43.1 Clinical Features and Laboratory Investigations

L-2-Hydroxyglutaric aciduria is a rare neurometabolic disorder with autosomal recessive inheritance. The children are initially normal. In the second year of life a delay in unsupported walking, abnormal gait, speech delay, or febrile convulsions form the presenting symptoms in most cases. In other patients no abnormalities are noted until learning disabilities become apparent during early school years. Over the years slowly progressive neurological dysfunction is noted, characterized predominantly by cerebellar ataxia with nystagmus, dysarthria, head titubation, trunk ataxia, dysmetria, and intention tremor. Slow intellectual decline is noted in all patients. Frequently noted abnormalities are extrapyramidal signs such as dystonia and choreoathetosis, pyramidal signs, pseudobulbar signs, myoclonus, and macrocephaly. Seizures occur in the majority of the patients, especially in the context of fever. In some patients stable mental retardation is the only manifestation for years and the slowly progressive decline of motor and cognitive functions only starts in adolescence or adulthood. There is increasing evidence that patients with L-2-hydroxyglutaric aciduria have an increased risk of CNS malignancies of various types.

Laboratory investigations reveal elevated urinary excretion of L-2-hydroxyglutaric acid; plasma and CSF levels are also increased. Lysine levels in urine, plasma, and CSF may also be elevated. Prenatal diagnosis is possible by assessment of the L-2-hydroxyglutaric acid concentration in the amniotic fluid.

43.2 Pathology

Only a few descriptions of brain pathology are available. In 1994, Larnaout et al. described diffuse demyelination, spongiosis, and cystic cavitation of the cerebral white matter in a patient who died at the age of 30 years. The abnormalities were most pronounced in the subcortical region, in the axis of cerebral convolutions. In the cerebellum, loss of granule cells and Purkinje cells and moderate pallor of the white matter were noted. The dentate nucleus and globus pallidus showed marked cell loss and severe spongiosis. The putamen and caudate nucleus were less severely affected. Myelin was normal in the corpus callosum, genu of the internal capsule, optic tracts, and optic radiations. Cerebral cortex, thalamus, brain stem, and spinal cord were normal.

43.3 Pathogenetic Considerations

L-2-hydroxyglutaric aciduria is caused by a deficiency of an FAD-linked, membrane-bound mitochondrial enzyme, L-2-hydroxyglutarate dehydrogenase, that catalyzes the oxidation of L-2-hydroxyglutarate to α-ketoglutarate. The gene encoding this enzyme, C14orf160, also called DURANIN, is located on chromosome 14q22.1. Elevated levels of L-2-hydroxyglutarate are probably toxic for the CNS. The elevations of lysine in blood and CSF may be secondary rather than primary, as lysine loading appears to have no effect on the level of L-2-hydroxyglutaric acid in blood.

Two patients have been reported with neonatal-onset encephalopathy, early death, and elevated L-2-hydroxyglutaric acid as well as lactate (Chen et al. 1996; Barth et al. 1998). It is likely that these patients had another, unrelated metabolic disease.

43.4 Therapy

Treatment is entirely symptomatic.

43.5 Magnetic Resonance Imaging

MRI in patients with L-2-hydroxyglutaric aciduria shows a highly characteristic and consistent pattern. The abnormalities begin within the subcortical white matter with multiple foci of high signal intensity on T2-weighted images (Figs. 43.1 and 43.2). The lesions have a tendency to become confluent, first in the frontoparietal region (Fig. 43.1), later involving all subcortical white matter in a confluent manner (Figs. 43.2 and 43.3). In relatively mildly affected patients, the abnormalities remain multifocal and confined to the U fibers, whereas in patients with more serious neurological handicap, the cerebral white matter is more diffusely involved, although a rim of periventricular tissue remains spared. The white matter abnormalities are mildly swollen with some broadening of the gyri (Figs. 43.1–43.3). The aspect of swollen white matter changes is related to the spongi-
form nature of the leukoencephalopathy at histopathology. Diffusion-weighted MRI has revealed a high ADC and low signal on diffusion-weighted images in the abnormal white matter, consistent with increased freedom of water movements. Centrally located white matter structures, including periventricular white matter, corpus callosum, internal capsule, and brain stem, are spared, although the internal capsule is involved in some cases. The lateral ventricles become slightly enlarged. In addition to the white matter abnormalities, changes in signal intensity are typically seen in the globus pallidus, caudate nucleus, and putamen (Fig. 43.1). The globus pallidus is usually most severely involved. The caudate nucleus may be partly confluent. Lesions are present in central gray matter structures, most prominently the globus pallidus and dentate nucleus. The sagittal image shows that part of the inferior vermis is absent.

Fig. 43.1. A 12-year-old girl who has L-2-hydroxyglutaric aciduria, showing the involvement of subcortical white matter and the sparing of the central white matter including the corpus callosum. The subcortical lesions are partly multifocal, partly confluent. Lesions are present in central gray matter structures, most prominently the globus pallidus and dentate nucleus. The sagittal image shows that part of the inferior vermis is absent.