

Phenotypic Variability of Krabbe Disease Across the Lifespan

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ABSTRACT: Krabbe disease (galactocerebrosidase deficiency) is an inherited leukodystrophy that results in severe neurological defects due to altered myelination. Classically, disease onset is within the first year of life. Juvenile and adult-onset cases may have less classic presentations, making diagnosis difficult and often delayed. Here, we review the literature to demonstrate the heterogeneity of presenting symptoms across all age groups. We also discuss diagnostic approach, emphasizing variation in biochemical, functional, and genetic results among Krabbe phenotypes. Better understanding of the various Krabbe disease phenotypes is critical to facilitate timely diagnosis and appropriate treatment of this clinically heterogeneous disorder.

RÉSUMÉ: Variabilité phénotypique dans la maladie de Krabbe au cours de la vie du patient. La maladie de Krabbe (déficit en galactocérébrosidase) est une leukodystrophie héréditaire qui donne lieu à des déficits neurologiques sévères dus à un trouble de la myélinisation. Chez les cas dont la présentation est classique, la maladie débute au cours de la première année de vie. Si la maladie commence chez un adolescent ou un adulte, le mode de présentation peut-être moins classique, ce qui rend le diagnostic difficile et souvent tardif. Nous analysons les articles traitant du sujet pour démontrer l'hétérogénéité des symptômes au moment de la première consultation et ceci dans tous les groupes d'âge. Nous discutons également de l'approche diagnostique en mettant l'accent sur la variation des résultats biochimiques, fonctionnels et génétiques des différents phénotypes dans la maladie de Krabbe. Une meilleure compréhension des différents phénotypes est cruciale pour faciliter un diagnostic précoce et un traitement approprié de cette maladie dont le mode de présentation clinique est hétérogène.

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Epidemiology

The incidence of Krabbe disease (OMIM # 245200) is estimated to be one case for every 100,000 members of the population in the United States and Europe¹. While there are a growing number of reported cases in adolescents and adults, population rates according to age of onset are not available. It affects the sexes equally and the carrier frequency in those with no family history is about one in 150¹. There may be an increased incidence in certain Israeli populations², where estimates of carrier prevalence are one in six¹.

Pathophysiology

Krabbe disease (galactocerebrosidase deficiency, galactosylceramidase deficiency, globoid cell leukodystrophy) is an autosomal recessive neurological disorder. Mutations in the galactosylceramidase gene (GALC; galactocerebrosidase) result in the phenotype of Krabbe disease by means of abnormal accumulation of galactolipids, such as galactosylceramide and psychosine, predominantly in cells that make myelin (oligodendrocytes)³. Macrophages containing undigested galactosylceramide can be observed as the pathognomonic globoid cells of Krabbe disease⁴. Pathologically, this metabolic disruption causes significantly decreased myelin production and demyelination due to depletion of oligodendroglia^{5,6}.

Histopathological correlation with magnetic resonance imaging (MRI) white matter abnormalities reveals that absence

of myelin is associated with areas of T2 hyperintensity, whereas perivascular accumulation of globoid cells can result in subtle, perivascularly oriented stripes of T2 hypointensity⁷.

Phenotypic Variability

The most recognized clinical presentation of Krabbe disease involves infantile onset of symptoms with rapid neurologic deterioration and progression to death before two years of age. However, there have been increasing reports of this disease presenting later in life, with substantial variability in presenting symptomatology and natural history (see Table 1 for summary). These phenotypes are less well characterized, leading to delays in diagnosis and treatment. The Krabbe patient population may be classified by age of onset into four different phenotypes:

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Table 1: Relative prevalence of presenting symptoms in Krabbe disease phenotypes

	Krabbe Disease Phenotypes			
	Early Infantile 0 - 6 months	Late Infantile 6 months – 3 years	Juvenile 3 years - 8 years	Adult > 8 years
Presenting Symptoms				
Irritability	+++	++	-	-
Hyperpyrexia	+++	-	-	-
Loss of motor ability	+++	+++	++	++
Spasticity	+++	+++	+++	+++
Ataxia	-	+++	+++	+++
Visual dysfunction	+	+++	+++	+
Seizures	++	+	-	-
Cognitive deterioration	+++	+++	++	+

(-) = uncommon (+) = possible (++) = likely (+++) = highly likely

early-infantile (0 months - 6 months); late-infantile (6 months – 3 years); juvenile (3 years – 8 years); adult (8+ years)^{1,8-10}.

Early-Infantile Phenotype

Presenting Symptoms

The early-infantile phenotype, which constitutes 85-95% of Krabbe disease,¹ demonstrates a clear sequence of progression. Children are initially developmentally normal but developmental delays typically appear before the age of six months¹¹.

Stage one involves non-specific generalized symptoms including irritability, failure to thrive, vomiting, and hyperpyrexia. Subtle neurologic findings like shoulder girdle hypotonia and intermittent thumb clasp may be found¹². Patients may show exaggerated startle responses due to auditory, tactile and visual hyperesthesia (increased sensitivity to sensory stimuli). Overall, the most common presenting symptoms described by families of early-infantile Krabbe disease are crying and irritability (90%), stiffness (27%), poor feeding (27%), poor head control (25%), seizures (23%), fistings (18%), and loss of smiling (15%)¹³. These symptoms are generally attributable to central nervous system dysfunction. Although peripheral neuropathy can be demonstrated electrophysiologically at this stage¹⁴, its manifestations (including weakness and hyporeflexia), are usually overshadowed by the more clinically apparent central nervous system dysfunction. Rarely, patients may present with profound muscular weakness, hypotonia, and areflexia indicative of isolated peripheral nerve dysfunction¹⁵.

Stage two is characterized by rapid clinical deterioration. Seizures are more common at this stage. Optic atrophy and slow pupillary light reflexes can occur. Other neurological findings include hypertonic flexion of the arms and extension of the legs, myoclonic jerks, hyper- or hyporeflexia, psychomotor deterioration, and point opisthotonus (spasm of back muscles causing trunk to arch forward)^{11,16}.

Stage three is often referred to as the “burnt-out stage”. Symptoms include blindness, deafness, decerebrate posturing, and loss of voluntary movement. The motor disability is attributable to a combination of pyramidal tract dysfunction and progressive peripheral neuropathy. Patients are unable to feed orally and typically require tube feeds¹¹. End-stage morbidities

include infection, respiratory failure, and feeding difficulties leading to emaciation^{1,16-18}.

Rate of Progression and Prognosis

Median survival rates range from 8 to 36 months-of-age for early-infantile cases^{1,12,13}. Generally, prognosis is much worse for early-infantile compared to late-infantile and juvenile subtypes¹³.

Late-Onset Infantile Phenotype

Presenting Symptoms

The late-infantile phenotype involves patients with onset of symptoms between six months and three to four years of age^{8,16}. Early development is typically normal and children initially meet their milestones. Initial symptoms are difficulty walking, frequent falling, and clumsiness^{10,19,20}. Neurologic exam shows common presenting signs of spastic paraparesis (54%), cerebellar ataxia (12.5%), isolated vision failure (12.5%), and isolated hemiplegia (8%)²⁰. These presenting complaints, which are predominantly in the gross motor domain, distinguish this phenotype from the early-infantile subgroup, which features irritability and lethargy as chief presenting complaints¹⁹. Some patients do present with seizures, although this is uncommon²⁰.

Advanced Symptoms

The natural history of the late-infantile phenotype is progressive deterioration of motor function, mainly secondary to pyramidal tract dysfunction. Patients typically regress to crawling and some lose the ability to sit unsupported. Progressive motor dysfunction leads to quadriplegia. Peripheral neuropathy may be present, and contributes to motor disability¹⁹. Visual changes range from intact vision to complete blindness. Some patients develop seizures¹⁰. Many patients become non-verbal, but some maintain communication abilities through the use of computers and other aids¹⁰. Feeding difficulties and emaciation may also occur²¹.

Rate of Progression and Prognosis

Life expectancy is variable in this phenotype, ranging from 2-14 years after initial presentation (average is seven years)^{19,20,22}.

In comparison to the early-infantile groups, patients in the late-infantile subtype have greater life expectancy, but with the burden of advanced disease¹³.

Juvenile Onset Phenotype

Age Range

Juvenile onset Krabbe disease, consisting of patients with symptom onset at three to eight years of age, has often been combined with the late-infantile form due to the relative rarity of these phenotypes. However, there is some evidence to suggest that this phenotype may have a different clinical course from earlier onset cases, with ramifications pertaining to prognosis and therapy²³.

Presenting Symptoms

Visual dysfunction is a common initial presenting symptom in the juvenile-onset subtype^{24,25}. Motor dysfunction, such as hemiparesis or ataxia, is still prominent^{19,22}. Pes cavus, or high arched feet, is another symptom that has been reported to appear prior to diagnosis, and is indicative of peripheral neuropathy¹⁰.

There is wide phenotypic variability in this subgroup, suggesting that environmental factors interact significantly with genetic factors. This phenomenon is particularly evident in cases of siblings with juvenile onset Krabbe disease, who have similarly decreased GALC activity, but nevertheless exhibit dramatically different clinical courses^{24,26}. For example, Phelps *et al*²⁴ report the case of a young girl who presented with visual impairment at five years-of-age, and progressed to being wheelchair bound with dystonic movements and incomprehensible speech by 12 years-of-age. Assessment of her 16-year-old brother revealed history of mild walking difficulties in early childhood and non-progressive reduced visual acuity with normal intellect. Unfortunately, genetic mutation analysis was not reported in these two cases.

Advanced Symptoms

Visual deterioration to light perception only or complete blindness is common. Patients also typically develop spasticity, quadriplegia, and cerebellar ataxia; many patients become wheelchair-bound¹⁰. The course of intellectual decline is highly variable and ranges from intact intellectual ability to severe cognitive dysfunction (²⁴, Case 1; ¹⁰ Cases 12, 13). Interestingly, the pace of decline in childhood may stabilize in adulthood²⁵. Some patients retain verbal skills²⁵, while others develop dysarthria (²⁴, Case 3) or complete verbal loss (¹⁰, Case 5; ²⁴, Case 1). End-stage disease may have swallowing difficulties leading to aspiration risk (¹⁰, Case 5), although some patients remain cognitively high-functioning²⁵.

Rate of Progression and Prognosis

Most juvenile cases show initial rapid deterioration in the first two to six months after onset of symptoms, followed by more gradual progression over years. Survival has been reported up to 26 years (¹⁹, Case 14).

Adult Onset Phenotype

Age Range

The definition of adult onset Krabbe disease has posed interesting challenges. It has been suggested that this subgroup should further be split into two categories; those who are a) clinically normal until onset of symptoms at age 20 years, and b) those who may have presented earlier in life, but whose symptoms were so subtle that biochemical testing was not warranted until later in life¹. Determination of whether patients with purported adult-onset Krabbe disease did have mild symptoms in childhood is difficult, as these patients may not have been previously formally assessed. As such, accurate generalized conclusions about this Krabbe disease phenotype are limited.

Like the juvenile subtype, there can be wide phenotypic variation within families. Verdru *et al*²⁷ report a family with an index patient who presented with weakness at 19 years-of-age. Investigation into family history revealed one brother who developed clumsiness at 14 months, deteriorated to spasticity and blindness, and died at four years-of-age. As such, family members with presumably the same Krabbe genotype can manifest with either the late-infantile and adult phenotype.

Presenting Symptoms

Presenting symptoms include limb weakness (upper extremity may be more common than lower extremity), clumsiness, recurrent falls, and worsening gait^{9,28}. Spasticity becomes prominent in the vast majority of patients, whereas manifestations of peripheral neuropathy are subtle (pes cavus or sensory abnormalities; significant neuropathic pain has not been reported)²⁹. Some patients are asymptomatic and identified through family screening.

Advanced Symptoms

Much like the presentation of these patients, clinical outcomes in this subtype are varied. Asymptomatic patients assessed due to a sibling's initial diagnosis tended to remain stable after several years follow-up (²⁴, Case 4; ²⁶, Case 2), but siblings who presented with clinical symptoms tend to decline in a similar pattern (³⁰ Cases 2 and 3). Outcomes of adult patients who present with motor dysfunction tend to follow the same course as earlier onset subtypes, developing progressive weakness and spasticity that can culminate in quadriparesis. Verbal and cognitive decline can also become severe (²⁴, Case 2), although in some cases cognition is preserved (⁹, Case 2;³¹). Genitourinary symptoms reported include urinary incontinence and erectile dysfunction⁹.

Rate of Progression and Prognosis

The majority of patients progressed in terms of physical, and sometimes cognitive, dysfunction, but were alive up to 10-15 years after the initial onset of symptoms. In this adult-onset subgroup there have been attempts to perform bone marrow transplantation. Whereas two twin sisters subsequently succumbed to complications of graft vs. host disease¹⁰, there is one report of a 24-year-old woman who initially declined very rapidly, but was stabilized by bone marrow transplantation³².

Table 2: Differential diagnoses of Krabbe disease phenotypes based on presenting symptoms

Early Infantile 0 - 6 months	Late Infantile 6 months - 3 years	Juvenile 3 years - 8 years	Adult > 8 years
Leukodystrophies			
Metachromatic leukodystrophy Peroxisomal biogenesis defects GM1 gangliosidosis GM2 gangliosidosis Canavan disease Alexander disease Pelizaeus-Merzbacher disease	Metachromatic leukodystrophy Adrenoleukodystrophy GM2 gangliosidosis (juvenile) Alexander disease Pelizaeus-Merzbacher disease	Metachromatic leukodystrophy Adrenoleukodystrophy GM2 gangliosidosis (juvenile)	Metachromatic leukodystrophy Adrenomyeloneuropathy GM2 gangliosidosis (adult)
Storage Disorders			
Mucopolysaccharidoses (type I, III) Gaucher disease Niemann Pick disease type A	Mucopolysaccharidoses (type II, VII) Gaucher disease Niemann Pick disease type C	Gaucher disease Sialodosis type II Niemann Pick disease type C	Niemann Pick disease type C Cerebrotendinous xanthomatosis
Amino Acidopathies			
Maple syrup urine disease Homocystinuria Phenylketonuria			
Mitochondrial Disorders			
MELAS Alpers disease Leigh disease Menkes syndrome	MELAS Alpers disease (late-onset) Leigh disease MERRF	MELAS MERRF Leigh disease (juvenile)	MELAS MERRF
Other Gray Matter Disorders			
Infantile ceroid lipofuscinosis Lesch-Nyhan disease Rett syndrome	Late-infantile ceroid lipofuscinosis	Juvenile ceroid lipofuscinosis Hereditary spastic paraparesis	Adult ceroid lipofuscinosis Motor neuron disease Hereditary spastic paraparesis
Other Myelin Disorders			
		Multiple sclerosis	Multiple sclerosis Charcot Marie Tooth (types 1, 2)
Infectious Disease			
AIDS encephalopathy	AIDS encephalopathy Congenital syphilis Subacute sclerosing panencephalitis	Subacute sclerosing panencephalitis	Syphilis

MERRF = Myoclonic Epilepsy with Ragged Red Fibers; MELAS = Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes.

Two brothers with onset at ages 41 and 45 years who were not transplanted died due to complications of respiratory failure³⁰.

Diagnosis

Clinical diagnosis of Krabbe disease is challenging. Patients with early-infantile onset typically present with nonspecific symptoms, leading to delays in diagnosis up to three years after the onset of symptoms¹⁷. Of early-infantile cases with initial incorrect diagnoses (n=28), family questionnaires have revealed that the most common misdiagnoses for Krabbe disease include cerebral palsy¹⁶, colic⁶, combined cerebral palsy and colic^{2,13}. Patients with later onset disease have symptoms and signs that often overlap with other metabolic, toxic and genetic disorders. Common misdiagnoses in the adult-onset population include Charcot Marie Tooth syndrome, multiple sclerosis, mild cerebral palsy, and amyotrophic lateral sclerosis (see Table 2 for summary of key (not inclusive) differential diagnoses for Krabbe disease phenotypes). Although the presentation of individual patients may eliminate many of the diagnoses listed in Table 2 from consideration, the many documented atypical presentations of various neurodegenerative disorders (including Krabbe disease), generally merit an initially broad differential diagnosis. As a result, clinical suspicion of Krabbe disease must be supplemented with diagnostic investigations (see Table 3 for features differentiating Krabbe disease from key differential

diagnoses). Once a white matter disorder is identified on neuroimaging, specific MRI characteristics have proven critical to narrowing the differential diagnosis³³. However, diagnostic results can also be variable between the different Krabbe phenotypes, and some results carry potential prognostic significance (see Table 4 for summary of pertinent investigations and results in Krabbe phenotypes)^{1,3,9,14,19,28,34-44}.

Screening biochemistry

Routine bloodwork in Krabbe disease is typically normal. Cerebrospinal fluid (CSF) protein can be elevated in all phenotypes, but does not correlate with disease progression¹². Ninety-two percent of early-infantile onset patients in one report had elevated CSF protein at initial neurodiagnostic evaluation (>25mg/dL above normative values for age)⁴⁵ and specific values range from 65-400mg/dL⁴⁶. In contrast, approximately 50% of juvenile-onset and adult-onset cases reveal elevated CSF, with specific values ranging from 13-77mg/dL in one study²⁹.

Functional Studies

Electromyography (EMG) and Nerve Conduction Studies (NCS)

Electromyography studies in Krabbe patients typically reveal a pattern consistent with peripheral nerve damage³. Most early-

Table 3: Features differentiating Krabbe disease from key differential diagnoses

	Possible Unique Clinical Features	CSF Abnormalities	Ophthalmologic Abnormalities	Nerve Conduction Studies	Neuroimaging Findings	Biochemical Abnormality	Genetic Testing
Krabbe disease	Irritability (infantile only)	Increased protein	Optic atrophy	Demyelinating pattern	++T2 hyperintensity (parieto-occipital predominance)	Galactocerebrosidase deficiency	GALC ¹
Metachromatic leukodystrophy	None	Increased protein	Optic atrophy	Demyelinating pattern	++T2 hyperintensity (periventricular predominance)	Arylsulfatase A deficiency	ARSA ²
GM2 gangliosidosis	Myoclonus Macrocephaly	Normal	Cherry red spot	Normal	Hypomyelination	Hexosaminidase A deficiency	HEXA ³
Niemann Pick C	Organomegaly Vertical supranuclear gaze palsy	Possible reduced hypocretin	Possible cherry red spot	Typically normal	Cerebellar vermis atrophy Possible T2 hyperintensity (periventricular predominance)	Abnormality of intracellular cholesterol homeostasis	NPC1, NPC2 ⁴
Mitochondrial disease	Diabetes Cardiomyopathy	Increased lactate	Retinitis pigmentosa Optic atrophy	Axonal pattern	Variable Possible cerebellar or cerebellar atrophy Possible ++T2 hyperintensity of basal ganglia or white matter	Increased serum lactate	Various
Hereditary spastic paraparesis	Hypertonic bladder	Normal	Typically normal	Typically normal	Possible corpus callosum or cerebral atrophy	Normal	Various (SPG ⁵)

¹galactocerebrosidase; ²arylsulfatase A; ³beta-hexosaminidase A; ⁴Niemann-Pick C; ⁵spastic gait loci. MERRF = Myoclonic Epilepsy with Ragged Red Fibers; MELAS = Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes.

infantile onset cases have abnormal NCS (23/24 patients; sensitivity >95%) with disease severity correlating with degree of demyelination¹⁴. The combination of pyramidal tract dysfunction (spasticity, hyperreflexia) with electrophysiological evidence of demyelinating peripheral neuropathy is classical for Krabbe disease and substantially narrows the differential diagnosis of a neurodegenerative disorder. Clinical evidence of peripheral neuropathy is often only apparent late in disease course when NCS are severely abnormal (but see ⁴⁷ for rare exceptions). Importantly, NCS can be normal in later-onset patients, so the absence of abnormalities should not be used to exclude the disease¹.

Electroencephalography (EEG)

Krabbe patients show a non-specific slowing of EEG background activity, with spikes generally absent³. While EEG may be normal at initial stages of the disease, progression of disease involves slowing and disorganization of background activity that may be asymmetric¹. A greater percentage of early-infantile onset patients (65%) may have abnormal EEGs compared to late onset cases (33%)³⁹. Correspondingly, seizures are more common in early-infantile onset patients^{48,49}. Seizure semiology has not been well characterized, but myoclonic seizures have been reported⁴⁸. Seizure activity is likely reflective of as yet poorly understood cortical involvement in Krabbe disease⁶. However, it is difficult to eliminate a contribution from co-existent disease processes in some cases (for example, toxicity post-hematopoietic stem cell transplant, trauma, or obstructive hydrocephalus)⁵⁰.

Visual Evoked Potentials (VEP) and Brain-stem auditory Evoked Potentials (BAEP)

Visual evoked potentials and brain-stem auditory evoked potentials in Krabbe disease may show nonspecific abnormalities more commonly in the earlier onset phenotypes. Brain-stem auditory evoked potentials may be one of the first diagnostic measures to become abnormal in Krabbe disease, as measured in pre-symptomatic genetically diagnosed patients⁴⁰. VEPs and BAEPs may help to monitor disease progression, as abnormalities correlate with disease burden on neuroimaging³⁹.

Computed Tomography (CT)

Brain CT can initially be normal or display hyperdensity in the posterior limb of the internal capsule, thalamus, and corona radiata^{12,51}. Over time, diffuse cerebral atrophy evolves, involving both gray and white matter¹. Diffuse hypodensity of white matter may also be present, particularly in the parieto-occipital regions. Interestingly, some evidence suggests that CT may show hyperdensities despite normal MRI¹.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging shows consistent changes of demyelination in periventricular white matter (prominent T2 hyperintensity and T1 hypointensity) with relative sparing of subcortical U-fibres⁴³. Stripes of perivascularly oriented T2 hypointensities within abnormal white matter can be observed, a feature which is shared with metachromatic leukodystrophy and GM1 gangliosidosis⁷. Involvement of the pyramidal tract and posterior corpus callosum is characteristic for all phenotypes, but “early-onset” patients tend to have consistent abnormalities in the cerebellum and brainstem that may predate supratentorial

Table 4: Comparison of diagnostic results in Krabbe disease phenotypes

	Krabbe Disease Phenotypes				Reference(s)
	Early Infantile 0 - 6 months	Late Infantile 6 months – 3 years	Juvenile 3 years - 8 years	Adult > 8 years	
Diagnostic Results					
CSF protein	Increased in > 90%	Increased in > 90%	Increased in 40-70%	Increased in 50-75%	(29, 34)
GALC enzyme activity (% of average control values)	0-5%*	< 15%	<15%	<15%	(9, 12, 19, 35)
Common GALC mutations	Large deletions 1538C>T 1652A>C 1954A>C	G270D G41S	G270D G41S	G270D G41S	(36, 37, 38)
Abnormal NCS - mixed sensorimotor demyelinating peripheral neuropathy	+++	+	+	+	Early-infantile: (14) Late-onset: (1)
Abnormal VEP/BAEPs – non specific changes, correlate with disease progression	+++	++	+	+	(39, 40)
Abnormal EEG – non-specific slowing, absent spikes,	+++	++	+	+	(1, 39)
Magnetic resonance spectroscopy (MRS) - ↑choline ↓N-acetylaspartate, and ↓glutamate	+++	++	-	-	(41, 42, 43)
Common localization of neuroimaging abnormalities	- cerebellum - pyramidal tract - parieto-occipital white matter	- pyramidal tract - corpus callosum - parieto-occipital white matter	- pyramidal tract - corpus callosum - parieto-occipital white matter	- normal - pyramidal tract - parieto-occipital white matter	(3, 9, 28, 41, 43, 44)

(-) = uncommon (+) = possible (++) = likely (+++) = highly likely. *activity up to 10% has been uncommonly reported³⁵.

changes⁴⁴. Gadolinium enhancement of cranial nerve roots and the cauda equina has also been noted in these “early-onset” patients only⁵². Another rarely reported “early-onset” feature is optic nerve enlargement, which may be due to globoid cell accumulation via poorly understood mechanisms⁵³.

In contrast, MRI of adult-onset patients often reveals the first changes within proximal corticospinal tracts⁴¹, though imaging can be normal^{19,28}. Notably, MRI can be normal or unchanged despite deteriorating clinical status regardless of phenotype⁵⁴ so MRI cannot be used to exclude the diagnosis or definitively assess clinical progression^{9,28}. A detailed description of the wide range of MRI findings possible in the various phenotypic presentations of Krabbe disease is beyond the scope of this review, but the reader is referred to several recent references included here^{41,55,56}.

Magnetic resonance spectroscopy (MRS)

Magnetic resonance spectroscopy findings in Krabbe disease are variable, but include increased choline, decreased N-acetylaspartate and decreased glutamate⁴¹⁻⁴³. These abnormalities may initially be localized to areas of abnormal signal on MRI, but can be seen more diffusely with disease progression^{41,42}.

GALC Enzyme Activity

Galactocerebrosidase enzyme activity is the preferred diagnostic test for patients suspected of having Krabbe disease, regardless of age of onset. There are some reports of lower levels of GALC enzyme activity in normal unaffected adults compared to similarly unaffected neonates⁵⁷, suggesting that GALC

activity may vary over lifespan although this finding is not consistent⁵⁸. While enzyme activity 0-5% of reference values is diagnostic, levels have not been consistently linked to disease severity^{1,16,36}. Enzyme activity is typically non-detectable in early-infantile subtypes³⁵, while varying levels of residual activity have been reported in the other age groups (Table 3). Overall, further investigation is required to assess how GALC activity levels relate to various phenotypes of Krabbe disease and what quantitative levels should be used for diagnosis across the population.

Genetic Analysis

In addition to enzymatic analyses, analysis of mutations in the galactocerebrosidase (GALC) gene testing is useful. Over 110 different mutations in this gene have been described⁵⁹, and some specific mutations seem to correlate loosely with age of disease onset and prognosis. Early-infantile forms in the European population are typically characterized by homozygosity for a 30kb deletion that begins in intron 10 (IVS10del30kb; OMIM 606890.0002)³⁶ or are compound heterozygotes for this deletion and another severe deleterious allele¹⁶. The overall allele frequency for this 30kb deletion is estimated at 40-50%³⁶. In the Japanese population, early infantile forms are often typified by a different deletion³⁷.

Later onset phenotypes are more commonly characterized by G286D (OMIM 606890.0008) or G41S (OMIM 606890.0010) mutations, regardless of the mutation contained in the second allele^{36,37,59,60}. In fact, the G41S (OMIM 606890.0010) mutation has been reported in up to 50% late-onset cases in some populations³⁸. Genetic mutation analysis may also inform

phenotype-specific prognosis, as the G41S (OMIM 606890.0010) mutation is associated with longer survival in late-onset phenotypes only¹⁹. Genetic testing is used for confirmation of diagnosis, carrier testing (as GALC enzyme activity levels are unreliable), prenatal diagnosis, and genetic counselling¹.

Management

Prior to the late 1990s, clinical treatment for Krabbe disease was mainly supportive. In patients of all phenotypes, key symptomatic treatments target spasticity, feeding difficulties and seizures, with the use of physical and occupational therapy to maximize functional outcome. Infantile-onset patients who display irritability (whether secondary to central or peripheral nervous system dysfunction) are treated to maximally reduce gastroesophageal reflux. Morphine has also been successfully used to control irritability⁵³.

With the advent of hematopoietic stem cell transplantation (HSCT) as a potentially viable therapy, the importance of effectively diagnosing these patients and providing appropriate therapeutic and prognostic counselling has become more apparent. Most HSCT has taken place among pre-symptomatic infantile cases^{23,32,61}, and while no patients have died of progressive disease, all have abnormalities of gross motor control and expressive language. These patients also characteristically display poor growth and microcephaly⁴⁹. Transplantation of juvenile- and adult-onset patients has been less frequent, although case reports suggest that these patients may derive benefit from the procedure as well^{32,62}. Hematopoietic stem cell transplantation involves significant risk of morbidity and mortality, and does not entirely prevent disease progression.

CONCLUSION AND FUTURE DIRECTIONS

Krabbe disease is a source of significant morbidity and mortality to those affected. Newborn screening for this disorder is being performed at select centres, allowing for improved understanding of its epidemiology and early identification of at risk patients. Importantly, early data derived from this screening suggests that the proportion of late-onset Krabbe disease has likely been under-estimated³⁴. In parallel to these diagnostic efforts, the search for more effective and less invasive therapeutics for Krabbe disease continues. Although currently in pre-clinical stages, therapies involving pharmacologic chaperones to increase activity of mutant GALC enzyme⁶³, viral vectors for gene therapy⁶⁴ and neural progenitor cells injected into the CNS⁶⁵ show promise. As Krabbe disease transitions to a potentially treatable disorder, clinicians will require understanding of its phenotypic variability to avoid misdiagnosis and allow for timely institution of therapy.

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