Globoid Cell Leukodystrophy (Krabbe Disease)

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Globoid cell leukodystrophy (krabbe disease) is a rare autosomal recessive lysosomal storage disorder caused by deficiency of galactoceramide β-Galactosidase enzyme and characterized by severe myeline loss and presence of globoid bodies in the white matter. This enzyme is responsible for the hydrolysis of galactolipids formed during white matter myelination. The pathologic changes in the peripheral and central nervous system (globoid cell formation and decreased myelin) appeare to result from the toxic nature of accumulated psychosin (galactosphingosine) and galactocerebroside (galactosylceramide) that can not be degraded. Nonmetabolized galactocerebroside stimulates the formation of the globoid cells that reflect the destruction of oligodendroglial cells. These cells are responsible for the elaboration of the myeline. Therefore, this loss leads to myelin breakdown and produce additional galactocerebroside and cause a vicious circle of myeline destruction. The galactosylceramidase gene (GALC), is located on chromosome 14q 31. More than 70 GALC mutations, including numerous small deletions and insertions, has been identified in patients with all clinical types of Krabbe disease. Some mutations result in the infantile type if found homozygous or with another severe mutation, and one mutation predicts a less severe phenotype. Disease incidence in the general population is estimated at 1 in 201000.

Most patients with Krabbe disease(KD) present during the first 6 months of life (early infantile form) and only 10 percent present later (juvenile or adult onset). A peripheral motor sensory neuropathy occurs in all patients but the CNS symptoms are dominated in the infantile form. Infants with KD present with irritability, rapidly progressive rigidity and tonic spasms, axial hypotonia, absent reflexes, optic atrophy and blindness, microcephaly, seizures and startle myoclonus.Tonic extensor spasms occure with light, sound, or touch stimulations. Unexplained low grade fever is present. During 2-4 months, infants remain in a permanent opistotonus position and regress rapidly to decerebrate condition and most die before 2 years old. In juvenile or adult form of disease, patients show the signs of progressive walking problems, spastic paraparesis, cerebellar ataxia and visual failure.

In children with infantile onset KD, brain MRI shows symmetric signal abnormalities in the periventricular region of the posterior cerebral hemispheres and in dentate nucleus and cerebellar white matter. In those with juvenile or adult onset disease, atrophy and increased T2 signal in white matter is present, but the dentate and cerebellum are generally spared. Brain magnetic resonance spectroscopy (MRS) shows elevation of myo-inositol and cholin- containing coumpounds in affected white matter. Spinal involvement may be evident on MRI as abnormal contrast enhancement of the lumbosacral nerve roots. Abnormalities of brainstem auditory and visual evoked potentials are present. Motor nerve conduction velocity of

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peripheral nerves is usually prolonged and the protein content of CSF is elevated. Deficient activity of galactoceramide β-Galactosidase in leukocytes or cultured fibroblasrs confirm the diagnosis. Molecular genetic test is available for genetic counseling.

There is no specific treatment for symptomatic patients with infantile form of KD. Supporting care is only option to manage irritability and spasticity. Hematopoetic stem cell transplantation from unrelated donor slows the course of disease in infantile form of KD diagnosed before the symptoms start. Newborn screening has been recommended for early detection and intervention by bone marrow transplantation to improve outcome. However the utility of screening is limited because neither enzyme activity nor knowledge of the genetic mutation can reliably predict phenotype. Prenatal diagnosis is prepared by measuring GALC activity in a chorionic villi sample or cultured amniocytes.

Keywords: Globoid cell leukodystrophy; Kkrrabe disease; Clinical manifestation; Diagnosis; Treatment