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CASE REPORT

Krabbe s disease - case report

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Abstract

Objective: report a case of Krabbe´s disease with necropsy.

Methods: review of medical and necropsy records.

Results: an 8 months-old male patient developed tremors, swallowing difficulty and excessive salivation for 4 months prior to admission, evolving with vomiting and fever. Physical examination showed microcephaly and diffuse pigmentation of the retinae. Neurological examination showed flexion of upper limbs with spastic hyperthony, symmetrical global hyperreflexia, nystagmus and spontaneous spasms. EEG showed multifocal irritative activity. There was increase in both CSF protein and gamaglobulin. The patient evolved with transitory hyperthermia, vomiting and pneumopathy, dying on the 23rd day after admission. Post mortem studies revealed microcephaly with widening of brain sulci. Histological examination revealed several globoid cells in the deep portion of the white matter, reactive gliosis and demyelination.

Conclusions: these findings were similar to those in the world literature, indicating a poor prognosis due to substantial brain damage.

J Pediatr (Rio J) 2000; 76(1): 79-82: Krabbe´s disease, galactosylceramidase, globoid cell leukodystrophy.

Introduction

Krabbe's disease, a leukodystrophy of the globoid cells, is an enzymatic autosomal recessively inherited disorder characterized by the accumulation of galactocerebroside and psychosine in the central and peripheral nervous system; it is caused by a dysfunction of the galactocerebroside beta-galactosidase lysosomal enzyme, also called galactocerebrosidase or galactosylceramidase. This disorder was first described in 1916, when Krabbe reported an uncommon case of familial diffuse sclerosis of the brain.[1] The authors present a case of Krabbe's disease, and this is, up to the present moment, one of the rare reports with necropsy in the Brazilian literature.[2]

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Case report

An 8-month old male patient developed tremors in the limbs, swallowing difficulty, and excessive salivation for 4 months prior to admission, evolving with vomiting and peaks of fever during the night. The neuropsychomotor development was normal until half of the 2nd month of life, when the patient ceased sustaining his head and following objects, started loosing interest for the environment, and developed irritability. Physical exam showed microcephaly, ogivoid palate, and diffuse pigmentation of the retina. Neurological examination evidenced flexion and spastic hypertonia of the upper limbs with abduction of thumbs, symmetrical global hyperreflexia with bilateral Balibinski sign, rotatory nystagmus, as well as spontaneous spasms, resulting from sound, tactile, and light stimuli. EEG showed multifocal irritative activity. Puncture demonstrated clear cephalorachidian fluid, at 5 cells/cm^3 (100% leukocytes), and 161 mg/dl of proteins (55.36% albumin and 12.43% gammaglobulin). The patient evolved with transitory hyperthermia and vomiting, diffuse snore and stertor of mean and thick bubbles, and died on the 23rd day after admission.

Necropsy revealed microcephaly, with the encephalon presenting widened and surfaced sulci and tenuous venous congestion. Microscopically, numerous globoid cells were identified, mainly in the deep white matter, presenting a voluminous cytoplasm, sometimes binucleated, with nuclei displayed peripherally, slightly colored by the periodic acid-Schiff reaction (Figure 1). We also identified moderate astrocyte reaction, demyelination, and a small number of mononuclear cells. At the right upper pulmonary lobe, we observed necrosed areas with numerous fungi, formed by oval spores and hyphae with aberrant septations, which were predominantly divided in an acute angle, characterizing a status of pulmonary aspergillosis (Figure 2).

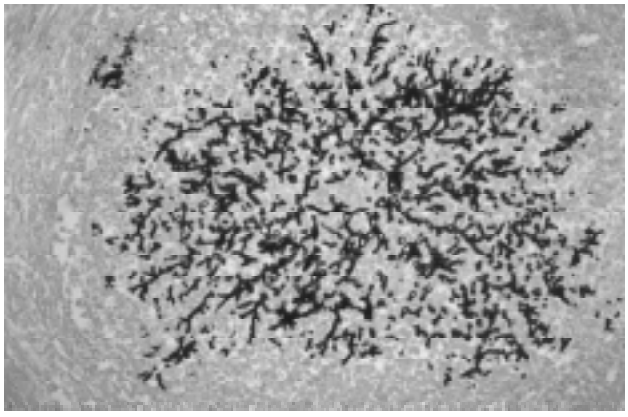

Figure 2 - Pulmonary tissue showing extended necrosis and numerous *Aspergillus sp* hyphae (Grocott x 100)

Discussion

Krabbe's disease is an autosomal recessive disorder of accumulation, characterized by the deficit of the enzyme galactosylceramidase, which is responsible for the catabolic transformation of galactosylceramide, and results in the accumulation of galactocerebroside in the microglia and macrophages of the central and peripheral nervous system.[2] This enzymatic dysfunction also determines the presence of psychosine,[3] which leads to the destruction of the oligodendrocytes and Schwann cells, evolving to a massive demyelination of the central and peripheral nervous system.

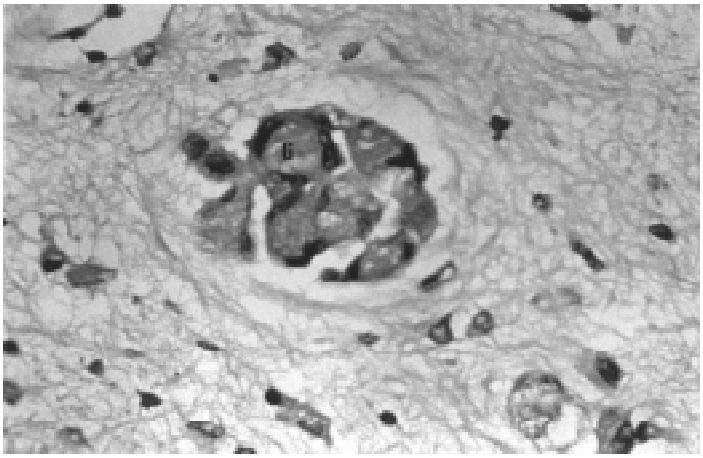

Figure 1 - Histological section of the brain showing a mass of globoid cells in the white matter, which constitutes a characteristic finding of Krabbe's disease (HE x 400)

In regard to incidence, Krabbe's disease may affect 6 cases for each 1,000 live newborns.[4] In Brazil, there are few reported cases of this entity.[5-7]

Krabbe's disease affects predominantly infants. In 25% of the cases, the symptoms appear before 3 months of age; in 80%, the onset of symptoms occurs between 3 and 6 months; in less than 10% of the cases, the symptoms appear after the 1st year of life, presenting a clinical course with accelerated progress.[8,9] Cases of juvenile Krabbe's disease have been described, affecting children between 2 and 6 years of age or more;[10] however, the clinical course could not be well established due to the scarcity of cases.

The clinical manifestations of Krabbe's disease are unspecific and progressive. The initial symptomatology is characterized by the interruption or regression of psychomotor development. Hagberg et al.[11] proposed a classification of the symptoms into three distinct stages: in the first, a neuropsychomotor deterioration is observed along with fever of unknown origin and irritability; in the second stage, a clear neurological disorder can be evidenced, as well as hypertonia and tendency to opisthotonus, evolving to vegetative life in the terminal stage. Other signs and symptoms observed consist of multiple spontaneous spasms, characterized by hyperextension of the limbs and head, presence of Babinski sign, lack of deep reflexes, vomiting, and head growth retardation, which results in microcephaly, as observed in the case here presented.

Diagnostic certainty of Krabbe's disease, as well as its prenatal diagnosis, is established by the dosage of galactosylceramidase in a fibroblast and leukocyte culture;[12] this test is not commonly performed in Brazil. However, the analysis of the clinical status, associated with protein dosage in the cephalorachidian fluid, electromyography, and ultrastructural analysis of the peripheral nerve[10] are very useful in helping establish the diagnosis. Molecular heterogeneity in juvenile Krabbe's disease has been demonstrated, and indicates that mutations in different sites result in the same disorder.[13]

The analysis of the cephalorachidian fluid demonstrates an increase in the rate of proteins, which may vary from 70 to 450 mg/dl. In the electromyographic study, we observed an important decrease in the nerve conduction velocity, which becomes accentuated as the disease develops. The EEG may present unspecific findings, compatible with diffuse cerebral distress. The ultrastructural analysis of the peripheral nerve biopsy showed crystalline, quadrangular or spicular inclusions, dense lamellar aggregates in the cytoplasm of Schwann cells, and mesenchymal cells of the nerve.[2]

In cases of study through necropsy, the neuropathological analysis evidences cerebral atrophy, diffuse demyelination, and calcifications in the white matter. Intense gliosis can be demonstrated in the cortex and in the basal nuclei, especially in perivascular spaces of the white matter. Globoid cells constitute the pathognomonic finding of Krabbe's disease, and they are represented by cells with 15 to 20 μm in diameter, mono or binucleated, derived from the microglia and macrophages distended due to the central accumulation of galactocerebroside, in which a strong Sudan staining can be noticed, as well as absence of reactivity to glial fibrillary acidic protein.[14]

The prognosis of patients affected by this entity is somber because of the progressive demyelination caused by the toxicity of psychosine. However, with the techniques created by biochemistry and molecular genetics, the diagnosis may be established early;[15] this emphasizes the importance of the physician, pathologist or pediatrician in the confirmation of the diagnosis, and the subsequent genetic advise for the family, since there is a 25% risk of recurrence for future generations.

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