



Krabbe Disease

Alternative Names

Globoid Cell Leukodystrophy;
Globoid Cell Leukoencephalopathy
GLD
GCL
Galactosylceramide Beta-Galactosidase
Deficiency
Galactocerebrosidase Deficiency
GALC Deficiency
Krabbe Leukodystrophy
Diffuse Globoid Body Sclerosis
Galactosylceramide Lipidosis
Galactosylsphingosine Lipidosis
Late-Onset Krabbe Disease
Psychosine Lipidosis

WHO International Classification of Diseases

Endocrine, nutritional and metabolic diseases

OMIM Number

245200

Mode of Inheritance

Autosomal recessive

Gene Map Locus

14q31

Description

Krabbe disease is one of a group of genetic disorders called the leukodystrophies. Leukodystrophies are rare inherited neurometabolic disorders resulting from defects in the synthesis or catabolism of myelin. Myelin, which lends its color to the white matter of the brain, is a complex substance made up of at least ten different chemicals. Each of the leukodystrophies affects one of these substances. Krabbe's disease is caused by a deficiency in the lysosomal enzyme galactocerebroside beta-galactosidase (GALC), resulting in accumulation of galactosylceramide within multinucleated macrophages of the white matter, forming globoid cells.

The disorder can be subdivided into three types: the more common infantile form with onset within the first six months; a juvenile form presenting between two and 10 years; and a rarer adult form with onset after 10 years. The infantile form is the most severe, with central demyelination causing irritability, spasticity, ataxia, and seizures. Blindness from optic atrophy, cortical blindness, and deafness may all occur. Peripheral demyelination presents with limb weakness and areflexia. Progressive psychomotor decline results in quadriparesis and death within a few years of onset. Juvenile and adult forms of the disease have a milder phenotype and a slower rate of progression. Symptoms and signs include spasticity, dementia, ataxia, peripheral neuropathy, and loss of vision. Investigations may show milder abnormalities, and nerve conduction can be normal or only mildly affected.

Molecular Genetics

Krabbe disease is caused by mutation in the galactosylceramidase gene (GALC), which maps to chromosome 14q32.1.

Epidemiology in the Arab World

Palestine

Zlotogora et al. (1985) indicated that Krabbe disease (globoid cell leukodystrophy) was found with very high incidence (6/1,000 live births) in a large Druze kindred. The clinical data of 12 of the affected children demonstrated clinical variability even though these children are homozygous for the same mutation by descent from a common ancestor. In 1991, Zlotogora et al. diagnosed 18 infants affected with Krabbe disease over a period of 15 years. All patients were of non-Jewish origins, six were Druze from a large kindred in which a very high incidence of the disease was previously reported. The 12 other patients were Moslem Arabs; 7 were from two adjacent villages and



most of them were found to be related, originating from a large kindred in which the incidence of the disease is 1/130 live births. Three other patients were from a third large kindred that also had a high incidence of Krabbe disease. Later, Zlotogora (1997) conducted a survey of 2000 different Palestinian Arab families. In 601 cases, an autosomal recessive disease was diagnosed or strongly suspected. The distribution of these disorders was not uniform and some disorders, such as Krabbe disease, were found at high frequency in only a small part of the population.

Korn-Lubetzki et al. (2003) studied eight children diagnosed with Krabbe disease. In two of these children (25%), peripheral neuropathy was the single initial symptom and the only neurologic finding noted for a period of months. In these patients, diagnosis of Krabbe's disease was delayed and established only 9-11 months after the initial symptoms. In two other children with "classical picture" Krabbe disease, areflexia was noted on admission. The occurrence of peripheral neuropathy as an initial symptom in early infantile Krabbe disease may be underestimated. Korn-Lubetzki et al. (2003) indicated that early infantile Krabbe disease is relatively frequent in the Muslim-Arab population in Palestine and suggested that it should be considered in the differential diagnosis of early infantile peripheral neuropathy.

Saudi Arabia

Al-Essa et al. (2000) studied a 2-year, 6-month-old Saudi male with infantile Krabbe's disease with fluorine-18-labeled-2-fluoro-2-deoxyglucose positron emission tomography (FDG PET) scan. The patient presented with a gradual loss of developmental milestones, irritability, and crying. At the advanced stage of the disease, he developed tonic-clonic seizures and became a microcephalic, extremely irritable, blind, spastic quadriplegic child, with no deep tendon reflexes. Magnetic resonance imaging of the brain revealed mild brain atrophy and white matter disease mainly in the centrum semiovale. Electroretinography was normal; however, electroencephalography and visual-evoked potentials were abnormal. Peripheral nerve conduction studies documented a demyelinating neuropathic process. The FDG PET study of the brain demonstrated a marked decrease in the metabolism of the left cerebral cortex and no uptake in the caudate heads. Since

the patient did not present for subsequent clinic visits, Al-Essa et al. (2000) presumed it was dead.

United Arab Emirates

Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth at Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 and January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with major malformation. Single gene disorders accounted for 24% of the cases, 76% were due to autosomal recessive disorders. In their study, Al Talabani et al. (1998) observed one case of Krabbe disease in a consanguineous family from the United Arab Emirates. Recurrence was reported in the family. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the whole United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

References

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