Infantile Krabbe Disease

Isabelle Korn-Lubetzki, MD; Yoram Nevo, MD

Infantile Krabbe disease is an autosomal recessive leukodystrophy involving both the central and peripheral nervous systems. Its diagnosis can now be established by modern laboratory methods, but effective treatment remains to be elucidated. It is important to recognize the typical and less common clinical manifestations to enable genetic counseling and prevention of the disease in high-risk populations.

FIRST DESCRIPTION

In 1916, Danish neurologist Knud Krabbe, MD, described 5 infants with what he called “a new familial, infantile form of diffuse brain sclerosis.” Although his description of this new syndrome had much in common with the 1908 description by Beneke of a 21-month-old boy, it was Krabbe who emphasized the familial occurrence (the first 2 patients in his series were siblings). He described the initial symptoms and signs as pointing to central nervous system involvement:

When 5 months old he began to cry frequently and convulsively. At the same time fits of stiffness of all extremities appeared, with obstetrical posture of the hands and crossing of the legs. . . . Ophthalmologic examination showed greyish discs with veiled outlines (early optic atrophy). . . . Body and limbs stiffly extended, head turned backwards, back crooked, hands often clenched, sometimes in tetanic posture; lower extremities strongly extended and adducted, toes spread . . . Babinski’s sign was present. During the examination attacks of convolution occurred.

This boy died at age 13 months. A similar clinical manifestation and course were observed in 4 other infants. Postmortem examination of the 5 brains revealed “the extraordinary hardness of the white matter of the brain and the spinal cord,” “the complete destruction of the axis-cylinders and medullary sheaths, the replacement of the destroyed tissue by neuroglia and the relative intactness of the nerve cells.”

Krabbe’s clinical diagnosis was “familial infantile diffuse sclerosis.”

The term diffuse sclerosis, probably first used by Strumpell in 1879 to describe the hard texture of the freshly removed brain of an alcoholic patient, was later applied to widespread cerebral gliosis of various causes. For example, Schilder diffuse sclerosis (encephalitis periaxialis diffusa) was described in 1912. In his description of the new disease, however, Krabbe characterized his patients as having a lack of inflammation and an extension of the pathologic findings to the whole cerebrum, thereby differentiating them from those of Schilder.

Krabbe also provided a detailed description of what he called “gigantic polynuclear glia-cells,” which had been described earlier by Beneke as well as Bullard and Southard. Collier and Greenfield were the first to label those numerous abnormal cells in the white matter as being globoid, the hallmark of Krabbe disease (globoid cell leukodystrophy):

In all regions where myelin destruction was active, . . . there were large “globoid” cells of peculiar character. Their nuclei were always multiple and sometimes were numerous, and were arranged as a chain of thin flattened nuclei under the capsule of the cell.

PERIPHERAL NERVE INVOLVEMENT

For nearly 50 years, Krabbe disease was thought to be a disorder limited to the central nervous system myelin. Although early reports did not mention any peripheral nervous system involvement, Krabbe himself reported that “the patellar reflexes could not be obtained on account of the rigidity” in case 2 of his series. Pe-
Peripheral nervous system involvement was first described by Matsuyama et al in 1963. In the first American report of peripheral neuropathy in a case of Krabbe disease, the clinical picture was dominated by central nervous system symptoms and signs:

Clinical examinations have often failed to be helpful in recognizing the peripheral neuropathy because, early in the illness, the central nervous system is usually more severely involved than the peripheral nerves. The child may have hyperactive deep tendon reflexes, as was the case in our patient, and at the same time show a prominent peripheral neuropathy when studied electrophysiologically.\textsuperscript{(Nep100)}

Conduction studies performed in this patient at age 22 months revealed a significant slowing of nerve conduction velocity and a delay in distal latency. Peripheral nervous system involvement was confirmed pathologically:

Peripheral nerves were enlarged, firm, and chalk white in color and had large discrete, firm fiber bundles. Complete loss or thinning of myelin sheaths, and fine PAS–periodic acid–Schiff–positive granules were noted in histiocytes.\textsuperscript{(Nep306, 1098)}

There was a relative preservation of the axons and marked endoneurial fibrosis. Peripheral neuropathy is mainly described late in the course of the disease, but it can also occur as the only initial symptom and thus result in delay of the diagnosis. Krabbe disease should be considered in the differential diagnosis of infantile demyelinating polyneuropathy.\textsuperscript{9}

**DIAGNOSIS**

In 1963, Hagberg et al\textsuperscript{10} described a significant relative increase of albumin and a decrease of β-globulins with electrophoresis of the cerebrospinal fluid in cases of Krabbe disease. A suggestion that globoid cells might contain a glucocerebrosidase was supported by the chemical studies of Austin.\textsuperscript{13} The experimental induction of globoid cell infiltration with intracerebral implantation of galactocerebrosides, but not with other lipids tested, further supported the association between globoid cells and cerbrosides.\textsuperscript{12} The biochemical diagnosis of the disease was established in 1970 by Suzuki and Suzuki,\textsuperscript{13} who demonstrated a profound deficiency of the enzyme galactocerebrosidase (GALC gene) in the brain, liver, and spleen of 3 patients with Krabbe leukodystrophy.

In patients with Krabbe’s disease, cerebrosides from the catabolized myelin cannot be disposed of owing to the enzyme deficiency. This cerebroside elicits globoid cell infiltration. While the globoid cell reaction in normal brain subsides when digestion of excess cerebroside is complete, globoid cells in Krabbe’s disease remain permanently because cerebroside cannot be degraded.\textsuperscript{(Nep308)}

**EPIDEMIOLOGIC CHARACTERISTICS AND MOLECULAR GENETICS**

Krabbe disease occurs worldwide. The incidence in Europe is approximately 1 in 15000 live births. In relatively unique populations such as the Druze of northern Israel or the Muslim Arabs of 2 villages near Jerusalem, where consanguineous marriage is very common, the incidence reaches 1 in 130 live births.\textsuperscript{14} This particularly high incidence and the presence of large kindreds helped map the disease to human chromosome 14 using linkage analysis.\textsuperscript{15} The molecular genetics of Krabbe disease is now well known. More than 40 mutations in the human GALC gene have been identified worldwide. In Israel, the Druze patients are homozygous for the 1748T to G (I583S) mutation, and the Arab Muslim patients for the 1582T to C (D528N) mutation.\textsuperscript{16}

**TREATMENT AND PREVENTION**

There is still no treatment for Krabbe disease. Preliminary studies using hematopoietic stem cells, bone marrow transplantation, and viral vectors to transduce transplantable cells are currently under way in animal models.\textsuperscript{17} In high-risk populations in which Krabbe disease constitutes a significant burden on society, prevention depends on prenatal diagnosis and genetic counseling. Accepted for publication December 4, 2002.

**REFERENCES**

6. Collier J, Greenfield JG. The encephalitis periaxialis of Schilder: a clinical and pathological study, with an account of two cases, one of which was diagnosed during life. Brain. 1924:47:489-519.