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Child Neurology: Krabbe disease

A potentially treatable white matter disorder

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Krabbe disease (glucocerebrosidase [GALC] deficiency) is an inherited leukodystrophy resulting in altered myelination. Most patients have early-infantile onset of disease (<6 months) characterized by rapid neurologic deterioration and death. Approximately 10%–15% of patients have late onset disease (late-infantile 6 months–3 years; juvenile 4–8 years; adult >8 years) with a milder course. Hematopoietic stem-cell transplantation (HSCT) may be used in some patients to improve outcome. Here we report an untreated patient with early-infantile onset disease and her presymptomatic sibling treated with HSCT to demonstrate the benefit this treatment can have on clinical outcomes. Chart review was approved by BC Children's & Women's Hospital Research Ethics Board (CW09-0290/H09-03031).

CASE REPORTS **Case 1: Untreated infantile-onset Krabbe disease.** After an unremarkable pregnancy and neonatal course, a female infant presented at 6 months of age with regression of motor development and irritability. Neurologic examination showed increased tone and reduced strength in all limbs, with diminished muscle stretch reflexes and extensor plantar responses. Krabbe disease was diagnosed at 8 months of age based on decreased GALC activity (0.5 nmol/h/mg protein). Genetic analysis showed a 30-kB deletion in 1 *GALC* allele (14q31) and a point mutation in the other allele (c.1538 C>T; p.T513M). Neuroimaging showed poor gray–white matter differentiation on CT and T2 hyperintensity of cerebellar white matter on MRI. Nerve conduction studies (NCS) and EEG were not performed. She developed extensor posturing and swallowing difficulties requiring G-tube insertion. She became unresponsive at 12 months of age and died at 22 months from respiratory complications.

Case 2: Treated infantile-onset Krabbe disease. This patient (original case report[1]), the sibling of case 1, was identified prenatally through mutation analysis in chorionic villus sampling. GALC activity was reduced postnatally in white blood cells (0.4 nmol/h/mg protein). Neurologic examination, neuroimaging studies, and EEG were normal. NCS showed a moderate peripheral demyelinating sensorimotor neuropathy. Transplantation of unrelated umbilical cord blood hematopoietic stem cells was performed at 24 days of life, after preparatory myeloablation with busulfan and cyclophosphamide, and graft vs host disease (GVHD) prophylaxis with methylprednisolone, cyclosporine, and antithymocyte globulin. Engraftment was successful, but the patient experienced transplant-related complications including grade 1 GVHD, septicemia, mild hypertension, and transient steroid-related cardiomyopathy.

Post-transplantation, GALC activity normalized. However, persistent peripheral neuropathy was demonstrated on NCS, and evidence of abnormal T2 hyperintensity of centrum semiovale with diffuse calcification was seen on neuroimaging within 6 months of transplantation. Abnormal white matter signal progressed in the periventricular white matter and white matter tracts during the first 12 months post-transplantation, but then stabilized for 3 years.

Development of neurocognitive skills post-transplantation progressed at a delayed rate. She could communicate by 6 months of age, and walked at 22 months. Neuropsychological assessment at 24 months showed normal receptive language and adaptive skills, with expressive language delayed by 7 months. At last clinical assessment (age 5 years), the patient was in kindergarten with a full-time aide. She was able to run, talk in 5-word phrases, color, use scissors, and feed herself. Neurologic examination was remarkable for pale optic discs, sustained ankle clonus, upgoing plantar responses, and a tendency to toe walk.

DIFFERENTIAL DIAGNOSIS The differential diagnosis of psychomotor delay with white matter

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abnormalities on neuroimaging is broad. An established approach classifies patients by pattern of neuroimaging abnormality and subsequently targets metabolic and genetic testing.[2] Krabbe disease typically shows white matter with confluent, prominent T2 hyperintensity and T1 hypointensity in a parieto-occipital or periventricular predominance. Other white matter disorders with these patterns include 1) parieto-occipital: X-linked adrenoleukodystrophy, Zellweger spectrum disorder, neonatal hypoglycemia; 2) periventricular: metachromatic leukodystrophy, Sjögren-Larsson syndrome, periventricular leukomalacia, HIV encephalopathy, neuronal ceroid lipofuscinosis. Early-infantile onset Krabbe disease has characteristic CT hyperdensities in brainstem, cerebellum, and thalamus, which can also be seen in Sandhoff disease, GM1 and GM2 gangliosidoses.

CRITERIA FOR HSCT There are currently no consensus criteria to evaluate patients with Krabbe disease for HSCT. Transplantation has been tried in patients of all ages, though most reported cases involve patients with infantile-onset disease.[3,4] A staging system based on clinical evaluation of early- and late-infantile onset patients has been developed to guide candidacy for HSCT.[5] Patients are classified into 1 of 4 disease stages. Outcome analysis has demonstrated that patients with minimal to no disease progression at time of HSCT (stages 1 or 2) have 100% survival post-transplant and make developmental gains, whereas patients with more advanced disease (stages 3 or 4) have significantly higher mortality post-transplant with no developmental gains. These studies suggest that HSCT should only be performed in this age group when symptoms are absent or mild.[5,6,e1] Conversely, juvenile or adult-onset patients with substantial cognitive and neurologic dysfunction at the time of transplantation can benefit from treatment.[3,7]

COMPLICATIONS HSCT carries significant morbidity and mortality. Mortality in a group of symptomatic infants with Krabbe disease treated with HSCT was 29% (4/14 patients), though all presymptomatic transplanted infants survived (11/11 patients).[4] Successful HSCTs have been carried out in juvenile and adult-onset patients, but there are also reports of mortality.[8]

Acute or chronic GVHD has been reported in up to 32% of transplanted patients.[4,7] Overall, risk counseling for HSCT in patients with Krabbe disease of any age remains imprecise, but is generally regarded as carrying significant risk of morbidity and mortality.

CLINICAL AND DEVELOPMENTAL OUTCOMES Thus far, no presymptomatic early- or late-infantile onset patients treated with HSCT have died of progressive disease.[4,6] A multicenter cohort of 16 of these infants showed that all had abnormalities of gross motor control and expressive language. Although receptive language and cognition were considered normal, proper assessment of these skills in young children with motor and expressive language abnormalities is difficult, and some children (as in case 2) may require school assistance.[6] These patients also had poor growth, and developed spasticity, loss of motor milestones, and microcephaly.[6] Thus, significant neurologic morbidity may still develop despite presymptomatic transplantation.

Symptomatic early-infantile onset Krabbe disease patients treated with HSCT show gross motor deterioration although they may show gains in language and cognitive development.[5] Several isolated cases of transplanted juvenile or adult-onset patients suggest that HSCT may lead to clinical benefits despite the presence of pretransplant neurologic symptoms. Juvenile- and adult-onset patients have experienced dramatic resolution of ataxia, tremor, motor incoordination, and cognitive difficulties after HSCT.[3,7] However, there are currently few published cases of HSCT in patients with late-onset Krabbe disease, so it is difficult to draw conclusions about the efficacy of transplantation in this population.

BIOCHEMICAL AND NEUROPHYSIOLOGIC OUTCOMES AFTER TRANSPLANTATION There is currently no known biomarker that parallels long-term clinical outcomes post-transplant.[1,6]

HSCT consistently increases, and in some cases normalizes, GALC activity.[1,3,7] CSF protein levels, elevated in most patients with Krabbe disease, decrease but do not reliably normalize after HSCT.[1,7]

In contrast to the consistent improvements in biochemical measures after HSCT, neurophysiologic and neuroimaging findings post-transplant are variable. Krabbe disease is accompanied by a severe demyelinating sensorimotor neuropathy. In one cohort of 12 patients with Krabbe disease, HSCT increased nerve conduction velocity in all patients, with detection of previously absent nerve responses in some.[9] Greater improvements in NCS were observed when HSCT was performed earlier in disease course. Adult-onset patients may experience stability, or even improvement in peripheral neuropathy, but these improvements are not always sustained,[9] and long-term outcome data are not yet available.

Neuroimaging in Krabbe disease shows demyelination involving periventricular white matter, cerebellum, and brainstem, with differences in distribution observed

in early- and late-onset disease.[e2] HSCT has resulted in stabilization of mild neuroimaging abnormalities and developmentally appropriate patterns of myelination in presymptomatic early-infantile onset cases.[4] However, as our case 2 demonstrates, progressive deterioration of neuroimaging can occur post HSCT even in presymptomatically transplanted patients.[1] Most symptomatic infants have significant MRI abnormalities prior to transplantation, and continued deterioration occurs post-transplant.[4] Some limited evidence suggests that in juvenile- and adult-onset patients with preexistent MRI abnormalities, HSCT can halt or even reverse progression of MRI deterioration.[3,7] The effect of HSCT on subsequent neuroimaging results appears to vary with Krabbe phenotype as well as pretransplant MRI abnormalities, and long-term follow-up studies are necessary.

FUTURE DIRECTIONS IN TREATMENT OPTIONS

Recent advances show promise for additional therapeutic options.[10] Pharmacologic chaperones, which protect misfolded proteins that would otherwise be degraded, could increase the activity of mutated GALC.[e3] Injection of recombinant proteins or neural progenitor cells into brains of animal models of Krabbe disease results in decreased neuropathology and some neurologic improvement.[e4,e5] Similar improvements occur when viral vectors are used to increase GALC expression in such models.[e6,e7] Currently, these therapies are not yet sufficiently established for human trials in patients with Krabbe disease.

DISCUSSION Krabbe disease is a rare disorder for which HSCT is a viable, albeit high-risk, therapy. Further studies are necessary to document long-term clinical outcomes post-transplant and establish guidelines for treatment of this severe neurologic disease.

AUTHOR CONTRIBUTIONS

Dr. Gelinas is responsible for case acquisition, article concept and design, and manuscript revisions. Dr. Liao is responsible for the article concept and drafting and revising the current manuscript. Dr. Lehman is responsible for manuscript revision. Dr. Stockler is responsible for developing the manuscript concept and case acquisition. Dr. Sirrs is responsible for drafting and revising the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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