17 Refsum’s Disease

17.1 Clinical Features and Laboratory Investigations

Refsum’s disease (RD), also called heredopathia atactica polyneuritiformis, is a rare disorder with an autosomal recessive mode of inheritance, characterized by accumulation of phytanic acid. The age at onset is known to vary from early childhood to the fifth decade. The onset is insidious and may be difficult to determine precisely. Symptoms sometimes appear to be precipitated by infections. Dramatic exacerbations and remissions of symptoms may occur spontaneously, without obvious antecedent cause.

The signs and symptoms of the disease can be divided into three groups.

Group 1 comprises congenital abnormalities. The commonest of these are the bone deformities which occur in up to 75% of all cases. The skeletal manifestations include abnormalities of the metatarsal bone, which may be short or elongated, pes cavus, hammer toes, and epiphyseal dysplasia of the shoulders, elbows, and knees.

Group 2 comprises symptoms and signs which develop gradually. The severity of the symptoms does not vary with transient changes in plasma phytanic acid. The commonest symptom in this category is blindness. Retinitis pigmentosa is present in all patients, although not always in the early stages of the disease. Night blindness is often the earliest symptom and may be present for years before the diagnosis is established. Gradual concentric constriction of the visual fields develops until finally only tubular vision remains. For many years central vision may be only slightly impaired or even normal. Optic atrophy, cataracts, and vitreous opacities occur rarely and contribute to the visual impairment. The pupils are often small, and reaction to light, convergence, and accommodation is often minimal or absent. Also other cranial nerves are affected, and anosmia and sensorineural deafness are common. Testicular atrophy has been reported. Rarely mental retardation is found.

Group 3 comprises the symptoms and signs which change rapidly. Sudden deterioration is usually associated with a decreased caloric intake, which causes a rise in the blood level of phytanic acid. When the neurological condition develops gradually, it shows itself as a peripheral neuropathy, which is usually symmetrical and initially distal, causing muscular atrophy and weakness. Distal cutaneous hypesthesia or painful paresthesiae may be present. The chronic progressive peripheral neuropathy may become apparent some years after visual and auditory impairment. When there is an acute exacerbation, the weakness is not merely peripheral, and the cranial nerves may also be involved. In an exacerbation the signs which develop rapidly respond well to therapeutic measures to lower the blood level of phytanic acid, but the more gradual peripheral neuropathy responds slowly. With severe weakness of long duration recovery may be incomplete in spite of almost normal plasma phytanic acid levels for several years. Ataxia and nystagmus of the cerebellar type also belong to this category. Cardiomyopathy is present in most patients, as shown by cardiac enlargement, tachycardia, and conduction disturbances with ECG changes. Sudden death is common during acute exacerbations and is probably associated with cardiac arrhythmias. Skin changes vary from a dry scaly skin to a condition of ichthyosis. The skin abnormalities change rapidly with the clinical state and are well correlated with the plasma phytanic acid level. Psychoses, particularly of paranoid type, occur more frequently than one would expect if it were a matter of pure coincidence.

An infantile variant of the disease has been described and has been called infantile RD (IRD). This disorder becomes manifest in the 1st year of life, with psychomotor retardation, retinitis pigmentosa, sensorineural deafness, hepatomegaly, osteopenia, facial dysmorphism, and growth retardation. Life expectancy is about 10 years. The elevated plasma phytanic acid level in the patients formed the basis for the designation of “infantile Refsum’s disease,” although the clinical phenotype differs markedly from classical RD. The name “infantile phytanic acid storage disease” would be preferable. The mode of inheritance of IRD has not been established; both males and females are affected. The data so far available are consistent with autosomal recessive inheritance.
The diagnostic test for RD is the demonstration of phytanic acid in serum. This is not normally present in detectable amounts. The clinical diagnosis of RD is difficult as no symptom is pathognomonic for the disease, and the various symptoms and signs may develop in succession at different times. The presence of excessive amounts of phytanic acid in the serum is the most valuable aid in the diagnosis of RD. The absence of phytanic acid in the serum of an untreated patient suspected of suffering from RD makes the diagnosis highly improbable. The protein in the CSF is increased to levels between 1 and 7 g/l or even higher. The cell count is normal. Neurophysiological studies show a greatly reduced motor and sensory nerve conduction velocity with evidence of denervation in the muscles. The nerve conduction velocity improves in conjunction with clinical improvement. The ERG shows no or a reduced reaction. ECG may reveal a prolongation of the QT segment and a widened QRS complex. When the urinary sediment of a patient with RD is stained for lipids, large amounts of fatty material can be detected.

In IRD it is not only the plasma level of phytanic acid that is raised. The fatty acid ratio C26:C22 is also elevated in the plasma as well as in cultured skin fibroblasts. The plasma has been found to contain abnormal bile acids and increased pипеcolic acid levels. Hypocholesterolemia and hypoalphalipoproteinemia are variably present. Plasmalogen metabolism is impaired, and the peroxisomal membrane enzyme dihydroxyacetone phosphate acyltransferase is deficient.

Both in RD and in IRD a deficiency of phytanic acid oxidase can be shown in cultured fibroblasts. By means of this technique it has been possible to demonstrate that the rate of oxidation of phytanic acid is less than 5% of that found in fibroblasts from normal skin, and that fibroblasts from parents of RD patients oxidize phytanic acid at about 50% of the normal rate, indicating a heterozygous state. The cell culture method can also be applied to make the diagnosis prenatally. In cultured amniotic cells the phytanic acid oxidase activity can be determined, allowing a diagnosis of a homozygous or heterozygous state ante partum.

17.2 Pathology

In RD the major site of involvement is the PNS. However, there is also some involvement of the CNS. On gross examination of the brain the leptomeninges appear thickened, but the brain appears normal. The abnormalities found by microscopic examination of the CNS show marked differences among patients. Usually a deposition of fat is noted in the leptomeninges, the ependyma and the choroid epithelium. Furthermore, fat is deposited in varying amounts in neurons, astrocytes, and microglial cells in the subpial parts of the cerebral cortex. The nerve cells are otherwise usually well preserved. In the cortex fat-filled pericytes or macrophages are numerous along the small vessels. Fat is also present in the cells of the pallidum. In the white matter perivascular clusters of fat-filled macrophages along vessels are commonly observed, but fat-laden macrophages are also found which have no distinct association with larger blood vessels. Fat has been deposited in apparently intact tissue. A focal loss of myelin sheaths with accumulation of fat-filled macrophages and reactive gliosis occurs in many parts of the brain stem. The axons tend to be relatively intact. Myelin destruction is diffuse around the inferior olivary nuclei and the dentate nuclei. There is a loss of neurons in the inferior olives, accompanied by a degeneration of olivocerebellar fibers. Within the dentate nucleus neuronal loss has been demonstrated, and there are degenerative changes in a number of Purkinje cells in the cerebellar cortex.

In the spinal cord there is a marked demyelination of the posterior columns and demyelination of less severity in both spinocerebellar tracts. Loss of motor neurons is observed in the anterior horns at all levels, and the remnant neurons show increased fat deposits. In the spinal roots, especially at the level of the cauda equina, many onion-bulb formations are present with demyelination and complete destruction of some axons, similar to the lesions found in the peripheral nerves. The peripheral nerves, both the somatic and the autonomic nerves, show macroscopic thickening. The changes in the peripheral nerves are constant, but their intensity varies greatly among cases. The nerve hypertrophy is usually most conspicuous in the lumbar and brachial plexuses. The hypertrophy is often irregular, forming localized swellings. Histological study of these swellings indicates that myelinated nerve fibers are reduced in number, and Schwann cell processes have given rise to typical onion-bulb formations. Many unmyelinated axons are present within the onion bulbs. The myelin sheaths are often of unequal thickness, and segmental demyelination has been found. Axonal destruction is also present. In some the whorls are closely packed, but in others they are more loosely disposed and separated by large extracellular spaces of variable width. In the cytoplasm of the whorl-forming Schwann cells several types of inclusions can be seen with help of electron microscopy: large crystalline inclusions and rounded osmiophilic bodies which are probably lipid in nature.