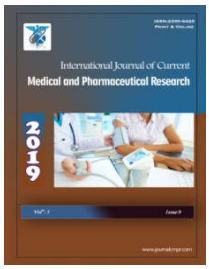
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 09(A); September 2019; Page No. 4509-4511
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201909732



Case Report

KRABBE'S DISEASE WITH LATE INJURY SYMPTOMS IN CHILD: CASE REPORT

Juliana Vieira de Oliveira[1], Renata da Silva Almeida[2], Francisco Tussolini[3], Larissa Vieira de Lima[4], Marcella Lopes Abitbol[5], Rafaela Monique Mendonça Barros[6], Laís Viana Lopes Sato[7] and Mario Jorge dos Santos Noel Filho[8]

[1,5,6,7,8]Pediatric Resident Doctor at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado- Brazil
[2]Pediatric Resident Doctor at Amazonas State University- Brazil
[3]Neuropediatrician and professor in the Service of Neuropediatric at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado- Brazil
[4]Pediatric Resident Doctor at Roraima Federal University- Brazil;

ARTICLE INFO

Article History:
Received 15th June, 2019
Received in revised form 7th July, 2019
Accepted 13th August, 2019
Published online 28th September, 2019

Key words:
Leukodystrophy, Krabbe's disease, chromosome 14q31, child

ABSTRACT

Krabbe's disease is rare, autosomal recessive, promotes the deficiency of the lysosomal galactosylceramide beta-galactosity enzyme, which produces a toxic metabolite for oligodendrocytes, leading to demyelination of the central nervous system and peripheral nervous system. It may manifest in the first months of life (90% of cases), in the juvenile stage or in adulthood. Marked by irritability, delayed psychomotor development, unexplained fever, progressive decrease in strength, ataxia, hemiparesis, cortical blindness and progressive dementia. There is no specific treatment, however the transplantation of bone marrow or non cord cells allows to improve the evolution. Measures such as physical therapy, cognitive and language stimulation may be used to improve the life quality. Currently, the diagnosis is a family guide to the prognosis and the possibility of familial recurrence. This article is a case of late presentation of Krabbe disease, beginning at 2 years of age, confirmed by the measurement of galactosylceramide beta galactosity in fibroblast culture.

INTRODUCTION

Krabbe disease (DK), or globroid cell leukodystrophy, is a rare disorder of lysosomal deposition called sphingolipidosis. It has an autosomal recessive inheritance caused by the deficiency of the lysosomal enzyme galactosylceramide beta galactosity, also called galactocerebrosidase (GALC), mapped on chromosome 14q31[1]. This enzyme is responsible for the hydrolysis of galactolipids formed during white matter myelination. This deficiency leads to the appearance of changes in the peripheral and central nervous system, resulting from the accumulation of toxic substances that should have been degraded by GALC. The main accumulated galactolipid is the psychosin, wich is toxic to oligodendrocyte, responsible for the destruction of these and Schwan cells, causing demyelination of the central and peripheral nervous system. Another consequence of psychosin is the activation of astrocytes and the formation of macrophages with accumulations of galactocerebrosides, called multinucleated globoid cells, which give the anatomopathological characteristic of the disease [4].

The incidence of this disease was initially estimated at 1: 100,000 [1,3]. Later, evidence of about two million cases by the New York State Krabbe Consensus indicated an incidence of 1: 400,000. Most patients have symptoms in the first six months of life, the early childhood clinical form; about 10% develop symptoms later, 6% between 13 and 24 months, 3% between 25 and 36 months and 1% after 5 years [6].

The clinical manifestations in infant form include irritability, delayed development or regression, limb spasticity, axial hypotonia, absence of reflexes, optic atrophy, and microcephaly. In the later form, in early juvenile typically present weakness, loss of skills, loss of vision. These patients are severely disabled and die two to seven years after diagnosis [6].

The authors report a case of this rare condition in the late form, witch is even rarer. The diagnosis was confirmed by the deficiency of lysosomal galactosylceramide beta galactosity enzyme in leukocyte dosage.

CASE REPORT

S.R.O, 2 years old, female, born in Manaus (AM), was born by cesarean section, without complications, at term, the only child of healthy and non-bloody parents. Negative family history for genetic disorders and abortions.

The child developed normally until 2 years, when started with difficulty in walking, irritability, unexplained fever. She was

Corresponding author:* **Juliana Vieira de Oliveira
Pediatric Resident Doctor at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado- Brazil

admitted at Pediatric Hospital in Manaus in August 2018 for diagnostic investigation. During hospitalization, the child evolved with dyslalia, difficulty swallowing, grasping objects, decreased visual acuity. Examination showed flexion and spastic hypertonia of the upper and lower limbs, with extension of the feet, generalized symmetrical hyperreflexia. The neurological picture was compatible with Krabbe disease and for diagnostic confirmation were requested enzymatic tests, electroencephalogram (EEG) and cranial nuclear magnetic resonance (MRI).

The EEG showed base activity slightly disorganized and the MRI showed involvement of the deep periventricular white matter, by these results Krabbe disease was included in the diagnoses. Enzymatic dosing of galactocerebrosidase and beta galactosidase demonstrated the deficiency of these enzymes, thus confirming the diagnosis (Figure 1).

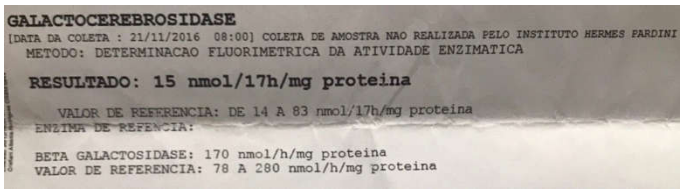

GALACTOCEREBROSIDASE
[DATA DA COLETA : 21/11/2016 08:00] COLETA DE AMOSTRA NAO REALIZADA PELO INSTITUTO HERMES PARDINI
METODO: DETERMINACAO FLUORIMETRICA DA ATIVIDADE ENZIMATICA
RESULTADO: 15 nmol/17h/mg proteina
VALOR DE REFERENCIA: DE 14 A 83 nmol/17h/mg proteina
ENZIMA DE REFENCIA:
BETA GALACTOSIDASE: 170 nmol/h/mg proteina
VALOR DE REFERENCIA: 78 A 280 nmol/h/mg proteina

Figure 1 Galactocerebrosity enzyme activity value. Values of 15nmol / 17h / mg protein or less close the diagnosis

During some months she was followed up with physical therapy, speech therapy, nutrition and neuropediatrics, but there was a marked progression of the disease with poor spontaneous movement, intense irritability, anorexia and, due to the impossibility of swallowing, was submitted to gastrostomy. At the moment the child has complete vision, speech and gait loss, unimpressive facies, repeated bronchial aspirations and has evolved to need tracheostomy.

DISCUSSION

Krabbe disease is rare, with an incidence of 1: 100,000 live births. It has autosomal recessive inheritance and GALC deficiency occurs due to mutation of the GALC gene located on chromosome 14q31. More than 60 mutations in this gene are known. Pathological changes in the peripheral and central nervous system (globoid cell formation and decreased myelin) are hypothesized as a result of the toxic nature of the accumulated psychosin (galactosylsphingosine), which cannot be degraded due to GALC deficiency [1,4].

Most patients with Krabbe disease have symptoms within the first six months of life; approximately 10 percent present later, including adulthood. A peripheral motor sensory neuropathy occurs in all patients, but early onset forms are dominated by symptoms related to central nervous system dysfunction. Infantile onset disease is associated with irritability, developmental delay or regression, limb spasticity, axial hypotonia, absent reflexes, optic atrophy, and microcephaly. Seizures and tonic extensor spasms eventually appear. Typically there is rapid regression to a decerebrate condition and death in most cases before two years of age [5].

The prognosis of the disease is poor. Patients progress with progressive neurological deterioration to coma and death, on average, at 24.1 months. There are some worse prognostic factors: symptom onset before 6 months of age (p = 0.0073) and presence of three symptoms: stiffness (RR = 3.26; 95% CI: 1.513-7.022), vision loss (RR = 2.701; 95% CI: 1.23-6.498) and dysphagia. (RR = 3.479, 95% CI: 1.129-0.72). The level of enzymatic activity and type of mutation have no relationship with prognosis [6].

The case presented a late start, the less frequent case. The juvenile form starts from fifteen months to ten years of age, usually before five years of age. The condition begins with progressive gait difficulty, lower limb spasticity and ataxia, sometimes beginning asymmetrically, as occurred in the patient described in the report. Signs of peripheral impairment are found in approximately 50% of cases at the onset of symptoms, but tend to become more obvious during evolution. Cortical blindness and optic atrophy are seen in most patients. Mental deterioration, behavioral changes and dementia appear progressively after the onset of motor symptoms.

The definitive diagnosis of Krabbe disease is made by measuring GALC activity in leukocytes isolated from whole blood or cultured skin fibroblasts. Typical values in patients with Krabbe disease are less than or equal to 15nmol / 17h / mg protein (Figure 1). The electroencephalogram is nonspecific, contributing little to the diagnosis. Cranial nuclear magnetic resonance shows atrophy lesions, especially in areas where myelination is earlier. Symmetrical white matter lesions with corpus callosum involvement and progressive brain atrophy are also described [1].

No proven specific therapeutic options currently are available for symptomatic patients with the infantile form of Krabbe disease. In such cases, supportive care is the only viable option to manage irritability and spasticity [1]. The available evidence, discussed in greater detail below, suggests but does not establish that hematopoietic stem cell transplantation is beneficial for the infantile form of Krabbe if performed before the onset of symptoms, and is possibly beneficial for patients with juvenile onset Krabbe disease [7,8].

The treatment of Krabbe disease using hematopoietic stem cells has become a safer procedure with the development of techniques such as accurate human leukocyte antigen (HLA) typing, depletion of donor T lymphocytes, and umbilical cord blood. However, the stem cell transplantation requires myelosuppressive therapy and is not without potential risk. Furthermore, long-term benefit for this intervention has not been established [1].

One report published in 2005 examined the effect of umbilical cord blood transplantation from unrelated donors in 11 asymptomatic (ages 12 to 44 days) and 14 symptomatic newborns (ages 142 to 352 days) with infantile Krabbe disease [8]. All patients received myeloablative chemotherapy prior to transplantation. The following observations were noted:

- At a median follow-up of three years, all 11 children who had transplantation as asymptomatic newborns remained alive and demonstrated normal progression of central myelination through MRI. In 10 of these children who had neurocognitive assessments after transplantation, all had age-appropriate language, and nine had age-appropriate cognitive function. Of some concern, four had mild to moderate delay in gross motor function. These findings contrasted with disease progression seen in a untreated control group of registry patients, most of whom experienced overwhelming spasticity, blindness, and death by one or two years of age [8].
- At an median follow-up of 3.4 years, only 6 of 14 infants who were symptomatic at the time of transplantation had survived; the survival rate for this group was not

considered statistically different from survival among untreated controls. None of the surviving patients in the symptomatic group showed appreciable improvement in any domain of neurocognitive function [8].

CONCLUSION

This is a rare condition, often not suspected, leading to death from subsequent complications. Although preliminary evidence suggests that haematopoietic stem cell transplantation is beneficial to the early form if performed before the onset of symptoms, there is currently no established way to predict the phenotype before symptoms appear and some will have minimal or absent symptoms without treatment [1]. There is limited evidence that symptomatic children with late onset (juvenile) form of Krabbe disease may benefit from transplantation even after the onset of symptoms. Therefore, rapid diagnosis is critical to a good prognosis. Currently, the objective of the diagnosis is family orientation regarding the prognosis and the possibility of family recurrence [5].

References

Wenger DA. Krabbe disease. Gene Reviews www.ncbi.nlm.nih.gov/books/NBK1238/ (Accessed on December 14, 2011).

Turgeon CT, Orsini JJ, Sanders KA, *et al*. Measurement of psychosine in dried blood spots--a possible improvement to newborn screening programs for Krabbe disease. *J Inherit Metab Dis* 2015; 38:923.

Luzi P, Rafi MA, Wenger DA. Structure and organization of the human galactocerebrosidase (GALC) gene. Genomics 1995; 26:407.

Orsini JJ, Kay DM, Saavedra-Matiz CA, *et al*. Newborn screening for Krabbe disease in New York State: the first eight years' experience. Genet Med 2016; 18:239.

Dunn HG, Lake BD, Dolman CL, Wilson J. The neuropathy of Krabbe's infantile cerebral sclerosis (globoid cell leucodystrophy). Brain 1969; 92:329.

Duffner PK, Jalal K, Carter RL. The Hunter's Hope Krabbe family database. Pediatr Neurol 2009; 40:13.

Krivit W, Shapiro EG, Peters C, *et al*. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. *N Engl J Med* 1998; 338:1119.

Escolar ML, Poe MD, Provenzale JM, *et al*. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *N Engl J Med* 2005; 352:2069.

How to cite this article:

Juliana Vieira de Oliveira *et al* (2019) 'Krabbe's Disease With Late Injury Symptoms In Child: Case Report', *International Journal of Current Medical and Pharmaceutical Research,* 05(09), pp 4509-4511.

****