

# Krabbe disease: the importance of early diagnosis for prognosis

Doença de Krabbe: a importância do diagnóstico precoce para seu prognóstico

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## ABSTRACT

Krabbe disease (globoid cell leukodystrophy) is an inherited recessive autosomal leukodystrophy caused by deficiency of the enzyme galactocerebrosidase. The lack of this enzyme leads to the build-up of galactolipids that will promote the death of oligodendrocytes and the demyelination of the central and peripheral nervous systems. There are two clinical forms: early onset and late onset. This article reports a case of late onset Krabbe disease and discusses the importance of early diagnosis for its prognosis.

**Keywords:** Leukodystrophy, globoid cell; Galactosylceramidase; Psychosine; Galactolipids; Early diagnosis; Case reports

## RESUMO

Doença de Krabbe (leucodistrofia de células globoides) é uma leucodistrofia de herança autossômica recessiva causada pela deficiência da enzima galactocerebrosidase. A falta dessa enzima leva ao acúmulo de galactolipídeos que irão promover a morte dos oligodendrócitos e a desmielinização do sistema nervoso central e periférico. Possui duas formas clínicas: de início precoce e de aparecimento tardio. O presente artigo relata um caso da apresentação tardia da doença de Krabbe e discute a importância do diagnóstico precoce para o seu prognóstico.

**Descritores:** Leucodistrofia de células globoides; Galactosilceramidase; Psicossina; Galactolipídeos; Diagnóstico precoce; Relatos de casos

## INTRODUCTION

Krabbe disease (DK) is a lysosome deposit disease caused by the deficiency of the enzyme galactocerebrosidase (GALC). It was first described in 1916, when Krabbe reported an uncommon form of familial diffuse brain sclerosis<sup>(1)</sup>. GALC is responsible for the hydrolysis of galactolipids (lipid components

of the myelin membrane). The main galactolipids are galactocerebrosides and psychosine<sup>(2)</sup>. Galactocerebrosides are also hydrolyzed by GM1-gangliosidase and do not degrade psychosine; therefore, there is a greater accumulation of this substance. Psychosine is the primary component responsible for the destruction of oligodendrocytes and Schwann cells, which produce myelin, resulting in demyelination of the central and peripheral nervous systems; additionally, it causes activation of astrocytes and the formation of multinucleate globoid cells (macrophages with accumulations of galactocerebrosides), characteristics of the disease in the pathological examination<sup>(3)</sup>.

There are two clinical forms of DK: early onset infantile and late onset. The first form is more common (90% of cases) and symptoms generally begin before 6 months of life (71%); in the late onset form, 6% develop symptoms between 13 to 24 months, 3% between 25 and 36 months, and 1% after 5 years. In the infantile form, the main symptoms are excessive crying, irritability, stiffness, seizures, and difficulty holding up the head. In the late onset form there are alterations in gait, motor development delay, stiffness, loss of vision, dysphagia, and seizures<sup>(4)</sup>.

## CASE REPORT

The patient named EBC, four-year-old, female, coming from and born in the city of Itu (SP). The onset of symptoms was in April 2010, with changes in gait due to weakness of the lower right limb. She evolved over 3 months to spastic tetraparesis, and was no longer able to walk or sit by herself. The patient also presented with divergent strabismus. She was admitted

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to *Hospital Israelita Albert Einstein* on August 19<sup>th</sup>, 2010, for diagnostic investigation. After one week of hospitalization, she presented with progressive dysphagia and decreased visual acuity. Upon examination, flexion and spastic hypertonia of the upper and lower members were evident, with extension of the feet, generalized symmetric hyperreflexia with bilateral Babinski sign and divergent strabismus. The neurological picture was consistent with DK and to confirm diagnosis, enzyme testing, electroencephalography (EEG), and magnetic resonance imaging (MRI) of the brain were ordered. The EEG demonstrated slightly disorganized base activity, due to diffuse slowing of cerebral activity. The MRI showed extensive alterations of white matter signals, with unspecific significance and consistent with a diagnosis of leukodystrophy. The determination of GALC activity was 6 nmoles/17 h/mg proteins (normal value: 15 to 53). An electroneuromyography was also performed and showed no alterations.

Based on the confirmation, the patient was referred to the hematopoietic cell transplant group (HCT) of the Pediatric Hematology Team, and received a transplant from a related donor. She evolved with no disease progression to date, with a significant improvement of dysphagia and visual acuity.

## DISCUSSION

DK is rare, with an incidence of 1/100,000 liveborns<sup>(4)</sup>. It presents as a hereditary recessive autosomal disorder, with a deficiency of GALC due to the mutation of the GALC gene located in chromosome 14q31 – there are also more than 60 known mutations in this gene<sup>(5)</sup>.

Most patients develop symptoms during the first months of life and the mean time between onset of symptoms and diagnosis is 5.3 months<sup>(4)</sup>. The diagnosis is made by determination of GALC activity in isolated leukocytes or in skin fibroblast cultures. Values of GALC activity lower than 15 nmol/17h/mg protein confirm the diagnosis<sup>(2)</sup>.

Other alterations found are proteinorachia; electroneuromyography with reduced rate of neural conduction. The EEG may demonstrate unspecific findings, consistent with diffuse cerebral distress<sup>(6)</sup>; on the MRI, as the disease progresses, the white matter becomes hypoattenuated and atrophied, and there is a T2 hyperintense signal in the thalamus, corona radiata, and body of the caudate nucleus<sup>(7)</sup>.

Prognosis of the disease is poor. Patients evolve with progressive neurological deterioration until coma and death within an average of 24.1 months. Some factors worsen the prognosis: onset of symptoms before 6 months of age ( $p=0.0073$ ) and presence of three

symptoms: stiffness (RR=3.26; 95% CI: 1.513-7.022), loss of vision (RR=2.701; 95% CI: 1.123-6.498), and dysphagia (RR=3.479, 95% CI: 1.129-0.72). The level of enzyme activity and the type of mutation are not related to prognosis<sup>(4)</sup>.

In the mid-1990s, the first studies of HCT for DK were initiated. Up until then there was no treatment for the disease. In patients with the late onset form and the asymptomatic infantile form, HCT showed a significant improvement on MRI of the levels of GALC and neurological functions; however, in the symptomatic infantile form, the course of the disease was not changed<sup>(8,9)</sup>. The study by Escolar et al.<sup>(8)</sup> compared 11 transplanted asymptomatic newborns (TNB), 14 transplanted symptomatic infants under 9 months of age (TI), and 190 non-treated patients (NT). In all those transplanted, the GALC levels normalized. Survival three years after the HCT in the TNB was 100%, in the TI it was 43%, and none of the NT survived. Survival in the TNB group was better than in the TI ( $p=0.01$ ), and better relative to the NT ( $p=0.001$ ). Comparing TI to the NT, there was no statistical difference in survival ( $p=0.28$ ). As to neuromotor development, 50% of the TNB showed some degree of impairment in gross motor function, while in the TI group, all presented with severe involvement. As to fine motor function, 20% of the TNB showed some degree of impairment, and all of the TI had alterations. Regarding cognitive function, all the TNB developed normally, and the TI and NT displayed late onset changes. In the study by Krivit et al.<sup>(9)</sup>, 11 patients with the late onset form were evaluated, and 10 years after the transplant, all had experienced improvement of the central nervous system and had normal cognitive development.

As of 2006, in the state of New York, GALC determination using newborn screening with the dried blood spot is mandatory<sup>(10)</sup>. Duffner et al. are trying to prepare a follow-up protocol to identify which patients with positive tests would benefit from undergoing an early HCT, since this would help only those with the asymptomatic infantile form and the late onset form<sup>(10)</sup>. However, there are various difficulties in implementing this screening as a public health measure, since this disease is rare. Another difficulty is foreseeing which phenotype the patient with a positive test will develop, since neither the level of enzyme activity nor the type of mutation predicts the clinical form.

## CONCLUSION

DK has a quick and lethal progression. Early diagnosis is fundamental for a good prognosis. HCT is more

effective in the asymptomatic infantile and late onset forms, impeding neurological progression. Therefore, the earlier the diagnosis, the lower the incidence of neurological sequelae.

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