11 GM₁ Gangliosidosis

11.1 Clinical Features and Laboratory Investigations

GM₁ gangliosidosis is an autosomal recessive disorder of GM₁ metabolism, resulting in variable neural and visceral accumulation. Two forms can be distinguished: generalized or type 1 GM₁ gangliosidosis and cerebral or type 2 GM₁ gangliosidosis.

Type 1 GM₁ gangliosidosis, also called infantile GM₁ gangliosidosis, presents at or soon after birth with poor sucking and feeding problems. The child is hypotonic and hypoactive and has facial and peripheral edema. There is a characteristic facial dysmorphism similar to that found in the mucopolysaccharidoses. The gums and tongue may appear hypertrophied. The cornea is, however, clear. Hepatomegaly is present, the spleen may also be enlarged. The dysmorphic features and hepatosplenomegaly gave the disease its name: pseudo-Hurler disease. Bilateral, cherry-red spots at the macula are found in about half of the patients. Failure to thrive and severe psychomotor retardation are present from birth onward. Macrocephaly may develop, but less markedly than in Tay-Sachs disease. As the child gets older, it becomes apparent that the hands are broad and the fingers short. Kyphoscoliosis is frequently found. The wrist and ankle joints are often enlarged, but not tender. Flexion contractures occur frequently at the elbows and knees. The child remains hypoactive and is weak. An exaggerated startle response to noise is frequently present. Movements are poorly coordinated and reflexes are hyperactive. After about a year neurological deterioration is evident, with occurrence of epileptic fits, progressive spasticity, and with eventually decerebrate rigidity, deafness, blindness, and loss of social contact. Respiratory problems are common with frequent infections. Flexion contractures of arms and legs may become extremely severe. Bronchopneumonia is a frequent cause of death, which usually occurs before the child is much over 2 years of age. Children with type 2 GM₁ gangliosidosis initially appear normal. The first clinical sign is progressive psychomotor deterioration which begins between 6 months (late-infantile form) and 5 years (juvenile form) of age. The disease is characterized by an increased startle response to noise, epilepsy, spastic tetraplegia, cerebellar ataxia, and extrapyramidal abnormalities. Hepatosplenomegaly, coarsening of facial features, and cherry-red spots are not found. The average life span varies between 3 and 10 years. Death is usually caused by recurrent bronchopneumonia.

Older patients, including adults, have been described with GM₁ gangliosidosis. The clinical manifestations are rather variable and include epilepsy, myoclonus, cerebellar ataxia, spasticity, cherry-red spots, mild intellectual deficit, and bony abnormalities. This type could be called type 3 GM₁ gangliosidosis.

In type 1 GM₁ gangliosidosis vacuolated lymphocytes are found in the peripheral blood smear, but they are not present in type 2. Large, foamy histiocytes are present in the bone marrow in type 1; these cells are fewer in number in type 2. Rectal biopsy shows neuronal storage of ganglioside in Meissner's plexus in types 1 and 2. Demonstration of a deficiency of β-galactosidase activity in leucocytes or cultured fibroblasts is the most effective means of establishing the diagnosis. Intermediate enzyme activity is found in heterozygotes. Prenatal diagnosis is established by enzyme analysis in cultured amniotic fluid cells. Radiological abnormalities in type 1 include kyphoscoliosis and hypoplasia and beaking of the vertebral bodies. The long bones are wide in the center and taper at both ends. There is a generalized rarefaction of the cortex of most bones. The bony changes are usually slight at birth, but become progressively more severe thereafter. In type 2 radiological changes are minor or absent and involve only the vertebral bodies. In both type 1 and type 2 GM₁ gangliosidosis the EEG shows progressive deterioration. Despite the occurrence of seizures in many of the patients, epileptic discharges appear to be rare.

11.2 Pathology

External examination of the brain usually reveals no abnormalities, sometimes some cortical atrophy. In type 1 GM₁ gangliosidosis neuronal storage is...
evident in the cerebral and cerebellar cortex, the brain stem, and the spinal cord. The neurons have a ballooning, foamy cytoplasm and the nucleus is displaced to the periphery. Accumulation of the same material in proximal nerve cell processes leads to the formation of megalineurites and megadendrites. There is loss of gray matter neurons. The white matter is gliotic and there is a diffuse loss of myelin.

Electron microscopy demonstrates that the inclusions consist of spirally wound membranous structures enclosed within a limiting membrane. These inclusion bodies are ultrastructurally similar to those seen in GM1 gangliosidosis.

In type 1 GM1 gangliosidosis visceral storage is found. The liver is enlarged and storage material is present in hepatocytes and in histiocytes in liver sinusoids. The renal glomerular epithelium shows marked vacuolization of the cytoplasm. The spleen and lymph nodes contain many foamy histiocytes. Large foamy histiocytes are present in bone marrow aspirates. Skin biopsies show foamy vacuolization of sweat gland epithelium, histiocytes, fibroblasts, and endothelial cells.

In type 2 GM1 gangliosidosis identical abnormalities are present in CNS gray matter with neuronal storage. White matter is either not affected at all, or only to a minimal extent. There are also some differences in visceral organ involvement. The liver parenchyma is normal except for some foamy histiocytes in the sinusoids, and the spleen contains few storage cells. Ballooning of renal epithelium is identical in type 1 and 2. Bone marrow aspirates show only few storage cells.

11.3 Chemical Pathology

The primary chemical pathology in type 1 GM1 gangliosidosis is a severe accumulation of the normal monosialoganglioside GM1, accompanied by a minor accumulation of its asialo derivative. The total brain GM1 level is several times the value in normal persons and GM1 constitutes 80%-90% of total ganglioside. Accumulation occurs in gray and white matter, whereby the degree of increase above normal levels is even greater in white matter. The level of total lipid is slightly decreased in the gray matter, primarily due to a moderate decrease of phospholipids.

Some 30% of the dry weight of membranous cytoplasmic bodies consists of GM1 ganglioside. Other components of these bodies are proteolipid protein, cholesterol, phospholipids, and glycolipids. One of the glycolipids, cerebroside, consists mainly of glucocerebrosides, which is unusual in adults.

Except for the high concentration of GM1 ganglioside the white matter chemical abnormalities in type 1 are nonspecific and reflect the moderate myelin destruction. The main findings are a low proteolipid protein, low total lipids, particularly glycolipids, and the presence of significant amounts of esterified cholesterol. The chemical abnormalities of isolated myelin in type 1 GM1 gangliosidosis are also nonspecific and consist of a very high concentration of cholesterol, a low level of glycolipids, especially cerebroside, and a low concentration of ethanolamine phosphoglyceride.

The liver and spleen of type 1 GM1 gangliosidose contain slightly increased amounts of GM1 ganglioside. In addition, there is an excessive accumulation of oligosaccharides.

In GM1 gangliosidosis type 2 there is also a marked increase in GM1 and asialo GM1 in the brain. However, the lipid composition of gray and white matter is otherwise relatively normal. The GM1 ganglioside concentration is not increased in this type in organs outside the CNS.

11.4 Pathogenetic Considerations

GM1 gangliosidosis is caused by a deficiency of the lysosomal degradative enzyme β-galactosidase. As a result hydrolysis of the terminal galactose of GM1 ganglioside is blocked. GM1 ganglioside and its asialo derivative accumulate in lysosomes due to the impairment of normal degradation. GM1 is a normal component of cellular membranes and its content is especially high in neuronal plasma membranes. Accumulation occurs predominantly in neurons. This accumulation of intralysosomal storage products finally results in death of the nerve cells. The mechanism which makes intralysosomal storage detrimental to the nerve cell function is largely unknown. Cytotoxicity or severe disturbance of intracellular transport which impairs cellular metabolism may form part of the explanation. Another possibility may be leakage of intralysosomal products or enzymes into the cytoplasm during the process of intralysosomal storage. Others point to the evidence of abnormal membrane production which leads to inappropriate proliferation of secondary neurites and aberrant formation of synapses and to the evidence of abnormal membrane function with reduced neurotransmitter uptake. They suggest that the neuronal dysfunction results from altered membrane structure. Accumulation of GM1 ganglioside in the neuronal membrane will result in alterations of membrane structure. Evidence of reduced membrane fluidity has been found. Gangliosides contain long, saturated fatty acids which in-