CASE REPORT

KRABBE DISEASE IN A 28 YEAR OLD ADULT – A RARE CASE REPORT

Subrata Chakrabarti, Koushik Pan
Department of General Medicine, Institute of Post-Graduate Medical Education and Research (IPGMER), West Bengal, India

Correspondence to: Subrata Chakrabarti (subratachakrabarti2011@gmail.com)

DOI: 10.5455/ijmsph.2014.150320141 **Received Date: 05.03.2014** **Accepted Date: 15.04.2014**

ABSTRACT
Krabbe disease (KD) or Globoid Cell Leukodystrophy (GLD) is a disorder involving the white matter of both the central and peripheral nervous systems. It is caused by congenital deficiency of a lysosomal enzyme, galactosylceramidase I, which is responsible for hydrolyzing the galactolipids in myelin. The disease is extremely rare occurring only one in 100,000 to one in 200,000 live births. The disease is classically of infantile origin but it can also occur in older children as well as adults. Adult variant is the rarest type. We hereby report a 34 year old male patient with progressively increasing ataxia, dysarthria. Typical MRI brain changes and diminished leucocyte galactocerebrosidase (GALC) enzyme levels clinched the diagnosis of Krabbe disease. There are very few cases of KD reported from India. This case report is to stress upon the fact that this rare entity should not be missed in an appropriate clinical setting.
Key Words: Krabbe Disease; Leukodystrophy; Galactosylceramidase; GALC Enzyme

Introduction

Leukodystrophies are a group of rare inherited neurometabolic disorders resulting from defects in the synthesis or catabolism of myelin. It includes Krabbe disease (KD) or globoid cell leukodystrophy (GLD), Canavan disease, Pelizaeus-Merzbacher disease and Alexander disease. KD results from the deficiency of the lysosomal enzyme galactocerebrosidase (GALC). The enzyme deficiency causes abnormal accumulation of galatosylcerebrosides, which convert macrophages into globoid cells. The combination of globoid cells and the direct toxic effect of galactosylphingosine (psychosine) results in extensive demyelination and severe astrogliosis.

Case Report

A 28 year old man presented to us with worsening spastic weakness for last 10 years and dysarthria and occasional seizures for last 4 years. He was born as a normal vaginal delivery in hospital out of a non-consanguineous marriage. He had an elder brother of 34 years with similar problem. He achieved motor milestones at appropriate age with normal scholastic performance. His motor problems started at age of 18 years with cramping leg pains and weakness after heavy exercise. His weakness progressed and later on developed difficulty with balance and coordination and manual dexterity and slurring of speech and partial seizures for last 4 years. He denied any presence of sphincter disturbance or sensory abnormality or cognitive problem. General examination was normal with no buccal pigmentation or skin lesions. Blood pressure was 130/84mm Hg with no postural drop. On neurological examination, both the tone and power in his upper limbs were normal and the reflexes were normal. However in the lower limbs, spastic paraparesis was present with increased tone, ankle clonus, significantly brisk reflexes and bilaterally extensor plantar responses. Superficial reflexes were lost. The cranial nerves and fundoscopic appearances were normal. Rest neurological examination was within normal limits.

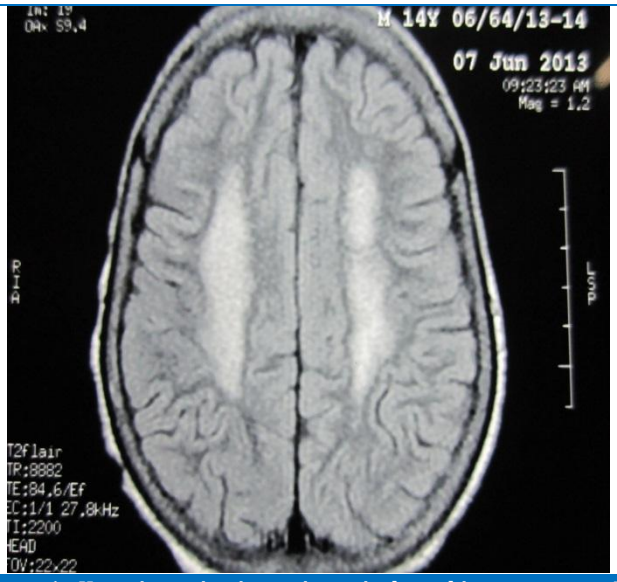

Figure-1: Hyperintensity in periventricular white matter on T2 weighted image in axial view

Laboratory investigations revealed normal routine blood tests including peripheral blood counts and peripheral smear, serum electrolytes, liver function tests, renal function tests, thyroid function test, vitamin B12 and folate assay, ceruloplasmin and serum copper assay. Syphilis serology profile and autoantibody profile was negative. Very long chain fatty acid and cortisol assay were normal. Electromyography as well as nerve conduction study were

within normal limits .Visual Evoked Potential (VEP) and Brainstem Evoked Response Audiometry (BERA) were also normal. MRI spine did not reveal any compressive lesion. CSF protein was slightly raised at 58 mg/dl. Oligoclonal bands were negative and IgG index was normal. MRI brain revealed symmetrical areas of hyperintensity in the periventricular white matter and posterior white matter on T2W images with no abnormal enhancement after intravenous contrast administration. Lysosomal enzyme testing showed galactocerebroside beta galactosidase or galactocerebrosidase (GALC) level which was almost undetectable and definitely much below the 99th percentile for age and sex confirming the diagnosis of Krabbe disease. DNA analysis was not possible for want of facilities.

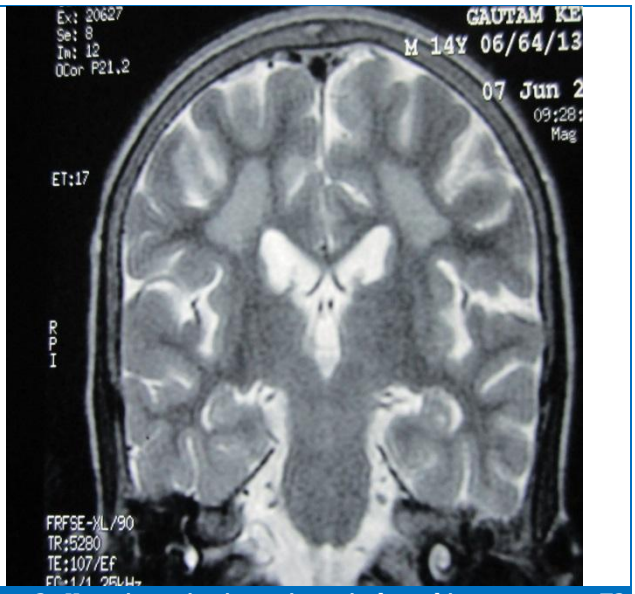

Figure-2: Hyperintensity in periventricular white matter on T2 weighted image in coronal view

Discussion

Globoid cell leukodystrophy (GLD) or Krabbe disease (KD) is an inherited neurodegenerative lysosomal enzyme disorder affecting the central and peripheral nervous systems. It is an autosomal recessive sphingolipidosis caused by deficient activity of the lysosomal enzyme galactosylceramide beta-galactosidase (GALC) which degrades galactosylceramide, a main component of myelin, and other terminal beta-galactose–containing sphingo-lipids, including psychosine (galactosylsphingosine).[1] Increased psychosine levels lead to widespread destruction of oligodendroglia and impaired Schwann cell function in the central and peripheral nervous systems and to subsequent demyelination.[2] It is so named due to the globoid cells (which are actually storage cells) infiltrating around cerebral blood vessels. Krabbe originally described this disease as 'diffuse cerebral sclerosis' in his article in 1916. This genetic disease is found in all ethnic groups.[3] The gene has been cloned and localized to the q21-q31 region of chromosome 14.[4,5] Krabbe disease currently has the following 4 clinical subtypes mainly distinguished by age of onset and severity[6]

- Type 1 - Infantile
- Type 2 - Late infantile
- Type 3 - Juvenile
- Type 4 - Adult.

The classical or infantile form which is also the most common one, manifests in the first six months of life with failure to thrive, fever, seizures, optic atrophy, visual loss, irritability, hypertonia, myoclonus, psychomotor retardation, vomiting. Death almost always occurs by 2 years of age. Late infantile Krabbe disease follows a similar but less rapid course. After a variable period of normal early development (6 month to 3 year), the child develops irritability, hypertonia, ataxia, and psychomotor arrest followed by progressive deterioration and vision loss. Pyramidal weakness and blindness predominate in the juvenile form (3-8 years). Adult onset disease is characterized by slowly progressive ataxia, spasticity, cerebellar dysfunction or peripheral neuropathy with relative preservation of intellect.[7] Diagnosis is suspected on the basis of clinical findings and radiological findings and confirmed by enzyme assay as was our case. CT features in early infantile Krabbe disease are increased attenuation in cerebellum, brainstem, thalami, caudate nuclei and corona radiata on non-contrast CT.[8] In the absence of confirmatory evidence of low or absent GALC levels, the characteristic distribution of lesions and MRI signal patterns on T2-weighted images can be diagnostic. Involvement of periventricular white matter, centrum semi-ovale, hemispheric deep grey matter is characteristic. Pyramidal tracts, parieto-occipital white matter, posterior corpus callosum, and cerebellar white matter involvement as well as lesions of deep grey matter is also a possibility.[8] GALC assay for the diagnosis is expensive and not widely available. Enzyme estimation in cultured skin fibroblasts or peripheral blood leukocytes accurately identifies homozygotes, but its value in detection of heterozygote is limited.[9] Mutation analysis can be vital in identifying the hetero-zygotes. Therapy for KD in the early stages is with hematopoietic stem cell transplantation with marginal radiological and clinical improvement.[10] Counselling and prenatal diagnosis (by enzyme estimation from cultured amniocytes, skin fibroblasts or fetal tissues like brain, kidney, and liver) are the only management strategies that can be offered at present.[11]

Conclusion

The purpose of this case report is to stress upon the fact that in an appropriate clinical setting, a diagnosis of Krabbe disease (KD) should be kept in mind.

References

1. Jesionek-Kupnicka D, Majchrowska A, Krawczyk J, Wendorff J, Barcikowska M, Lukaszek S, et al. Krabbe disease: An ultra-structural study of globoid cells and reactive astrocytes at the brain and optic nerves. Folia Neuropathol 1997; 35: 155-162.
2. Besley GTN, Gatt S. Spectrophotometric and fluorimetric assays of galactocerebrosidase activity, their use in the diagnosis of Krabbe's disease. Clinica Chimica Acta 1981; 110: 19-26.
3. Dunn HG, Lake BD, Dolman Cl, Wilson J. The neuropathy of Krabbe's infantile cerebral sclero-sis (globoid cell leucodystrophy). Brain 1969; 92: 329-344.
4. Suzuki Y, Suzuki K. Krabbe's globoid cell leukodystrophy: Deficiency of galactocerebro-sidase in serum, leukocytes and fibroblasts. Science 1971; 171: 73-75.
5. Fu L, Inui K, Nishigaki T, Tatsumi N, Tsukamoto H, Kokubu C, et al. Molecular heterogeneity of Krabbe disease. J Inherit Metab Dis 1999; 22: 155-162.
6. Farrell DF, Swedberg K. Clinical and biochemical heterogeneity of globoid cell leukodystrophy. Ann Neurol 1981; 10: 364-368.
7. Verdru P, Lammens M, Dom R, Elsen AV, Carton H. Globoid cell leukodystrophy: A family with both late infantile and adult type. Neurology 1991; 41: 1382-1384.
8. Loes DJ, Peters C, Krivit W. Globoid cell leukodystrophy: Distinguishing early-onset from the late-onset disease using a brain MR imaging scoring method. Am J Neuroradiol 1999; 20: 316-323.
9. Luzi P, Rafi MA, Wenger DA. Characterization of the large deletion in the GALC gene found in patients with Krabbe disease. Hum Mol Genet 1995; 4: 2335-2338.
10. Krivit W, Shapiro EG, Peters C, Wagner JE, Cornu G, Kurtzberg J, et al. Hematopoietic stem cell transplantation in globoid-cell leuko-dystrophy. N Engl J Med 1998; 338: 1119-1126...
11. Tullu MS, Muranjan MN, Kondurkar P, Bharucha BA. Krabbe Disease - Clinical Profile. Indian Pediatrics 2000;37: 939-946.

Cite this article as: Chakrabarti S, Pan K. Krabbe Disease in a 28 year old adult – A rare case report. Int J Med Sci Public Health 2014;3:635-637.
Source of Support: Nil
Conflict of interest: None declared