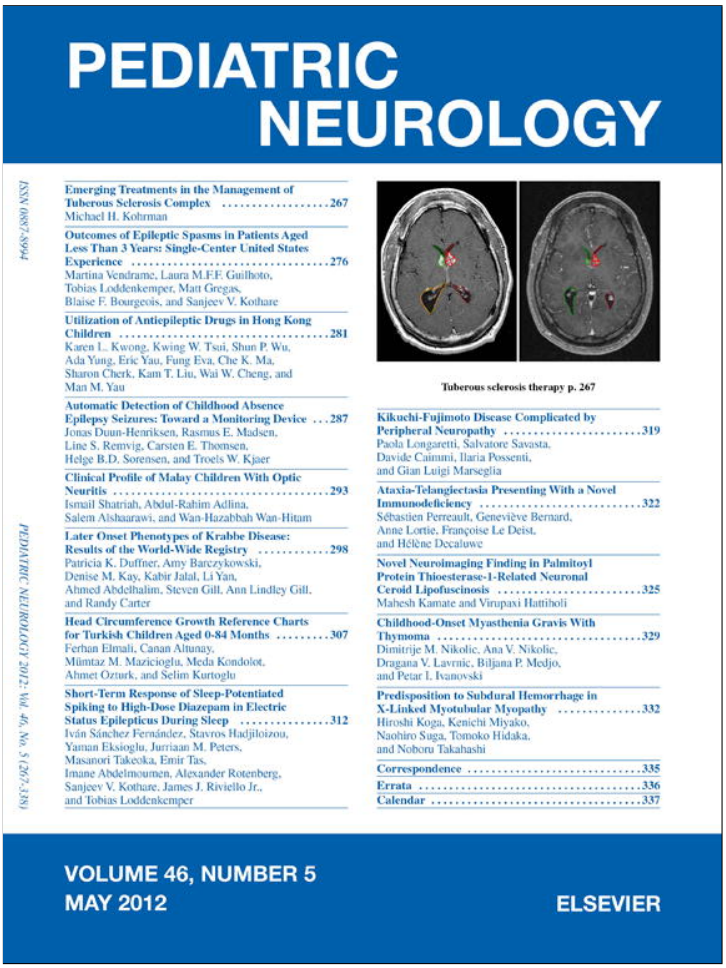

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Original Article

Later Onset Phenotypes of Krabbe Disease: Results of the World-Wide Registry

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ABSTRACT

The majority of newborns screening positive for Krabbe disease have not exhibited the expected early infantile phenotype, with most clinically normal despite low galactocerebrosidase activity and two mutations. Most are expected to develop the later onset phenotypes. The World-Wide Krabbe Registry was developed in part to expand our understanding of the natural history of these rare variants. As of June 2011, 122 patients were enrolled in the registry: 62% manifested early infantile onset (previously reported), 10% manifested onset at 7-12 months (late infantile), 22% manifested onset at 13 months to 10 years (later onset), and 5% manifested adolescent/adult onset. Data on disease course, galactocerebrosidase activity, DNA mutations, and results of neurodiagnostic studies were obtained from questionnaires and medical records. Initial signs (late infantile) included loss of milestones and poor feeding, whereas later onset and adolescent/adult phenotypes presented with changes in gait. Elevated cerebrospinal fluid protein and abnormal magnetic resonance imaging results were present in most, but not all, patients at diagnosis. Phenotypic variability occurred in four sibships. Five-year and 10-year survivals for all later onset phenotypes were at least 50%. The later onset Krabbe phenotypes differ from those with early infantile disease, but no specific predictor of phenotype was identified.

Introduction

In August 2006, New York State began a program of universal newborn screening for Krabbe disease. The anticipated incidence of Krabbe disease was 1/100,000, with >90% of patients expected to manifest the early infantile phenotype [1]. Later onset phenotypes were recognized to exist, but these cases were expected to be rare.

In an effort to predict which children with positive newborn screening and low galactocerebrosidase activity would manifest the early infantile phenotype and be considered for emergent hematopoietic cell transplantation, the Krabbe Consortium of New York State established a standardized protocol that included longitudinal neurologic examinations and neurodiagnostic studies, the frequency and extent of which were based on the amount of galactocerebrosidase activity [2]. The researchers had hoped that over time, the results of enzyme activity, mutation analyses, and neurodiagnostic studies of affected children would allow investigators to predict phenotypes with certainty.

By 2008 (2 years into the program), however, only two infants with the early infantile phenotype had been identified, whereas the majority of infants with very low enzyme activity and two mutations remained normal throughout the first year of follow-up. Whether these children would develop later onset forms of the disease or remain clinically unaffected was unknown. This finding was of more than academic interest, because the only treatment for Krabbe disease is hematopoietic cell transplantation, which involves significant morbidity and a mortality rate of 15%, and to be effective, must be performed before the onset of signs or symptoms [3]. In the absence of firm predictors of phenotype, clinicians ran the risk of referring children for transplant who might not develop signs for many years, if at all.

The World-Wide Registry for Krabbe Disease was therefore established with the primary goal of determining whether clinical, biochemical, genetic, or neurodiagnostic parameters could predict phenotype when data from large numbers of symptomatic patients with Krabbe disease were analyzed. In addition, the registry could provide extensive natural history data on patients with an extremely

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rare disease, increase awareness of the disease (leading to earlier diagnosis), and improve the ability to assess the results of established and novel therapies, especially if survival was the outcome measure. The World-Wide Krabbe Registry data on the early infantile phenotype were previously reported [4]. This study will present the results of patients with later onset forms of the disease, an increasingly important subset.

Materials and Methods

The World-Wide Krabbe Registry was established at the Hunter James Kelly Research Institute (Buffalo, NY) in 2008. Referrals to the registry came primarily from the Hunter's Hope Foundation, child neurologists, and geneticists, and from self-referrals. The registry was approved by the Children and Youth Institutional Review Board of the School of Medicine at the State University of New York at Buffalo. After families consented to the study, they received a form to complete that included questions on demographics, birth history, family history, age at onset of signs, initial and later signs, age at diagnosis, survival, and, if transplantation had occurred, where and when the procedure was performed and the outcome. In addition, families received a release form for medical information to be sent to the child's physicians. The requested medical records included age at onset of signs, signs, results of the initial neurologic examination, and survival. Galactocerebrosidase activity, DNA mutations, and results of initial neurodiagnostic studies were also requested. Over time, it became clear that few patients had been tested for DNA mutations. To increase the numbers of patients tested, mutation analysis, using samples of saliva, was added to the project.

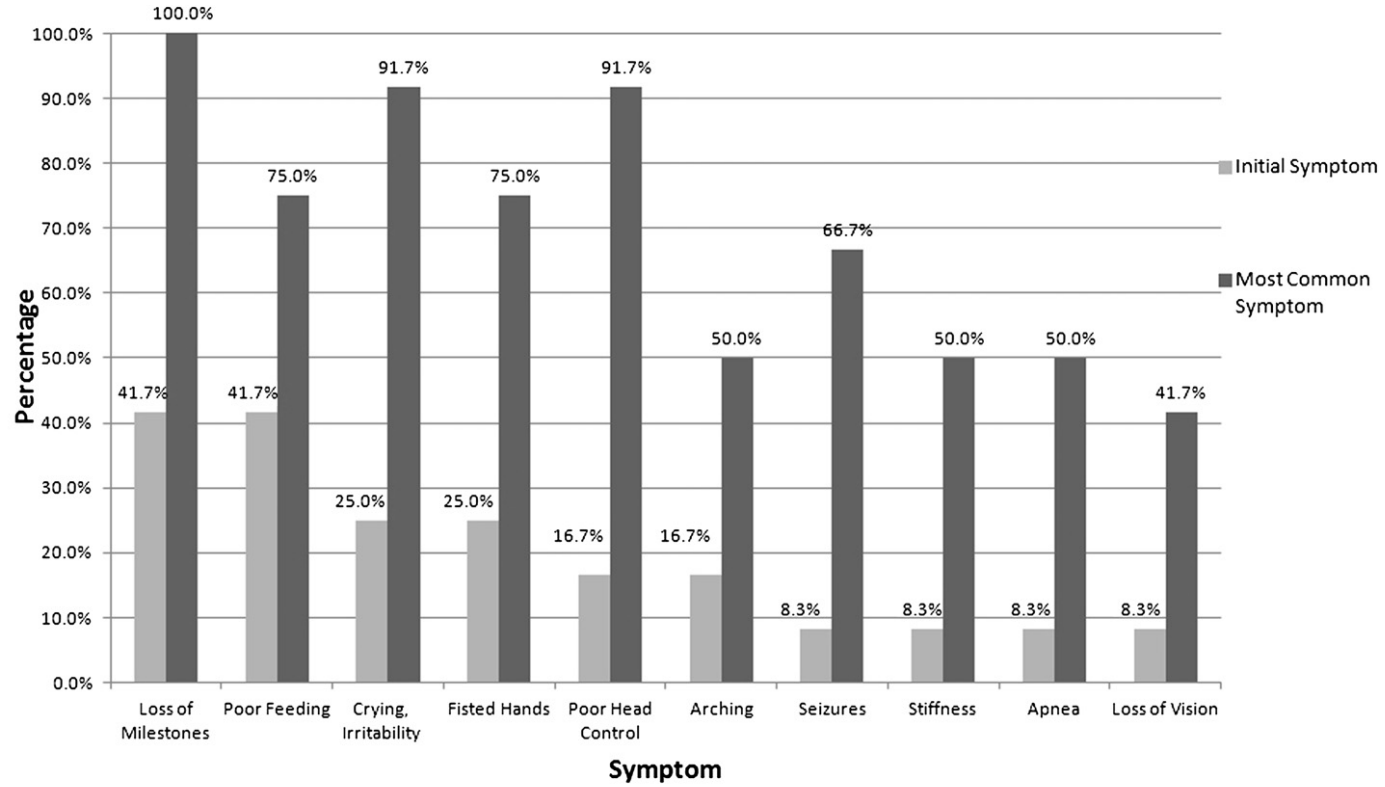
Results

As of June 2011, 122 patients were entered in the registry. Sixty-eight (56%) were male, and 54 (44%) were female. They included citizens of eight countries (Australia, Belgium, Canada, England, Germany, Scotland, Sweden, and the United States) and 30 states in the United States. Seventy-six (62%) manifested the early infantile phenotype (age at onset, 0-6 months), 12 (10%) manifested the late infantile phenotype (age at onset, 7-12 months), 27 (22%) manifested the later onset phenotype (age at onset, 13 months-10 years), three manifested onset in adolescence (ages 11-20 years), and four were adults, with an onset at >20 years of age.

Late infantile Krabbe disease (onset of signs or symptoms, age 7-12 months)

Twelve patients with the late infantile phenotype were entered in the registry. The male/female ratio was 1:1. Three patients had a positive family history for other inherited conditions, including Huntington disease, spinal muscular atrophy, and the Chiari malformation. Two children underwent transplant after the onset of their signs, and were excluded from the survival analysis.

More patients developed their first sign at age 8 months than during any other month. The most common initial signs included loss of milestones and poor feeding, followed by crying/irritability



	Loss of Milestones	Poor Feeding	Crying, Irritability	Fisted Hands	Poor Head Control	Arching	Seizures	Stiffness	Apnea	Loss of Vision
Initial	f=5	f=5	f=3	f=3	f=2	f=2	f=1	f=1	f=1	f=1
Most Common	f=12	f=9	f=11	f=9	f=11	f=6	f=8	f=6	f=6	f=5

Figure 1. The most common initial signs compared with the most common signs reported during the course of disease in 12 patients with late infantile Krabbe disease. Some families listed more than one initial sign. f, frequency (i.e., number of patients with a particular sign).

and cortical fisting (Fig 1). The most common signs reported during the course of the disease included loss of milestones, crying and irritability, poor head control, poor feeding, and cortical fisting (Fig 1).

Three children exhibited unusual presentations and courses. One previously normal child awoke in the morning, acutely unable to pull himself into a standing position. The second developed sudden unilateral visual loss at age 10 months, and then remained stable until 4 years of age, when he developed gait problems. One child demonstrated an extremely rapid downhill course, with duration from onset of signs to death of only 2 months.

On initial examination, 50% were ≤5th percentile for weight, and 44% were ≤5th percentile for height. Fifty percent manifested head circumferences ≥90th percentile, whereas 20% were ≤5th percentile. The initial neurologic examination revealed normal cranial nerves in 8/10: one manifested unilateral optic atrophy, and one manifested ptosis. Esotropia was reported in two. Motor examinations revealed increased tone in the extremities in 9/10, whereas axial hypotonia was reported in 7/10. Poor head control was cited in 7/10, and two demonstrated focal motor signs. Deep tendon reflexes were normal in 2/7, decreased in three, and increased in one. Two patients each manifested clonus and extensor plantar responses.

Galactocerebrosidase activity was assessed at the Lysosomal Disease Laboratory of Jefferson Medical College (Philadelphia, PA) in 10 of 12 children, and at the Lysosomal Disease Laboratory of Tulane University (New Orleans, LA) in one patient. Of the 10 patients tested at Jefferson Medical College, nine of 10 demonstrated galactocerebrosidase activity of 0.07 nmol/hour/mg protein or less, and one demonstrated galactocerebrosidase activity of 0.2 nmol/hour/mg protein.

Mutation analysis

The results of mutation analyses in six patients are presented in Table 1.

Initial neurodiagnostic studies

Twelve children underwent magnetic resonance imaging scans. Of these, local radiologists reported that two revealed normal results and 10 revealed abnormal results, including one that was considered borderline. The scan that was coded as borderline indicated "a slight fullness of the anterior optic chiasm of uncertain significance." Of the clearly abnormal scans, seven demonstrated an increased T_2 signal in the periventricular white matter, two demonstrated an increased T_2 signal in the cerebellar white matter, two demonstrated an increased T_2 signal in the internal capsule, and one demonstrated mild central atrophy. Comments regarding these magnetic resonance images included "normal myelination for age" (n = 2), "spares subcortical U fibers" (n = 1), "delayed myelination versus leukodystrophy" (n = 2), and "compatible with acute disseminated encephalomyelitis" (n = 1).

Seven children underwent lumbar punctures. All demonstrated elevations in cerebrospinal fluid protein.

Nerve conduction velocities were performed in three children. All revealed abnormal results, compatible with generalized sensorimotor demyelinating polyneuropathy.

Initial neurophysiologic studies

Electroencephalograms were performed in seven children. Two revealed abnormal results. One demonstrated diffuse background slowing, and one demonstrated asymmetric central spikes. Two children performed visual-evoked responses. One was abnormal because of profoundly prolonged latencies bilaterally.

Three children performed brainstem auditory-evoked responses, and all were abnormal. Two revealed prolonged interpeak latencies between waves I and V. One exhibited slow conduction in the eighth nerves bilaterally, but normal conduction within the brainstem. Magnetic resonance imaging of the spine was performed in three children. One revealed abnormal results, demonstrating the enhancement of T11 and T12 and the cauda equina.

Table 1. Mutations

Phenotype	Mutation 1	Mutation 2	GALC Activity*	Age at Onset (Months)	Survival following Onset (Months)
Late infantile	30 kb del	c.1543C>T/p.R515C	Unknown	8	27
Late infantile	c.1538C>T/p.T513M	c.1538C>T/p.T513M	0.2	11	57 (+)
Late infantile	c.860 + 1G>A**	c.1865G>T/p.G622V**	0.06	11	37
Late infantile	30 Kb del	Possible deletion in exons 12 and 13†,**	0.05	8	2
Late infantile	c.1652A>C/p.Y551S	c.580A>T/p.R194X**	0.27	9	150 (+)
Late infantile	c.1652A>C/p.Y551S	Unknown	0.05	10	158 (+)
Later onset	c.956A>G/p.Y319C	c.121G>A/p.G41S	0.2	15	11
Later onset	30 kb del	Unknown	0.17	29	5
Presymptomatic (transplanted) Later onset‡	30 kb del	c.809G>A/p.G270D	0.11	Not evaluable§	Not evaluable§
Later onset‡	30 kb del	c.809G>A/p.G270D	0.13	60	324 (+)
Later onset‡	30 Kb del	c.809G>A/p.G270D	0.15	60	246 (+)
Later onset	30 kb del	c.802G>A/p.G268S	0.0	16	86 (+)
Later onset	c.860 + 1G>A**	c.908A>G/p.Y303C	0.0	29	9
Later onset¶	30 kb del	No mutation detected	0.26	16	581 (+)
Later onset	30 kb del	Unknown	0.06	36	17
Adult‖	30 kb del	p.W115R**	0.05††	384	144 (+)
Adolescent‖	30 kb del	p.W115R**	0.24††	132	382 (+)

Abbreviation:
GALC = Galactocerebrosidase
Complementary DNA and amino acid changes are listed if known; complete information was not available for all mutations. Mutations are numbered beginning with the downstream initiator as codon 1. +, still alive.
* Unless otherwise designated, the assessment of galactocerebrosidase activity was performed at Jefferson Medical College and measured as nmol/hour/mg protein.
† Both parents tested; results inconclusive.
‡ Siblings.
§ Not evaluable. The patient was not evaluable for survival because of a presymptomatic transplant.
¶ Although phenotypically this patient was compatible with later onset Krabbe disease, he may represent a Krabbe variant.
‖ Siblings.
** Novel mutations.
†† United Kingdom.

Survivals

The 1-year, 3-year, and 5-year survival rates from onset of signs or symptoms were 90%, 70%, and 50% of patients, respectively, with the longest survival to date of more than 12.5 years (Fig 2).

Later onset Krabbe disease (onset of signs or symptoms at ages 13 months to 10 years)

Twenty-seven patients manifested later onset Krabbe disease. Sixty-three percent were male, and 37% were female. (Four children underwent transplant before their onset of signs, and were excluded from the analysis of signs, neurologic examinations, and survivals.) All children manifested their onset of signs at age 5 years or less. The most common initial sign comprised change in gait (Fig 3). When this cohort was subdivided into onset of signs at ages 13-36 months and ages 37-60 months, differences in symptomatology became evident. The most common initial sign in the younger children comprised change in gait, followed by loss of milestones, crying, fisting, and visual loss. Three children presented with sudden blindness as their first manifestation. None reported seizures as their initial sign. In contrast, most children whose onset of signs occurred at ages 37-60 months also presented initially with change in gait, but none demonstrated visual loss as a presenting sign, whereas two presented with seizures. The most common signs occurring during the course of disease for the group as a whole included change in gait, fisting, stiffness, poor feeding, and visual loss (Fig 3). A comparison of the most common signs occurring during the course of disease between the younger and older cohorts also revealed differences. Visual loss occurred in 75% of the younger children, compared with no reports of visual change in the older group. In contrast, hemiparesis was reported in 71% of the older children, whereas it was not reported in any of the younger group.

Unusual presentations

Two symptomatic patients deteriorated acutely after anesthesia: one for placement of a gastrostomy, and one for heel-cord lengthening. An additional, previously normal child presented with acute hemiparesis after a myringotomy. Initially the child was thought to have undergone a cerebrovascular accident. One year later, after much of the deficit had resolved, the child underwent anesthesia again for a tonsillectomy and adenoidectomy, after which the child was never able to walk again. Three months after this acute deterioration, loss of head and truncal control, loss of vision, and difficulty swallowing were observed.

An acute onset of signs also occurred in four patients, unrelated to anesthesia. One patient was suddenly unable to walk or crawl, and was initially diagnosed with acute cerebellar ataxia. Another suddenly developed unilateral leg weakness that rapidly became bilateral. A third child presented with seizures after a flu-like syndrome. The child had been developmentally delayed before this event, but had manifested a static course. The fourth child demonstrated a sudden onset of confusion, initially diagnosed as encephalitis.

An acute onset of signs after fever occurred in two patients. One demonstrated fever and acute visual loss, and was initially diagnosed with acute disseminated encephalomyelitis, and the other developed signs after an episode of febrile seizures.

Most of the children presented with heights and weights within normal range. None manifested microcephaly, whereas 33% manifested macrocephaly. Neurologic examinations revealed initially normal cranial nerves in the majority, with the exception of optic atrophy and visual loss in three. One patient demonstrated slurred speech. A motor examination revealed increased tone in the extremities in 80%, whereas a third demonstrated hypotonia. Reflexes were increased in 43% and decreased in 36%, whereas plantar extensor responses were reported in 50%.

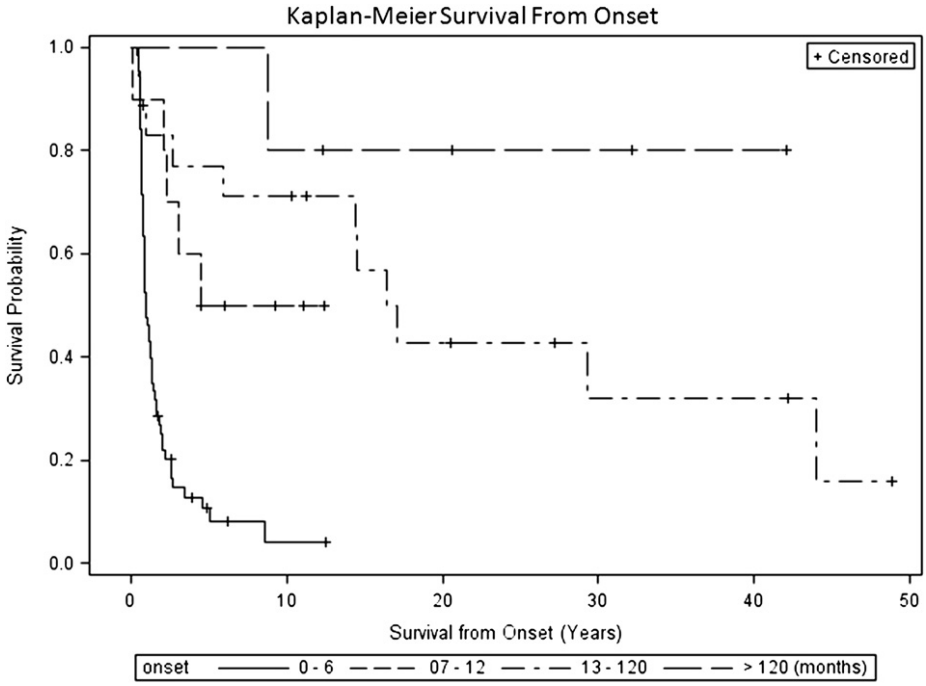
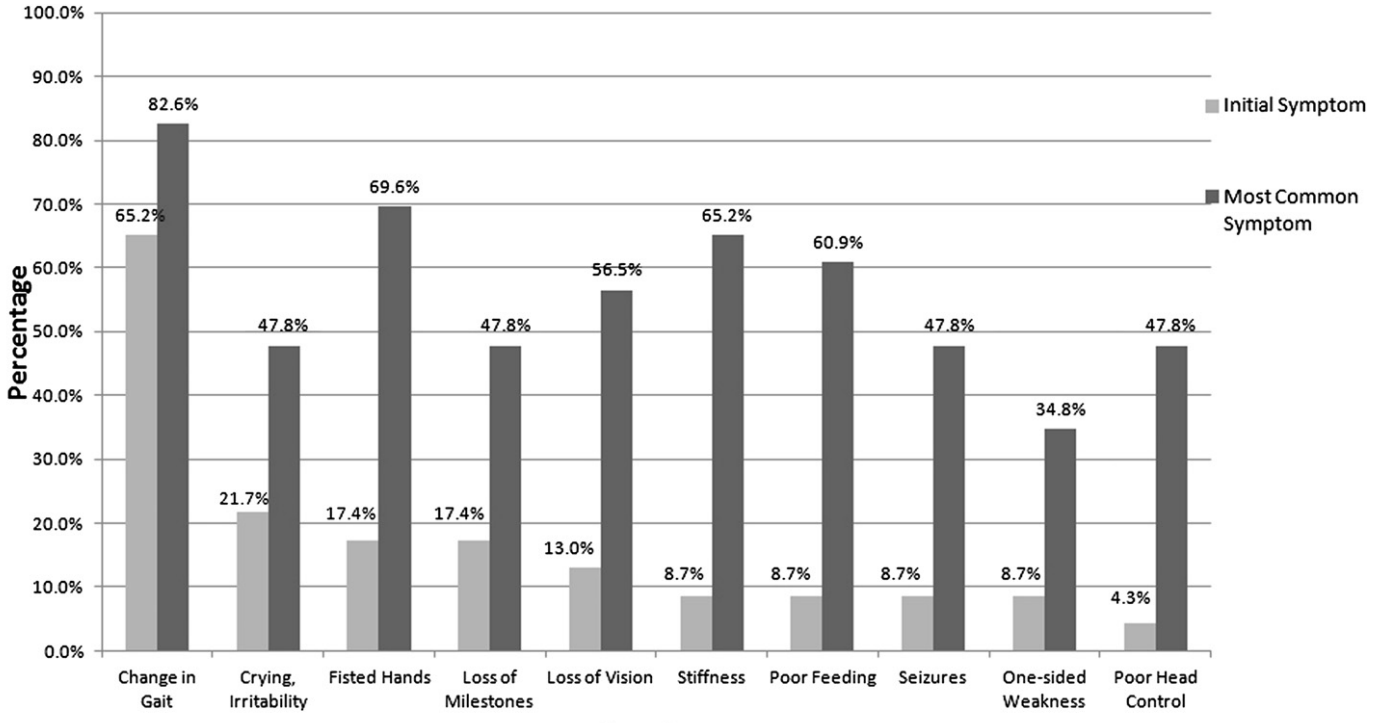


Figure 2. Survival after the onset of signs (Kaplan-Meier test) in patients with various phenotypes of Krabbe disease. One-year, 5-year, and 10-year survivals after the onset of signs: the early infantile cohort (63 children) = 47%, 10%, and 4%, respectively; the late infantile cohort (10 children) = 90%, 50%, and 50%, respectively; the later onset cohort (23 children) = 83%, 77%, and 71%, respectively; and the adolescent/adult cohort (five patients) = 100%, 100%, and 80%, respectively. Survivals were significantly different when the early infantile cohort was compared with the other phenotypes. No significant differences were evident between the other phenotypes.



	Change in Gait	Crying, Irritability	Fisted Hands	Loss of Milestones	Loss of Vision	Stiffness	Poor Feeding	Seizures	One-sided Weakness	Poor Head Control
Initial	*f*=15	*f*=5	*f*=4	*f*=4	*f*=3	*f*=2	*f*=2	*f*=2	*f*=2	*f*=1
Most Common	*f*=19	*f*=11	*f*=16	*f*=11	*f*=13	*f*=15	*f*=14	*f*=11	*f*=8	*f*=11

Figure 3. The most common initial signs compared with the most common signs occurring during the course of disease in 23 patients with later onset Krabbe disease. f, frequency (i.e., number of patients with a particular sign).

Galactocerebrosidase activity was assessed in 19 patients at the Lysosomal Disease Laboratory of Jefferson Medical College. Results were available for 16. Of these, 50% demonstrated values of 0.07 nmol/hour/mg protein or less, and 50% demonstrated values of 0.1 nmol/hour/mg protein or greater, with a range of 0.0-0.26 nmol/hour/mg protein. (The patient with the highest galactocerebrosidase activity exhibited only one mutation with polymorphisms, and although phenotypically compatible with the later onset phenotype, it may represent a Krabbe variant, or else a second mutation may not have been detected.)

Mutations

Results of mutation analyses in nine patients are detailed in Table 1.

Initial neurodiagnostic studies

Magnetic resonance imaging scans were performed in 16 children, and all but one was reported as abnormal by the local radiologist. All demonstrated an increased T_2 signal in the periventricular white matter, often with a posterior predominance. None exhibited abnormalities in the cerebellar white matter or atrophy. Five demonstrated an increased T_2 signal and/or atrophy of the splenium of the corpus callosum. Five demonstrated an increased T_2 signal in the pons. One demonstrated an enhancement of the trigeminal nerves.

Twelve children underwent lumbar punctures. Sixty-seven percent demonstrated elevated cerebrospinal fluid protein.

Nerve conduction velocities were performed in eight children. Six revealed abnormal results, including the slowing of nerve conduction velocities in six, prolonged F waves in two, and absent sensory action potentials in one.

Initial neurophysiologic studies

Electroencephalograms were performed in seven children. Three produced abnormal results: one demonstrated both diffuse and focal slowing, one demonstrated sharp waves and diffuse slowing, and the third demonstrated focal sharp waves.

Visual-evoked responses were performed in four children. One produced abnormal results, demonstrating prolonged latency bilaterally. Brainstem auditory-evoked responses were performed in four children. Two produced abnormal results. One demonstrated an absent wave V, and one demonstrated abnormalities in both peripheral and central conductions bilaterally.

Computed tomography scans were performed in two patients. One produced abnormal results, demonstrating hypodensity in the white matter.

Survivals

Survivals (Fig 2) after the onset of signs in the later onset phenotype included 83% at 1 year, 77% at 5 years, and 71% at 10 years. Survivals differed significantly between those whose onset

of signs occurred at 13-36 months vs 37-60 months ($P = 0.018$). The 1-year, 5-year, and 10-year survival for the younger cohort comprised 74%, 64%, and 59%, respectively, compared with 100% survival at 1, 5, and 10 years among those with an onset of signs at ages 37-60 months.

Adolescent/adult onset (adolescent onset of signs at age 11-20 years, and adult onset of signs at age >20 years)

Three patients manifested adolescent onset (one male and two females). One presented with stiffness of the legs, one developed a foot-slapping gait, and one developed acute weakness in one leg. Two of the three deteriorated over a period of 6 months to 2 years, whereas one remained stable for 28 years before disease progression. One patient died at age 27 years, whereas the other two are alive at ages 43 and 32 years. The patient alive at age 32 years had undergone hematopoietic cell transplantation at 19 years of age.

Three of the four patients with adult onset presented with changes in gait, whereas the fourth was asymptomatic and identified because of a positive family history. The course of disease in adults was much slower than in the adolescent group, although steady progression occurred over decades. All are alive and range in age from 44-61 years, and all manifest significant neurologic compromise. Two of the four adults exhibit tremors of the head, whereas three manifest spastic paraplegia and neurogenic bladders. One patient received a transplant at age 43 years.

Galactocerebrosidase activity analysis was performed in five patients at laboratories in the United Kingdom and at the Mayo Clinic (Rochester, MN). All results revealed low activity compared with normative values.

Neurodiagnostic studies

Cranial magnetic resonance imaging was performed in four patients. Two scans produced normal results. One adult patient exhibited selective involvement of the pyramidal tract, whereas one adolescent manifested a focal lesion in the parietal lobe, extending from the upper thalamus to the centrum semiovale.

Four patients underwent lumbar punctures. Three demonstrated modest elevations in cerebrospinal fluid protein.

Nerve conduction velocities were performed in three patients. One revealed abnormal results, demonstrating diffuse sensorimotor polyneuropathy.

Neurophysiologic studies

One adult patient presented normal results of an electroencephalogram. Two adult patients performed visual-evoked responses that proved normal, and one adult patient demonstrated a normal brainstem-evoked response.

Survivals

The 1-year, 5-year, and 10-year survival of the combined adolescent and adult phenotypes comprised 100%, 100%, and 80%, respectively. Two patients received transplants after their onset of signs (one adult and one adolescent), and were not included in the survival analysis.

Phenotypic variability in families

Variability in age at onset, severity of disease, and/or rapidity of progression was evident in four families in the registry. One family was previously described [4], and two families were briefly reported elsewhere [5,6]. In the fourth family, the index case presented at age 4 years with a slapping gait. She declined over a 3-year period and died at age 27 years, without speech, demented, and with spastic quadriplegia. Her sibling became symptomatic at 4 years of age, presenting with a stumbling gait. She demonstrated a slowly progressive course and died at 47 years of age. Variability in age at onset was also present in two other families, in which both later onset and adolescent/adult onset phenotypes occurred in siblings, whereas a third family involved the onset of signs in one sibling during adolescence (11 years), whereas another sibling was unaffected until adulthood (at age 32 years). In addition to variability in age at onset, the progression of the disease was also highly variable. In one family, the index case rapidly developed severe neurologic disability with intractable epilepsy, whereas a sibling continues to ambulate without assistance 25 years later. In yet another family, the index case manifests spastic quadriplegia and seizures and requires total care, whereas a sibling demonstrates only mild spastic paraplegia and has a full-time job.

Results of hematopoietic cell transplantation

Nine patients received a transplant after their onset of signs. The transplant centers were located in the United States (three sites) and the United Kingdom (one site). Two patients manifested the late infantile phenotype, five manifested the later onset phenotype, one was an adolescent, and one was an adult at the time of transplant. Two of the patients died from complications of the transplant (both because of infection). Of the remainder, all demonstrate significant neurologic deficits including the need for ambulatory assistance, and most demonstrate difficulty with expressive language. Their levels of cognition vary.

Four patients predicted to manifest the later onset phenotype because of a positive family history and low galactocerebrosidase activity received transplants before their onset of signs at four transplant centers in the United States. All are alive. Two patients demonstrate mild spastic diplegia, but independent ambulation. One of them also manifests a seizure disorder. One patient who received a transplant during childhood and is now in his mid-20s is reportedly neurologically normal, living independently with a full-time job. The fourth child has demonstrated multiple complications from his transplant, and it is too soon to assess outcomes.

Discussion

The literature regarding the later onset Krabbe phenotypes is confounded by differences in nosology. The definition of early infantile Krabbe disease, with its onset from birth to age 6 months, is well accepted. However, the late infantile phenotype (age 7-12 months at onset of signs) is variably defined as "infantile" (combined with the early infantile phenotype), or is combined with the later onset phenotype as "early childhood." In this series, late infantile Krabbe disease is distinguished from both the early infantile and later onset phenotypes according to differences in signs and survival (Table 2). In contrast to the early infantile phenotype, where crying and irritability are the most common initial signs, children with the late infantile phenotype typically present with a loss of milestones and poor feeding. Crying and irritability are common later in the course, but not as initial signs. The sign of poor feeding was reflected in initial physical examinations, where 50% of the babies in this series were at $\leq$5th percentile for weight. Neurologic examinations of the two phenotypes, however, were similar, with evidence of increased tone in the extremities, decreased axial tone, and cortical fisting. Neurodiagnostic studies of the early and late infantile phenotypes revealed elevated cerebrospinal fluid protein in most patients. Despite extensive neurologic deficits, magnetic resonance imaging scans were reported as abnormal in only 76% of the early infantile phenotype and in 83% of those in the late infantile cohort. This result likely reflects the difficulty in interpreting abnormal

Table 2. Krabbe disease phenotypes

	Early Infantile	Late Infantile	Later Onset	Adolescent/Adult
Age at onset	0-6 months	7-12 months	13 months to 10 years	11 years to adulthood
Initial signs	Crying, irritability	Loss of milestones	Change in gait	Change in gait
Failure to thrive	36%	50%	8%	Unknown
Head circumference				
≥90%	20%	50%	33%	Unknown
≤5%	10%	20%	0%	Unknown
Neurologic examination	↑ Tone Ext. ↓ Axial	↑ Tone Ext. ↓ Axial	↑ Tone Diplegia/quadriplegia	Paraplegia Hemiparesis
CSF (↑ protein)	92%	100%	67%	75%
MRI (abnormal findings)	76%	83%	94%	50%
Survival following onset				
5 years	10%	50%	77%	100%
10 years	4%	50%	71%	80%
Galactocerebrosidase activity (nmol/hour/mg protein)*	100%, ≤0.1	90%, ≤0.07 (one patient, 0.2)	50%, ≤0.07 50%, ≥0.1	Performed in other laboratories

Abbreviations:
↑ = Increased
↓ = Decreased
CSF = Cerebrospinal fluid
Ext. = Extremities
MRI = Magnetic resonance imaging
* Jefferson Medical College Lysosomal Disease Laboratory.

white matter in young babies, where myelination is incomplete. The most striking difference between the two groups was survival, involving a 50% 5-year and 10-year survival in the late infantile cohort, compared with 10% and 4%, respectively, in the early infantile group ($P = 0.0006$) (Fig 2) [4].

The later onset phenotype has also been variably classified as "early childhood" or "juvenile." Lyon et al. reported the largest series of what they termed the later onset phenotype, and their definition for onset of signs at ages 15 months to 10 years (or when the child begins walking) has been largely adopted in recent articles [7]. The age at onset of signs in later onset Krabbe disease was expanded to 13 months rather than 15 months in this study, because most children have begun walking by then. Of interest, no child in the registry demonstrated an onset of signs between 5 and 10 years of age. Lyon et al. [7] and Fiumara et al. [8] also reported that most, but not all, of their cases presented before 5 years of age. The recognition that most patients with this phenotype present with initial signs by age 5 years is important in the newborn screening arena, because less frequent neurologic monitoring can likely be provided after that interval.

Although change in gait was the most common initial sign in the later onset phenotype, differences existed according to age. Those with onset at ages 13-36 months were more likely to manifest visual loss, either initially or during the course of disease, whereas visual loss did not occur in any patient in the cohort aged 37 months to 5 years. In other reports, however, visual loss, attributable to either optic nerve involvement or damage to the optic radiations, was reported as also occurring in children aged >3 years [7,9,10].

The results of neurodiagnostic tests in patients with later onset Krabbe disease also differ from those in younger phenotypes. Although cerebrospinal fluid protein was elevated in most patients with the early and late infantile phenotypes, an elevation of cerebrospinal fluid protein was identified in only 67% of the later onset group. Similar results were reported by Lyon et al., i.e., only 50% of later onset patients exhibited elevated cerebrospinal fluid protein [7]. Magnetic resonance imaging revealed abnormal results in 94% of our later onset patients, compared with 76% of those with early infantile Krabbe disease and 83% of the late infantile group. In addition, the pattern of magnetic resonance imaging abnormalities in the later onset phenotype differed from those in the early and late infantile patients, insofar as no child with later onset disease demonstrated either involvement of the cerebellar white matter or atrophy. The lack of involvement in the cerebellar white matter in the later onset phenotype (defined as >2 years of age) was reported by others [11,12].

The survival of children with the later onset phenotype was significantly longer than among those with early infantile disease ($P < 0.0001$) (Fig 2). Survival also varied significantly within the phenotype, depending on age at onset of signs, with 25% of the younger cohort (aged 13-36 months) dying in 1 year. These results are compatible with those of Lyon et al., in which one third of children less than 3 years of age at the onset of their signs demonstrated a rapidly progressive form of the disease [7]. Recognizing that variability in survival depends on age at onset will be critical as the results of therapy are analyzed.

The adolescent and adult phenotypes are distinctly different from the younger phenotypes, primarily in terms of rate of progression. Patients in these cohorts may not develop progressive disease for years or even decades. They also may manifest a combination of both lower and upper motor neuron signs, although the initial sign is almost always change in gait attributable to spastic paraparesis [13,14]. Pes cavus deformities are common [15]. Misdiagnoses include amyotrophic lateral sclerosis, multiple sclerosis, vitamin B 12 deficiency, Charcot Marie Tooth disease, and hereditary spastic paraplegia [5,13]. The cerebrospinal fluid protein may be elevated, but usually to a milder degree than is evident in the younger onset phenotypes. Magnetic resonance imaging, despite extensive neurologic signs, can produce normal results [5]. Although the finding of primary involvement of the pyramidal tract is classic [16-18], there have been infrequent reports of similar magnetic resonance imaging findings in children (a 2-year-old and a 4-year-old) with the later onset phenotype [19,20].

Relatively few patients in the registry, regardless of phenotype, received baseline neurophysiologic testing. In the previously reported early infantile series, brainstem-evoked responses were abnormal in five of six patients, and nerve conduction velocities were abnormal in 5/5 [4]. Similar results were identified in the present study among children with the late infantile phenotype, in which three of three children exhibited both abnormal brainstem-evoked responses and nerve conduction velocities. Brainstem-evoked responses were not as helpful in the later onset phenotype (2/4 abnormal), whereas six of eight children manifested abnormal nerve conduction velocities. Because of differences in the definitions

of phenotypes, these results cannot be directly compared with those of Husain et al. [21] and Aldosari et al. [22], where later onset was defined as age >6 months at the onset of signs. Brainstem-evoked potentials were abnormal in 40% of their later onset group, and nerve conduction velocities were abnormal in 20%. Only one of three adolescent/adult onset patients in the present study demonstrated an abnormal nerve conduction velocity. This finding is in contrast to reports of peripheral neuropathy occurring as the presenting feature in some patients with adult onset Krabbe disease [13,14].

In this series, several patients presented acutely with symptom onset after infections, fever, and surgery. Initial diagnoses included acute disseminated encephalomyelitis, encephalitis, and acute cerebellar ataxia. Reports in the literature cited similar precipitating factors, including influenza A, gastroenteritis, fever of unknown origin, upper respiratory infection, and varicella [10,23,24].

The survival of untreated patients with later onset phenotypes can be quite prolonged, making interpretations of the results of transplantation problematic. Moreover, especially in the later onset and adult/adolescent phenotypes, the course of disease can be variable, with some patients exhibiting no progression of signs for many years. This result is in contrast to children transplanted for early infantile Krabbe disease, in which the disease course of untreated children is always relentlessly progressive. The ability to interpret the results of transplantation in the later onset phenotypes is also hampered by phenotypic variability in families. This variability among sibships is characterized by differences in age at onset, severity of disease, and rate of progression [7,15,25-28]. Although most of the reported families have involved children with the later onset phenotype in conjunction with either adolescent or adult onset phenotypes, one report of three families involved both early infantile and later onset phenotypes in the same sibship [7]. This finding is of particular concern, because the presymptomatic transplantation of infants with a positive family history of early infantile Krabbe disease is often recommended. The question arises of whether those children with the best response to transplantation may not have manifested the early infantile phenotype.

The positive results of transplantation in symptomatic, later onset phenotypes reported by Krivit et al., citing improvements in findings of neurologic examinations, were not evident in the registry population [29]. At best, transplantation appeared to stabilize disease in symptomatic patients. As with the early infantile phenotype, those treated presymptomatically demonstrated the best outcomes, often with minimal or no deficits, although durations of follow-up were limited. The known variability in the outcomes of patients with the later onset phenotypes, even among family members, confounds the meaningful interpretation of results.

Although the Krabbe World-Wide Registry has provided extensive information on various phenotypes, neither biochemical, genetic, nor neurodiagnostic studies have been identified that predict phenotype with certainty. Jalal et al. suggested that although very low galactocerebrosidase activity may be observed in all phenotypes, higher values in the abnormal range likely do not occur in the early infantile phenotype, and are unusual in the late infantile phenotype [30]. Most previous reports, however, did not reveal this association, and therefore larger series will be necessary to confirm this finding.

Few mutations identified to date are pathognomonic of phenotype, other than the 30 kb homozygous deletion for early infantile disease and the 809G>A later onset mutation [6]. In part, this finding may reflect the limited number of mutation analyses that have been performed. In an effort to better understand the influence of mutations on disease course, we have expanded the project to include mutation analysis, with parental consent, on blood spots of newborn patients in the registry. With this information, genotype/phenotype correlations may be possible.

Finally, although abnormal results of neurodiagnostic tests, including elevated cerebrospinal fluid protein, brainstem-evoked responses, and nerve conduction velocities, are present in the majority of patients, regardless of phenotype, these abnormalities are nonspecific, and negative results do not exclude the diagnosis. The pattern on magnetic resonance imaging of involvement of the cerebellar white matter in the early infantile and late infantile phenotypes, which does not appear to be present in later onset phenotypes, could constitute an important predictor of phenotype, but only if the changes occur before the onset of signs. A central review of magnetic resonance imaging scans of registry patients is ongoing.

After 5 years and >1,000,000 babies screened, the incidence of Krabbe disease in New York State is 1/250,000. Only four babies have been identified with early infantile Krabbe disease to date. Eighty percent of babies identified with low galactocerebrosidase activity and two mutations are clinically unaffected at this time. If these children eventually develop clinical evidence of disease, then presumably many children with Krabbe disease in the United States and elsewhere are being misdiagnosed with other white matter diseases. Although the registry has not yet identified predictors of phenotype, data on the natural history of later onset phenotypes will constitute a valuable resource to clinicians and researchers in the field.

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