

of ALD/AMN. Diets low in VLCFAs and supplemented with Lorenzo's oil (erucic and oleic acids) reduce the levels of VLCFAs and increase the levels of C22 in serum, fibroblasts, and liver; however, several large, open-label trials of Lorenzo's oil failed to demonstrate efficacy.

### REFSUM'S DISEASE

Refsum's disease can manifest in infancy to early adulthood with the classic tetrad of (1) peripheral neuropathy, (2) retinitis pigmentosa, (3) cerebellar ataxia, and (4) elevated CSF protein concentration. Most affected individuals develop progressive distal sensory loss and weakness in the legs leading to footdrop by their 20s. Subsequently, the proximal leg and arm muscles may become weak. Patients may also develop sensorineural hearing loss, cardiac conduction abnormalities, ichthyosis, and anosmia.

Serum phytanic acid levels are elevated. Sensory and motor NCS reveal reduced amplitudes, prolonged latencies, and slowed conduction velocities. Nerve biopsy demonstrates a loss of myelinated nerve fibers, with remaining axons often thinly myelinated and associated with onion bulb formation.

Refsum disease is genetically heterogeneous but autosomal recessive in nature. Classical Refsum disease with childhood or early adult onset is caused by mutations in the gene that encodes for phytanoyl-CoA  $\alpha$ -hydroxylase (*PAHX*). Less commonly, mutations in the gene encoding peroxin 7 receptor protein (*PRX7*) are responsible. These mutations lead to the accumulation of phytanic acid in the central and peripheral nervous systems. Refsum's disease is treated by removing phytanic precursors (phytols: fish oils, dairy products, and ruminant fats) from the diet.

### TANGIER DISEASE

Tangier disease is a rare autosomal recessive disorder that can present as (1) asymmetric multiple mononeuropathies, (2) a slowly progressive symmetric polyneuropathy predominantly in the legs, or (3) a pseudo-syringomyelia pattern with dissociated sensory loss (i.e., abnormal pain/temperature perception but preserved position/vibration in the arms [Chap. 456]). The tonsils may appear swollen and yellowish-orange in color, and there may also be splenomegaly and lymphadenopathy.

Tangier disease is caused by mutations in the ATP-binding cassette transporter 1 (*ABC1*) gene, which leads to markedly reduced levels of high-density lipoprotein (HDL) cholesterol levels, whereas triacylglycerol levels are increased. Nerve biopsies reveal axonal degeneration with demyelination and remyelination. Electron microscopy demonstrates abnormal accumulation of lipid in Schwann cells, particularly those encompassing unmyelinated and small myelinated nerves. There is no specific treatment.

### PORPHYRIA

Porphyria is a group of inherited disorders caused by defects in heme biosynthesis (Chap. 430). Three forms of porphyria are associated with peripheral neuropathy: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). The acute neurologic manifestations are similar in each, with the exception that a photosensitive rash is seen with HCP and VP but not in AIP. Attacks of porphyria can be precipitated by certain drugs (usually those metabolized by the P450 system), hormonal changes (e.g., pregnancy, menstrual cycle), and dietary restrictions.

An acute attack of porphyria may begin with sharp abdominal pain. Subsequently, patients may develop agitation, hallucinations, or seizures. Several days later, back and extremity pain followed by weakness ensues, mimicking GBS. Weakness can involve the arms or the legs and can be asymmetric, proximal, or distal in distribution, as well as affecting the face and bulbar musculature. Dysautonomia and signs of sympathetic overactivity are common (e.g., pupillary dilation, tachycardia, and hypertension). Constipation, urinary retention, and incontinence can also be seen.

The CSF protein is typically normal or mildly elevated. Liver function tests and hematologic parameters are usually normal. Some patients are hyponatremic due to inappropriate secretion of antidiuretic hormone

(Chap. 401e). The urine may appear brownish in color secondary to the high concentration of porphyrin metabolites. Accumulation of intermediary precursors of heme (i.e.,  $\delta$ -aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen) is found in urine. Specific enzyme activities can also be measured in erythrocytes and leukocytes. The primary abnormalities on EDx are marked reductions in compound motor action potential (CMAP) amplitudes and signs of active axonal degeneration on needle EMG.

The porphyrias are inherited in an autosomal dominant fashion. AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporphyrin oxidase, and VP is associated with protoporphyrinogen oxidase deficiency. The pathogenesis of the neuropathy is not completely understood. Treatment with glucose and hematin may reduce the accumulation of heme precursors. Intravenous glucose is started at a rate of 10–20 g/h. If there is no improvement within 24 h, intravenous hematin 2–5 mg/kg per day for 3–14 days should be given.

### FAMILIAL AMYLOID POLYNEUROPATHY

Familial amyloid polyneuropathy (FAP) is phenotypically and genetically heterogeneous and is caused by mutations in the genes for transthyretin (TTR), apolipoprotein A1, or gelsolin (Chap. 137). The majority of patients with FAP have mutations in the TTR gene. Amyloid deposition may be evident in abdominal fat pad, rectal, or nerve biopsies. The clinical features, histopathology, and EDx reveal abnormalities consistent with a generalized or multifocal, predominantly axonal but occasionally demyelinating, sensorimotor polyneuropathy.

Patients with TTR-related FAP usually develop insidious onset of numbness and painful paresthesias in the distal lower limbs in the third to fourth decade of life, although some patients develop the disorder later in life. Carpal tunnel syndrome (CTS) is common. Autonomic involvement can be severe, leading to postural hypotension, constipation or persistent diarrhea, erectile dysfunction, and impaired sweating. Amyloid deposition also occurs in the heart, kidneys, liver, and corneas. Patients usually die 10–15 years after the onset of symptoms from cardiac failure or complications from malnutrition. Because the liver produces much of the body's TTR, liver transplantation has been used to treat FAP related to TTR mutations. Serum TTR levels decrease after transplantation, and improvement in clinical and EDx features has been reported.

Patients with apolipoprotein A1-related FAP (Van Allen type) usually present in the fourth decade with numbness and painful dysesthesias in the distal limbs. Gradually, the symptoms progress, leading to proximal and distal weakness and atrophy. Although autonomic neuropathy is not severe, some patients develop diarrhea, constipation, or gastroparesis. Most patients die from systemic complications of amyloidosis (e.g., renal failure) 12–15 years after the onset of the neuropathy.

Gelsolin-related amyloidosis (Finnish type) is characterized by the combination of lattice corneal dystrophy and multiple cranial neuropathies that usually begin in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops. Autonomic dysfunction does not occur.

### ACQUIRED NEUROPATHIES

#### PRIMARY OR AL AMYLOIDOSIS (SEE CHAP. 137)

Besides FAP, amyloidosis can also be acquired. In primary or AL amyloidosis, the abnormal protein deposition is composed of immunoglobulin light chains. AL amyloidosis occurs in the setting of multiple myeloma, Waldenström's macroglobulinemia, lymphoma, other plasmacytomas, or lymphoproliferative disorders, or without any other identifiable disease.

Approximately 30% of patients with AL primary amyloidosis present with a polyneuropathy, most typically painful dysesthesias and burning sensations in the feet. However, the trunk can be involved, and some patients manifest with a mononeuropathy multiplex pattern. CTS occurs in 25% of patients and may be the initial manifestation. The neuropathy is slowly progressive, and eventually weakness