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Krabbe Disease (Galactocerebrosidase Deficiency)

Background

Krabbe Disease is a neurodegenerative disorder of both the central and peripheral nervous system. It is included in the sphingolipid degradation group of lysosomal storage disorders and is a leukodystrophy because the myelin sheath is compromised. Krabbe Disease is defined by the deficiency of the lysosomal enzyme galactocerebrosidase (GALC). GALC is needed to metabolize galactosylceramide, a major component of myelin. As galactosylceramide accumulates, globoid cells, containing undigested galactosylceramide, develop. This leads to demyelination. The overall incidence is 1 in 100,000-141,000. Most cases include European ancestry; late onset forms are more commonly seen in people with southern European ancestry. There is a higher incidence in Sweden (nearly 2 in 100,000) and the Druze Community in Israel (6 in 1000 births).

Clinical

Symptoms can vary widely in severity and age at onset. Unlike other lysosomal storage disorders, organomegaly, dysmorphic features, skeletal abnormalities and direct cardiovascular complications are not associated with Krabbe Disease.

There are 4 clinical subtypes that are defined by the age of onset: Infantile (3-6 months), Late-Infantile (6 months-3 years), Juvenile (3-8 years) and Adult (>8 years). The Infantile form is the most severe and most common presentation of Krabbe Disease and it accounts for 85-90% of cases. Key signs include developmental delay, hypertonia, spasticity, extreme irritability with hypersensitivity, failure to thrive, and rapidly progressive neurological manifestations (deafness, blindness, seizures, brain inflammation). Untreated patients typically do not survive beyond 2 years of age. The late-Infantile form has a similar course as the Infantile form but has a less rapid progression of symptoms. There is a longer period of normal development. Death usually occurs within two years of disease onset.

Later-onset can present at any time from six months to 50 years of age and has a slower overall symptom progression. The Juvenile form has a greater variability in the rate of disease progression. There is normal development early on but it is still followed by progressive degeneration. Adult-onset Krabbe Disease has a varied clinical presentation and progression: from rapid to delayed manifestations. Patients with this form exhibit mental regression, peripheral neuropathy, cerebellar dysfunction, blindness, and spasticity. These patients are ambulatory at disease onset but begin to experience muscle weakness and ataxia. The typical life span is significantly longer that infantile-onset Krabbe Disease. Morbidity occurs in all types from progressive neurodegeneration of the CNS and PNS. Death can be brought on by infections and respiratory failure (from muscle weakness).

Testing

Diagnosis is made through enzyme assay with deficient GALC activity being considered <5% of normal. The enzyme activity is measured in peripheral blood leukocytes and fibroblasts, so skin biopsy is not necessary. The level of GALC enzyme activity does not indicate the clinical subtype. Enzyme analysis cannot reliably detect carriers. Gene analysis for GALC gene is useful in determining age at first symptoms. Newborns should be evaluated for early signs of neurological dysfunction with the help of brain MRI and CT scans as well as evaluation of cerebral spinal fluid by lumbar puncture. Elevated protein levels in the cerebral spinal fluid indicate diseased white matter, especially for Infantile and Late-Infantile forms. Globoid cells are the histological hallmark of Krabbe Disease. It is important to rule out Gaucher Disease and Niemann-Pick Disease in suspected cases of Krabbe Disease. Prenatal testing of amniotic fluid or CVS can also help to diagnose Krabbe Disease.

Treatment

Bone marrow transplant (HSCT) from an unrelated donor has been beneficial, especially when administered early in the disease presentation (<1 month of age for infantile form), before neurological involvement is detected. Early intervention with HSCT improves quality of life, increases life span and delays neurodegenerative progression. Patients are able to retain some language skills and the ability to walk with assistance. Though HSCT has been found to ameliorate the disease progression, it is not a cure; the neurologic deficits will still manifest. HSCT mortality rate is 15%. Symptom management includes physical therapy, especially for managing muscle strength.

Because the diagnosis and treatment of Krabbe Disease is complex, the pediatrician is advised to manage the patient in close collaboration with a metabolic geneticist who specializes in lysosomal storage disorders and who is also familiar with HSCT.

Inheritance

Krabbe Disease is mapped to chromosome 14q31.3. Seventy mutations have been found as well as some polymorphisms that are thought to play a role in describing the various phenotypes. Genotype-phenotype correlations are being studied.

This disorder follows an autosomal recessive inheritance pattern; affected patients have two copies of a disease gene (or mutation). People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder. As with all genetic diseases, genetic counseling is appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

References

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