AntiThrombin III, plasminogen, increased fibrin, increased platelet activity
- Key complications:
  - Stroke, PE, DVT, MI (RR 4.4)
  - Renal vein thrombosis, which is particularly common in membranous glomerulonephritis; symptoms include flank pain, hematuria, large kidney

- Prophylactic anticoagulation? Possibly for high risk patients (serum albumin <2.0g/dL)
- Known chronic asymptomatic RVT? Idea is to prevent PE, but no evidence that this works
- Known symptomatic RVT, PE, DVT: heparin then warfarin for 6-12 months; *note heparin may be less effective given low ATIII levels*

Infection: low levels of IgG leads to susceptibility. Consider pneumo, influenza vaccines

Low binding proteins

- Affects absorption of metals (iron, copper, zinc), vitamins (especially D)
- Affects levels of thyroid, corticosteroids (though little evidence of clinical sign)
- Drug binding – prednisolone, warfarin and other drugs need to be watched carefully

Treatment:

- Treat underlying cause: Some responsive to corticosteroids (e.g. minimal change) and/or immunosuppressants (FSGS, MGN)
- Reduce proteinuria:
  - ACE inhibitors/ARBs: *requires one month of treatment before effect peaks;* only partly explained by lower BP
  - Low protein diet? Not worth the risk of protein malnutrition (top cause death in ESRD), but low-fat soy protein diet still works well (0.7 g/kg/day)
- Hyperlipidemia: Statin plus ACE/ARB; little evidence that diet helps (other than soy)
- Anticoagulation: consider ASA or dipyramidole (some evidence it might help for proteinuria too); heparin/warfarin only if known thromboembolic event

Sources: UptoDate online
Orth, S et al. "The Nephrotic Syndrome," NEJM, Vol 338 No 17, 1202-1211.
Appel, G. "Improved Clinical Outcomes in Nephrotic Syndrome." Cleveland Clinic, Feb 2006.