Acute Disseminated Encephalomyelitis (ADEM)

e. prognosis: 90% 5-year survival in fulminant disease; 70% 5-year survival in relapsing-remitting disease

2. Marburg’s variant of multiple sclerosis
   a. pathophysiology: the pathophysiology is generally considered to be the same as that for multiple sclerosis, although there is evidence that Marburg’s variant is related to expression of an immature or modified form of myelin basic protein
      i. histology: a large, acute demyelinating lesion of a single hemisphere (60% of cases) that rapidly increases in size and is associated with mass effect due to edema
   b. symptoms: predominantly relate to rapidly increased in intracranial pressure
   c. diagnostic testing
      i. cerebrospinal fluid is usually normal except for a minimal pleocytosis
      ii. neuroimaging: lesions are often mistaken for tumor or cerebritis because the lesion contrast enhances and shrinks after steroid treatment
   d. treatment: glucocorticoids, IVg, plasmapheresis, mitoxantrone, cyclophosphamide
   e. prognosis: mortality is usually due to mass effect and herniation, or to involvement of the brainstem in the demyelinating process

3. Balo’s concentric sclerosis (Box 4.2)
   a. histology: demyelinating lesions that are centered around a perivascular collection of inflammatory leukocytes, wherein demyelination and inflammation occur in concentric rings that alternate with areas of preserved myelin that are of decreasing severity with increasing distance from the center
      i. areas of preserved myelin exhibit small amounts of demyelination and remyelination, suggesting active suppression of the disease process or else a lesion involving acute and chronic demyelination
   b. symptoms: headache, impaired cognitive and behavioral function, seizures
   c. diagnostic testing
      i. neuroimaging demonstrates multiple concentric ring-enhancing lesions that may have mass effect (Fig. 4–3); typical multiple sclerosis lesions are also observable
      ii. cerebrospinal fluid usually exhibits monocyte pleocytosis and occasionally oligoclonal bands
   d. treatment: as per multiple sclerosis
   e. prognosis: usually has a fatal outcome within a few weeks, although spontaneous remission is possible; survivors do not reliably develop multiple sclerosis

IV. Acute Disseminated Encephalomyelitis (ADEM)

1. Pathophysiology: typically develops during or within 2 weeks of a preceding infection with measles, rubella, smallpox, or chickenpox, or after a vaccination (rabies or smallpox vaccines), although a preceding infection or vaccination is not necessary to establish the diagnosis
   a. mumps, influenza, and Mycoplasma pneumoniae upper respiratory tract infection are rare associations
2. Histology: diffuse and extensive demyelination with axonal sparing involving perivascular cuffing with lymphocytes and reactive astrocyte hyperplasia; demyelination often involves the cortical–subcortical junction
3. Epidemiology: common in children
4. Symptoms: acute-onset multifocal neurological abnormalities that increase in severity over a few days and that may involve any part of the brain and spinal cord; ADEM typically has encephalopathy, fever, meningismus, and (possibly) seizures

Figure 4–3  Balo’s concentric sclerosis demonstrating the hallmark alternating layers of demyelination and preserved myelin (straight arrow), as well as a confluent area of demyelination (curved arrow). (From Charagoozoo AM, Poe LB, Collins GH. Antemortem diagnosis of Balo concentric sclerosis. Radiology 1994; 191:818, Fig. 2A. Reprinted by permission.)

Box 4.2  Schilder’s Disease
✧ This unclear disease entity typically is thought to have a monophasic course of focal neurological injury and elevated intracranial pressure.
✧ Neuroimaging often demonstrates large enhancing lesions with mass effect.
5. **Diagnostic testing**
   a. cerebrospinal fluid exhibits mild lymphocytosis and increased protein but a normal opening pressure
      i. differentiate ADEM from Reye syndrome, which has normal cerebrospinal fluid and elevated serum ammonia levels; oligoclonal bands are likely to be present in postinfectious ADEM
      ii. serology also for measles, mumps, varicella zoster, and herpes simplex virus (HSV)
   b. neuroimaging: unlike the MRI lesions of multiple sclerosis, ADEM may involve the basal ganglia and thalamus, and have large confluent lesions with mass effect (Fig. 4–4)

6. **Treatment:** High-dose glucocorticoids; IVg, cyclophosphamide, or plasmapheresis in refractory cases

7. **Prognosis:** 20% mortality and at least 35% eventually will develop multiple sclerosis
   a. focal neurological deficits generally improve but 95% survivors with infectious ADEM and 30% with postvaccine ADEM have residual psychiatric disorders, dementia, or epilepsy

V. **Acute Necrotizing Hemorrhagic Encephalomyelitis**

1. **Pathophysiology:** essentially a hyperacute form of ADEM that may be associated with *Mycoplasma pneumoniae* upper respiratory tract infection
   a. histology: intense lymphocytic perivascular inflammation with necrosis and hemorrhage from small blood vessels, causing petechiae; progresses to liquefactive destruction of the white matter of both hemispheres, brainstem, and cerebellar peduncles

2. **Symptoms:** initially meningitis-like symptoms but rapidly develops seizures and focal neurological injury; progresses to coma that rapidly is fatal

3. **Diagnostic testing**
   a. systemic evidence of infection (e.g., increased WBC count)
   b. cerebrospinal fluid exhibits increased opening pressure, monocytopsis, increased protein, and normal glucose
   c. neuroimaging: large areas of increased T2 signal intensity with small areas of reduced T2 signal representing hemorrhage; lesions have significant edema and mass effect

4. **Treatment:** as per multiple sclerosis

5. **Prognosis:** usually fatal within several days

VI. **Nutrition- and Electrolyte-Related Demyelinating Disorders**

1. **Central pontine myelinosis**
   a. pathophysiology: usually occurs as a reaction to the rapid correction of severe, long-standing (i.e., > 2-day duration) hyponatremia
      i. prolonged systemic hyponatremia causes loss of sodium and potassium from the brain extracellular fluid into the cerebrospinal fluid, and the loss of intracellular organic molecules (e.g., myoinositol, taurine, glutamate) that maintain cellular tonicity; rapid increases in the extracellular tonicity do not permit water equilibration with the intracellular environment, thereby causing cell death
      ii. particularly at risk are alcoholics (e.g., 10% occurrence after Wernicke’s encephalopathy), burn victims, patients with liver failure or transplantation, anorexics, malnourished patients, and patients on prolonged diuretic therapy
iii. histology: symmetric areas of myelin sheath splitting with some axon swelling that does not lead to axon loss; inflammation develops several days after injury

(1) involves a large demyelinating lesion in the center of the pons that spares a rim of the tegmentum and does not involving the tectum (Fig. 4–5); 10% also have demyelinating lesions elsewhere in the brain

b. symptoms: usually has a biphasic course that progresses over several days
i. encephalopathy and seizures caused by hyponatremia, which remit with correction to normonatremia
ii. dysarthria and dysphagia developing several days after correction to normonatremia, progressing to flaccid quadriparesis (locked-in syndrome)

(1) involvement of the tegmentum may result in pupillary and ocular motor abnormalities

c. treatment: prevention with gradual correction of hyponatremia, for example, no more than 8 mmol/L in 24 hours using 3% saline required sodium in mmol — ([Na]target — [Na]actual) • (30 L) (Box 4.3)

wherein 1 mL of 3% saline has 0.5 mmol Na

d. prognosis: unpredictable recovery

2. Marchiafava-Bignami disease
a. pathophysiology: classically described in chronic alcoholics who drink red wine but may occur in any alcoholic or malnourished patient; no known relation to nutritional deficiency, although associated with niacin deficiency (i.e., pellagra; see Chapter 13)

i. histology: symmetric areas of demyelination develop in the corpus callosum with histological changes similar to central pontine myelination but more frequently involving necrosis; demyelination may occur in any other region of white matter including the optic nerves

b. symptoms: most commonly resembles a rapid-onset frontal lobe dementia but its clinical course is highly variable and dependant upon the location of demyelination

c. treatment: vitamin supplementation

d. prognosis: often remits but may be acutely fatal

VII. Dysmyelinating Disorder (Box 4.4)

1. Pelizaeus-Merzbacher disease
a. pathophysiology: caused by abnormalities of the proteolipid protein (PLP) gene (Box 4.5); alternative splicing of this gene produces PLP (which accounts for 50% of myelin protein) and DM-20 protein (a minor myelin protein), which are necessary for myelin compaction

i. abnormalities in the PLP gene

(1) segmental aberrations: cause PLP overproduction; phenotype is

of variable severity, depending upon involvement of surrounding genes

(2) point mutations that prevent PLP translation: causes dysmyelination; phenotype is mild

(3) point mutations that cause incorrect PLP folding: causes oligodendrocyte apoptosis; phenotype is severe

(4) complete gene deletion: prevents PLP production; causes dysmyelination; phenotype is mild

ii. X-linked inheritance; mosaic inactivation of the X chromosome in heterozygous females leads to

(1) no symptoms if the abnormal PLP gene causes oligodendrocyte apoptosis because the few dead oligodendrocytes are replaced by healthy oligodendrocytes

"Dysmyelinating disease" is a misnomer—these diseases are not always characterized by abnormal myelin.

PLP is also mutated in a hereditary spastic paraplegia (SPG-2)
(2) minimal, transient symptoms during childhood if abnormal PLP gene only causes abnormal myelin compaction

iii. histology
(1) with oligodendrocyte apoptosis: patchy, tiger skin-like ("tigroid") myelination with a reduced number of oligodendrocytes [Fig. 4–6]; severity may be such that no myelin or oligodendrocytes are present in affected areas
(2) with abnormal oligodendrocyte myelination: diffusely reduced myelin staining of the white matter with a normal number of oligodendrocytes

b. symptoms (Table 4–2)
c. diagnostic testing: genetic testing for PLP duplications
   i. neuroimaging: large, symmetric areas of increased T2 signal in the white matter with diffuse atrophy
d. treatment: none specific
e. prognosis: severe disease with stridor causes death by 10 years of age

2. Alexander's disease

a. pathophysiology: caused by mutations in
   i. glial fibrillary acidic protein (GFAP) (in 90% cases): mutations cause a toxic gain-of-function that disrupts the normal ability of astrocytes to maintain oligodendrocyte viability
   ii. nicotinamide adenine dinucleotide (NADH) ubiquinone oxidoreductase flavoprotein-1: an uncommon association that has yet to be substantiated by autopsy confirmation

b. histology
   i. infants: a failure of normal central nervous system myelination followed by demyelination that is associated with eosinophilic inclusion bodies in swollen astrocyte processes (Rosenthal fibers); areas with these abnormalities develop in a perivascular and subependymal distribution
   ii. adult form: central nervous system demyelination is minimal; the key histological feature is a predominance of Rosenthal fibers that contain GFAP, heat-shock proteins, and α-β-crystallin
      (1) difficult to distinguish from multiple sclerosis or conditions with reactive gliosis, which also have Rosenthal fibers

c. symptoms (Box 4.6)
   i. infantile form: onset of symptoms < 2 years of age
      (1) developmental regression; megalencephaly with progressive head enlargement that can be (but is not always) due to underlying hydrocephalus
      (2) spasticity
      (3) seizures

Table 4–2 Symptoms of Diseases with Proteolipid Protein (PLP) Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Neonatal PMD</th>
<th>Classic PMD</th>
<th>Spastic paraplegic type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual impairment</td>
<td>Severe</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Motor impairment</td>
<td>Severe</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Speech acquisition</td>
<td>None</td>
<td>Normal</td>
<td>Motor aphasia</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Severe</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Other features</td>
<td>Stridor, seizures</td>
<td>Dystonias</td>
<td>Vision loss</td>
</tr>
</tbody>
</table>

Abbreviations: PMD, Pelizaeus-Merzbacher disease.