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Late-Onset Krabbe Disease: Case Report of Two Patients in a Chinese Family and Literature Review

Yujun Sun[1] | Jiayuan Zheng[1] | Lei He[2] | Xiaojuan Li[3] | Wenzhou Liu[1] | Jionglin Wu[1] | Jiajie Li[1] | Taolue Zhou[1] | Gang Zeng[1] | Weidong Song[1] | Yanbo Chen[1]

[1]Department of Orthopeadic Surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, People's Republic of China | [2]Department of Neurology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, People's Republic of China | [3]Cellular and Molecular Diagnostics Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, People's Republic of China

Correspondence: Gang Zeng (zengg5@mail.sysu.edu.cn) | Weidong Song (songwd@mail.sysu.edu.cn) | Yanbo Chen (chenyb75@mail.sysu.edu.cn)

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Keywords: case report | GALC gene | Globoid cell leukodystrophy | Krabbe disease | late-onset

ABSTRACT

Background: Krabbe disease (KD; globoid cell leucodystrophy) is a rare autosomal recessive lipid storage disorder that affects the white matter of the peripheral and central nervous. Late-onset KD is less frequently diagnosed and often presents with milder symptoms, making accurate diagnosis challenging, especially when distinguishing it from peripheral neuropathy. In this report, we present two cases of late-onset KD in a Chinese family. The first case involves a 25-year-old female who sought treatment due to long-standing spastic gait and deformities in her lower limbs. A muscle biopsy revealed muscle atrophy, and electromyography indicated neurogenic damage. Her 27-year-old sister (Case 2) exhibited similar lower limb weakness, along with more severe central and peripheral neurological symptoms.

Methods: The patients' peripheral blood was retained for galactocerebrosidase (GALC) enzyme activity assaying and whole exome gene sequencing.

Results: GALC enzyme activity assaying showed decreased GALC activity and gene sequencing revealed homozygous mutation of p.L634S (c.1901T>C) in the two cases.

Conclusion: This study broadens the scope for considering of KD in the diagnosis of patients presenting with muscle weakness and deformities in the lower limbs.

1 | Background

Krabbe disease (KD), or globoid cell leukodystrophy, is a rare disease of autosomal recessive lysosome storage disorder (Compston 2013). The incidence of KD disease is estimated at 1 1/100, 000, with 90% of patients classified as early infantile phenotypes (Duffner et al. 2011, 2012). Symptoms of central and peripheral nervous system impairment resulting from the demyelination of nerve fibers are the main manifestations. In 1993, it was found that the mutation of the galactocerebrosidase (GALC) gene (OMIM:245200) located on chromosome 14q24.3-q32.1 was the root cause of its pathological changes (Oehlmann et al. 1993). These genetic mutations lead

Abbreviations: CMT, Charcot–Marie–Tooth; CSF, cerebrospinal fluid; GALC, galactocerebrosidase; HGMD, human gene mutation database; HSP, hereditary spastic paraplegia; iPSC, induced pluripotent stem cell; KD, Krabbe disease; WES, whole exome sequencing.

Yujun Sun, Jiayuan Zheng, Lei He, Xiaojuan Li have contributed equally to this work.

to the deficiency of galactoceramidase, which triggers the progressive accumulation of the neurotoxic galactosylsphingosine in macrophages (globoid cells) as well as neural cells. This accumulation causes demyelination and neurodegeneration, primarily affecting the white matter of the central nervous system (Won, Singh, and Singh 2016; Suzuki 2003; Sakai 2009).

The phenotypes of KD show age-related differences, which can be categorized into early infantile (age 0–6 months), late infantile (age 7–36 months), juvenile/adolescent (age 37–180 months), and adult onset (> 180 months) (Komatsuzaki et al. 2019). Typical patients with early infantile KD are often observed with rapidly progressive neurological deterioration, which often leads to mortality before the age of two. The late-onset form (late infantile, juvenile/adolescent, and adult onset) usually has less severe symptoms and develops much more slowly than the early onset. Symptoms of late-onset KD include myasthenia and atrophy in the distal limbs, spasticity in the lower limbs with gait disorder, as well as frequent falls. High arches are the most common deformity (Komatsuzaki et al. 2019; Debs et al. 2013; Liao, Gelinas, and Sirrs 2014). It can be confused with motor neuron disease and peripheral neuropathy in disguised due to similar performance (Henderson, MacMillan, and Bradfield 2003; Bajaj et al. 2002). At present, GALC enzyme activity test and identification of GALC mutation are the most effective methods to diagnose KD (Hwang et al. 2024).

In this paper, we describe the clinical details of a Chinese family with two late-onset KD patients and summarize previous case reports of late-onset KD with the same mutation site, presenting their clinical characteristics. The proband was initially diagnosed with Charcot–Marie–Tooth (CMT) due to muscle weakness in both distal lower extremities and neurogenic lesion of left anterior tibial muscle as indicated by electromyography. Further investigation revealed that her siblings had similar KD symptoms, and her parents were from a consanguineous family. Finally, we ascertained this Chinese family with KD disease caused by GALC missense mutation (c.1901T>C (p.L634S)) through the GALC enzyme activity test and gene detection.

2 | Case Presentation

2.1 | Ethical Compliance

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital (Approval number: SYSKY-2024-886-01). Written informed consent was obtained from all participants before publication.

2.2 | Clinical Symptoms of Case 1

A 25-year-old female patient (Case 1) and her 27-year-old sister (Case 2) were admitted to our hospital for “gait abnormalities”. Eight years ago, the patient (Case 1) began experiencing an unsteady gait and foot fatigue after prolonged walking. Over the past 2 years, her symptoms have worsened, prompting her to visit our hospital. Prior to this, she had never received any medical or surgical treatment. Physical examination revealed a slightly thinner right gastrocnemius muscle compared to the left, flexion deformities of the distal interphalangeal joints in both feet, and elevated arches in both feet (Figure 1A). Muscle strength testing showed Grade 4/5 muscle strength in left foot eversion and Grade 3/5 in the right; dorsiflexion strength in the toes of both feet was Grade 4/5; muscle tone in both lower limbs was increased, and bilateral pathological signs were positive. Bilateral ankle x-rays (standing position) revealed: (1) elevated right foot arch and (2) flexion deformities of the distal interphalangeal joints in both feet (Figure 1B). Brain MRI revealed signs of demyelination (Figure 1C). Electromyography (EMG) showed neurogenic damage in the tibialis anterior muscle. A muscle biopsy of the right lower leg showed clustered muscle atrophy, nuclear chains, and angulated fibers (Figure 2), consistent with neurogenic atrophy, raising the possibility of Charcot–Marie–Tooth disease (CMT). Electron microscopy indicated mild focal myofibril tearing and dissolution, with a slight increase in lipid droplets between muscle cells and myofibrils. Based on these findings, CMT was strongly suspected; however, the brain MRI results were inconsistent with this diagnosis.

2.3 | Clinical Symptoms of Case 2

Her sister (Case 2) had a longer disease course and suffered more severe symptoms. Over 10 years ago, she began experiencing lower limb weakness and pain, predominantly in the right leg, with a dragging gait. A brain MRI revealed symmetric strip-like abnormal signals in the bilateral thalamus and corona radiata, and enlargement of the bilateral lateral ventricles, third ventricle, suprasellar cistern, ambient cistern, pre-pontine cistern, and bilateral cerebellopontine angle cisterns (Figure 3), suggestive of “demyelination disease.” Additionally, she experienced severe headaches, and during intense episodes, she had experienced confusion and urinary and fecal incontinence, with cognitive decline following recovery. Physical examination revealed cognitive impairment (assessed with the Montreal Cognitive Assessment scale) (Nasreddine et al. 2005), scissoring gait, increased muscle tone, decreased muscle strength, and bilateral positive pathological signs. Notably, she did not have any previous surgical history since the onset of these symptoms.

3 | Family History

The patient also had a 22-year-old younger brother, who exhibited no significant abnormalities in cognition, gait, muscle strength, or tone. Another brother passed away at the age of 2 months. Both of her parents exhibited no obvious symptoms. The results of muscle strength and tone examinations for the cases and their family are summarized in Table 1. A detailed inquiry into the family's reproductive history revealed that the patient's maternal grandparents were consanguineous.

4 | Diagnostic Testing

Based on these findings, we performed GALC enzyme activity assaying and whole exome gene sequencing on the patient and her family. The patient's GALC activity was 11.63 nmol/17 h/mg (reference range: > 12.70 nmol/17 h/mg, normal values: 29.46–34.40 nmol/17 h/mg). Her sister's activity level was 11.65, her brother's was 70.44, her father's was

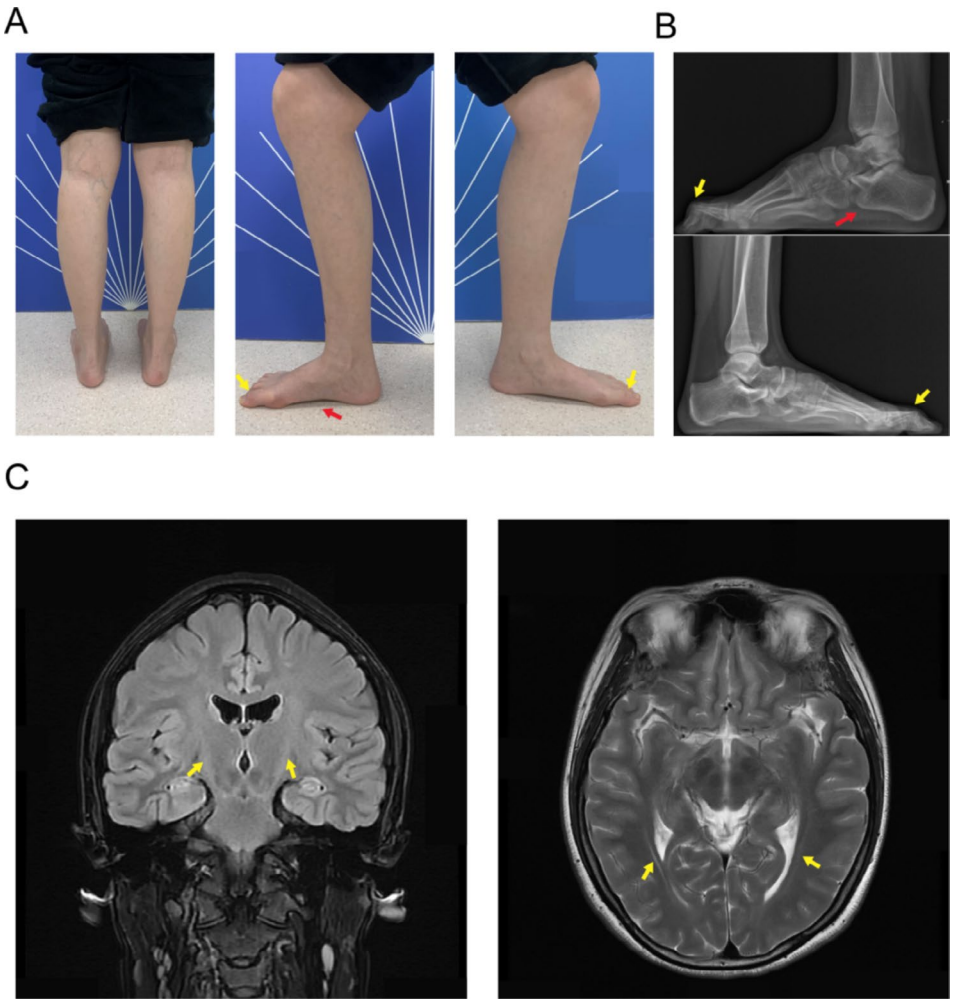

FIGURE 1 | Physical and imaging examination of the patient (Case 1). (A) Physical examination showed the right gastrocnemius muscle was slightly thinner compared to the left side. Flexion deformities in the interphalangeal joints of the distal toes (yellow arrow) in both feet, and elevated arches (red arrow) in right feet. (B) Anteroposterior and lateral x-ray images of both ankle joints (weight-bearing). The results of x-ray of ankle joints revealed elevated arches (red arrow) in right feet and flexion deformities of the distal interphalangeal joints in both feet (yellow arrow). (C) Brain MRI (T2W) revealed symmetrical strip-like abnormal signals (yellow arrow) in the corticospinal tract, suggestive of demyelinating changes. The images are shown in coronal (left) and axial (right) views.

23.61, and her mother's was 65.21. Further genetic sequencing revealed a missense mutation in the GALC gene on chromosome 14 (NM_000153.4(GALC).1901T>C (p.Leu634Ser)) (Reference genome version Human GRCH37/hg19), with the patient inheriting the homozygous mutation from her parents (who were both heterozygous carriers of this mutation). This mutation occurs in exon 16, where the 1901st nucleotide is replaced from T to C, resulting in a substitution of leucine with serine at position 634 of the protein. According to the American College of Medical Genetics and Genomics (ACMG) guideline, this variant was assessed as pathogenic (Richards et al. 2015).

The patient's sister also had the homozygous mutation, while her 22-year-old brother was a heterozygous carrier. These findings suggest that the patient and her sister should be diagnosed with KD rather than CMT. Their brother who passed away at 2 months, is suspected of infantile-onset KD. The pedigree chart and genetic testing results of the family are displayed in Figure 4.

We used PolyPhen-2 software (Adzhubei et al. 2010) to predict the pathogenicity of GALC missense variant p.Leu634Ser (Figure 5). By using HumDiv and HumVar, both results predicted the variant to be probably damaging with a score of 1.00, indicating that the 634 position of amino acid change from Leu to Ser showed a very high probability to affect GALC protein structure and function.

We performed a posterior tibial tendon transfer combined with anterior talofibular ligament repair and reinforcement on the patient (Case 1). Postoperatively, she reported a significant improvement in her symptoms during the follow-up. She has also been receiving long-term neurological medication. Meanwhile, her sister (Case 2) has been undergoing long-term treatment with neurological medications as well.

Video recordings of the abnormal gait of both the cases are included in the Data S1.

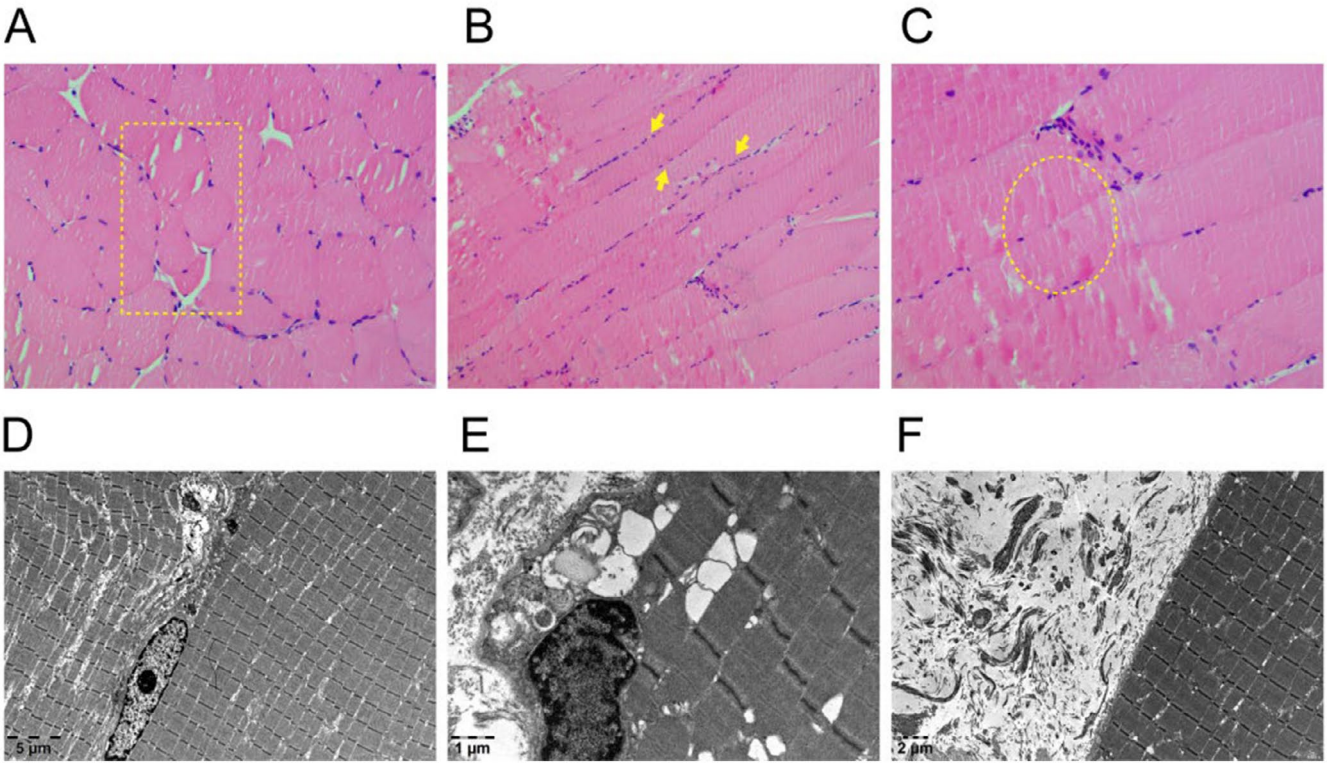

FIGURE 2 | Muscle biopsy pathology of the patient's right fibular muscle. (A–C) H&E staining. The results showed small clusters of muscle atrophy (indicated by the yellow box), with the formation of nuclear chains (yellow arrows) and angulated muscle fibers (yellow circle). There was no significant proliferation of fibrous or adipose tissue, and no marked infiltration of inflammatory cells. These findings were consistent with neurogenic muscle atrophy. Considering the clinical context, the possibility of peroneal muscular atrophy could not be ruled out. (D–F) Electron microscope images, which revealed mild focal tearing and dissolution of myofibrils, with a slight increase in lipid droplets between individual myofibrils and sub-sarcolemmal regions of some muscle cells.

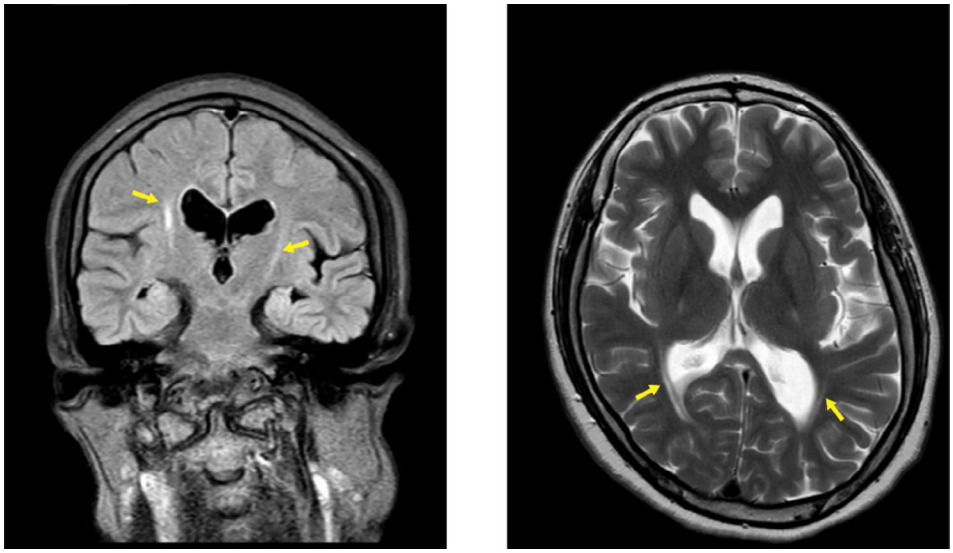

FIGURE 3 | Brain MRI (T2W) of the patient's sister (Case 2). The MRI revealed symmetrical strip-like abnormal signals (yellow arrow) in the periventricular region and corticospinal tract, suggestive of demyelinating changes. Enlargement of the bilateral lateral ventricles, third ventricle, suprasellar cistern, ambient cistern, prepontine cistern, and bilateral cerebellopontine angle cisterns was also observed. The images are shown in coronal (left) and axial (right) views.

5 | Discussion

Herein, we report two cases of late-onset KD with GALC homozygous mutations in a Chinese family. The proband initially presented to the orthopedic department with gait abnormalities and foot deformities. Mild brain radiology changes and indistinguishable clinical features from CMT obscured the diagnosis of this rare condition. Further exploration into

TABLE 1 | Orthopedic physical examination findings for the patient and her family members.

		Patient (Case 1)		Patient's sister (Case 2)		Patient's brother		Patient's father		Patient's mother	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Muscle strength	Foot dorsiflexion	5	5	3	3	5	5	5	5	5	5
	Foot plantarflexion	5	5	5	5	5	5	5	5	5	5
	Foot inversion	5	5	3	3	5	5	5	5	5	5
	Foot eversion	4	3	3	3	5	5	5	5	5	5
	Toe dorsiflexion	4	4	4	4	5	5	5	5	5	5
	Toe plantarflexion	5	5	5	5	5	5	5	5	5	5
Muscle tone		High	High	High	High	Normal	Normal	Normal	Normal	Normal	Normal
Pathological signs		+	+	+	+	−	−	−	−	−	−

Note: +, positive sign; −, negative sign.

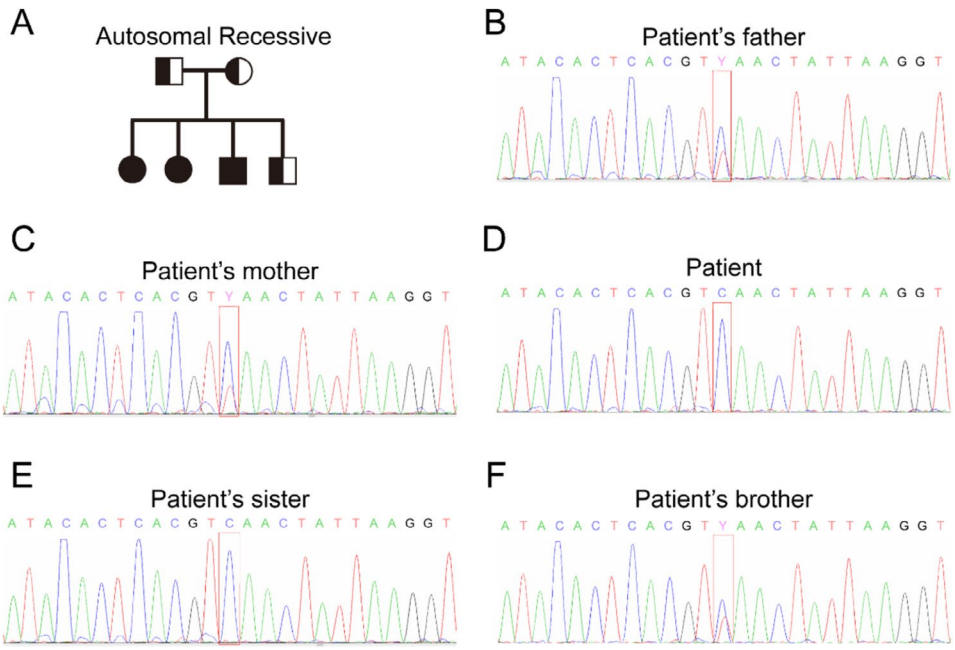

FIGURE 4 | Pedigree chart and genetic testing results of the family. (A) Pedigree chart (autosomal recessive inheritance pattern). (B–F) Genetic testing results. The results indicated that the patient (Case 1) and her sister (Case 2) carried a missense mutation on chromosome 14 in the GALC gene: NM_000153.4(GALC).1901T>C (p.Leu634Ser) (Reference genome version Human GRCH37/hg19), a homozygous variant inherited from both parents. Her parents and brother were heterozygous for the mutation.

her family history raised doubts about the initial diagnosis. The low activity of the GALC enzyme in peripheral blood and the identification of GALC mutations finally provided evidence for their definitive diagnosis of late-onset KD. This case underscores the challenges in diagnosing lower limb disorders characterized by spastic paraplegia and pes cavus. We hope that our experience contributes to raising awareness of late-onset KD as a potential differential diagnosis. And a comprehensive assessment using multiple diagnostic tools, including brain MRI, enzyme activity testing, and gene sequencing, is essential.

KD is one of six autosomal recessive sphingolipid diseases. In the past decade, neuropathological studies on KD and

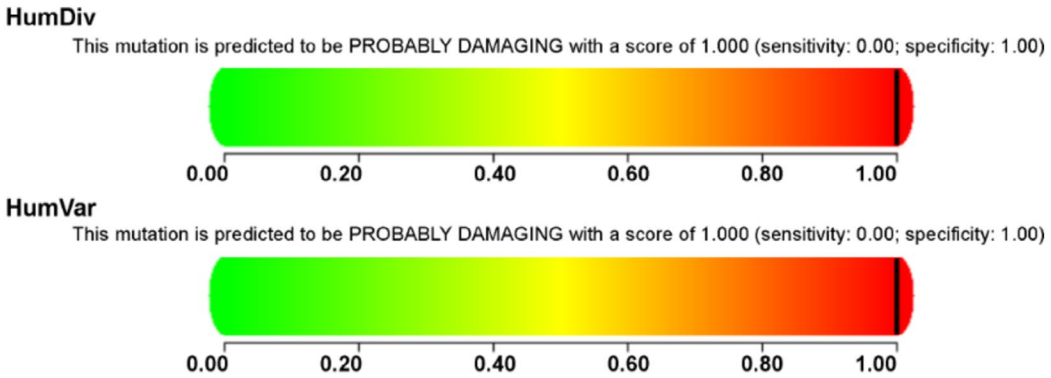

FIGURE 5 | Prediction of functional effect using PolyPhen-2. The prediction scores for both HumDiv and HumVar were 1.00, which indicating a very high probability to affect GALC protein structure and function.

other sphingolipidoses have helped us better understand how these diseases cause nerve cell toxicity (Spassieva and Bieberich 2016). In 1972, Miyatake and Suzuki proposed the "psychotic hypothesis", which refers to cytopathological changes caused by the accumulation of specific sphingolipids or membrane destruction caused by their neurotoxic sphingolipid soluble byproducts (Miyatake and Suzuki 1972). In patients with deficient GALC enzyme, a substrate called psychosine (sphingolipid metabolite galactosylsphingosine) accumulates in the lipid rafts of neurons, which will disturb the membrane microdomain organization of the lipid rafts, leading to neuronal apoptosis or dysfunction, axonal degeneration and neuromuscular junction disorder (Spassieva and Bieberich 2016; Castelvetri et al. 2011; Husain, Altuwaijri, and Aldosari 2004; White et al. 2009; Cantuti-Castelvetri et al. 2012).

During this complex series of micropathologic events, neuroimaging signs indicating demyelination of oligodendrocytes and Schwann cells become valuable and detectable clues for the diagnosis in suspected KD. In the brain MRI of a typical KD patient, predominant parietooccipital white matter changes and involvement of the splenium of the corpus callosum are often observed. T2-hyperintense changes along the corticospinal tracts, the posterior limb of the internal capsule and the pyramidal tracts in the brainstem are also signs of central demyelination (Resende et al. 2019). In addition, when the peripheral nervous system is affected, electromyography can detect reduced motor nerve conduction speed or abnormal somatosensory evoked potentials (Iacono et al. 2022; Adachi et al. 2016; Yang et al. 2013). In this paper, our findings in the proband and her sister were consistent with previously reported symptoms of patients with KD.

However, not all neuroimaging abnormalities are noticeable, especially when demyelinating lesions are too small to be visualized (Alderson and Ghosh 2019). The delayed phenotype of KD is typically mild and slowly progressive, characterized by sensorimotor neuropathy and spastic paraplegia or quadriplegia. When typical imaging findings are not detected, narrowing the differential diagnosis requires extensive clinical expertise. In fact, the proband in this study was initially misdiagnosed with for patient of CMT disease because of myasthenia and abnormality in EMG. Despite similar distal weakness, atrophy, sensory loss, and pes cavus, it is unusual to observe brisk reflexes in the demyelinating form of CMT (Barohn and Amato 2013). Additionally, hereditary spastic paraplegia (HSP) shares overlapping symptoms with KD including pronounced lower extremity spasms, hyperreflexes, plantar extensors, and sometimes urinary symptoms and impaired distal vibration sensation. However, HSP often presents more complex clinical features (lower extremity pyramidal tract signs, cerebellar ataxia, neuropathy) (Fink 2006). In this case, due to the difficulty of differential diagnosis, whole exome sequencing (WES) was employed to achieve an accurate diagnosis. A homozygous pathogenic mutation in the GALC gene (c.1901T>C (p.L634S)) was identified, along with the low GALC enzyme activity in plasma, confirming KD.

The GALC gene consists of 17 exons and 16 introns, spreading over about 58 kb (Graziano and Cardile 2015). Up to now, 296 GALC gene mutations associated with GLD have been recorded in the Human gene Mutation Database (HGMD), including missense mutations, non-sense mutations, deletion, and insertion (Wu et al. 2022). The homozygous mutation of GALC gene (c.1901T>C (p.L634S)) detected in this case results in the substitution of leucine by serine at position 634 in GALC enzyme. To date, this mutation is most commonly found in Chinese and Japanese populations, and is often presented as late-onset phenotype. Due to the longer survival time observed in patients with this mutation, it is considered a mild form (Xu et al. 2006; Zhao et al. 2018). This mutation was first reported in a Japanese patient with late-onset KD (Furuya et al. 1997). The patient looked for treatment because of the spasmodic gait progression of over 20 years. In China, Zhang et al. (2018) reported a family carrying this mutation for the first time. The proband exhibited symptoms of acute hemiplegia at age 20, and brain MRI showed selective pyramidal tract involvement. Genetic sequencing revealed that he carried a complex heterozygous mutation of c.1901T>C and c.1901delT. Interestingly, the proband's father was subsequently confirmed to carry the c.1901T>C homozygous mutation, but he remained asymptomatic until the 50th year of his life, even though brain MRI selective pyramidal tract involvement and low GALC activity were found in the examination. In contrast, the second reported late-onset case with homozygous mutation showed psychiatric symptoms such as forced crying and laughter, as well as cognitive impairment (Xia et al. 2020). In the cases we report, the proband mainly

TABLE 2 | A review of previous literature on late-onset KD patients with mutation c.1901T>C (p.L634S).

No	Origin	Age at onset	Genotype	GALC activity	Spastic paraplegia	Enhanced muscle tension	Tendon hyperreflexia	Pathologic reflex	Pes cavus	Cerebellar dysfunction	Visual impairment	Dysarthria	Mental retardation	Abnormal EMG	Abnormal brain MRI	Reference
1	China	40	c.1901T>C (p.L634S) and c.1005C>G (p.Y335X)	1.5 nmol/17 h/mg	+	+	+	+	+	−	−	−	−	−	+	(Meng et al. 2020)
2	China	37	c.1658G>A (p.G553E) and c.1901T>C (p.L634S)	0.7 nmol/17 h/mg	+	−	+	+	−	−	−	−	−	N	+	(He et al. 2022)
3	Japan	20	[L618S]*; [IVS6 + 5G-A]	5.61 nmol/h/mg	+	N	N	N	N	N	N	N	−	N	+	(Furuya et al. 1997)
4	China	13	c.1901T>C (p.L634S)	3.3 nmol/17 h/mg	+	−	−	−	−	−	−	−	+	+	−	(Xia et al. 2020)
5	China	20	c.1901T>C (p.L634S) and c.1901delT (p.L634X)	1.326 nmol/17 h/mg	−	−	+	+	+	−	−	−	−	−	+	(Zhang et al. 2018)
6	China	22	c.1901T>C (p.L634S)	3.3 nmol/17 h/mg	+	+	+	+	+	+	−	+	+	+	+	(Wang et al. 2022)
7	Japan	38	c.1901T>C (p.L634S)	3.009 nmol/mg/h	+	−	+	+	−	+	−	+	−	+	+	(Satoh et al. 1997)
8	China	20	c.1901T>C (p.L634S) and unknown mutation	4.21 nmol/17 h/mg	+	N	N	N	N	N	N	N	+	N	N	(Zhao et al. 2018)
9	China	46	c.1901T>C (p.L634S) and c.599C>A (p.S200X)	1.0 nmol/17 h/mg	+	−	+	+	−	−	−	−	−	−	+	(Zhang et al. 2021)
10	China	12	c.1901T>C (p.L634S) and c.1321C>T (p.Q441X)	2.07 nmol/17 h mg	+	N	N	N	N	+	−	−	−	−	−	(Xie et al. 2020)
11	China	26	c.1901T>C (p.L634S) and c.2041G>A (p.V681M)	5.9 nmol/17 h mg	+	N	N	N	N	−	−	−	−	−	−	(Xie et al. 2020)
12	China	29	c.1901T>C (p.L634S) and c.908+5 G	2.76 nmol/17 h/mg	+	−	+	+	−	+	−	−	+	N	N	(Su et al. 2024)

(Continues)

TABLE 2 | (Continued)

No	Origin	Age at onset	Genotype	GALC activity	Spastic paraplegia	Enhanced muscle tension	Tendon hyperreflexia	Pathologic reflex	Pes cavus	Cerebellar dysfunction	Visual impairment	Dysarthria	Mental retardation	Abnormal EMG	Abnormal brain MRI	Reference
13	China	23	c.1901T>C (p.L634S) and c.749T>C (p.I250T)	0.1 nmol/17h/mg	+	+	+	+	–	+	–	–	–	–	+	(Zhang, Liu, and Dong 2021)
14	China	14	c.1901T>C (p.L634S) and c.283_284del (p.L95fs)	1.1 nmol/17h/mg	+	+	–	+	–	–	+	–	–	–	–	(Zhang, Liu, and Dong 2021)

Note: +, positive finding; –, negative finding; N, not reported. *GALC activity assay was extracted from the patient's lymphocytes and all data were converted to nmol/h/mg.
Abbreviations: EMG, electromyography; GALC, galactocerebrosidase; KD, Krabbe disease; MRI, magnetic resonance imaging.

presented with abnormal gait, while her sister presented with more severe neurological symptoms.

To provide a more comprehensive comparison of our findings with previous studies, we investigated late-onset KD patients with c.1901T>C (p.L634S) mutation that were available on PubMed. The inclusion criteria were as follows: (1) any late-onset KD patients (age of onset > 6 months) from case reports, systematic reviews or epidemiological investigations; (2) Evidence of genetic sequencing to prove the c.1901T>C (p.L634S) mutation (either homozygous or heterozygous); (3) Result of GALC enzyme activity; (4) Description of at least one significant symptom. Their clinical characteristics are shown in Table 2. Although brain MRI abnormalities were observed in the majority of patients, central nervous system symptoms were relatively rare. In contrast, patients carrying this mutation exhibited more pronounced symptoms in the peripheral nervous system and musculoskeletal system.

Previously, it was suggested that different mutant alleles lead to varying degrees of decreased GALC activity, which might explain the phenotypic heterogeneity of KD (Bernardini et al. 1997; De Gasperi et al. 1996). But differences in phenotype between siblings carrying the same homozygous mutation have been noted (Bajaj et al. 2002). In our case report, despite having the same homozygous mutation and similar levels of GALC activity, the sister showed more severe neurological symptoms than the proband. Given that the sister's symptoms appeared much earlier than the proband's, this suggests that GALC activity is not the only factor influencing disease severity; other factors, such as age of onset, may also contribute.

Currently, an appropriate biomarker to predict the severity of KD in patients has not yet been identified or validated. Cerebrospinal fluid (CSF) protein concentration may be seen as a potential candidate as it somewhat reflects the activity of the neurons demyelinating and degeneration process. Research by Komatsuzaki et al. showed that earlier onset was associated with higher CSF protein concentrations. Moreover, patients with protein levels below or equal to 61.5 mg/dL had significantly longer survival times than those above this threshold (Komatsuzaki et al. 2019). However, unspecific confounders causing CSF protein elevation like central nervous system infections, tumors, and multiple sclerosis, must be exclude before we take it into account. In this study, we were not able to obtain CSF samples for purpose beyond the treatment.

In the treatment of KD, achieving stable improvements in GALC levels within the central nervous system through gene therapy remains challenging. But recent research has revealed key aspects of KD pathogenesis and potential therapeutic targets, offering hope for overcoming current barriers. The KD patient-specific human induced pluripotent stem cell (iPSC) model has been established, which highlighted the role of GALC deficiency in progressive psychopeptide storage and oligodendroglia/neuronal deficits (Mangiameli et al. 2021). Additionally, Khanal et al. identified key elements within the KD-associated neuronal protein network. The compound T-5224, which inhibits the Jun/CRE complex, shows promise as a therapeutic agent based on its strong binding affinity and stability in molecular dynamics simulations (Khanal et al. 2024).

6 | Conclusion

In conclusion, we report a family with the c.1901T>C (p.L634S) mutation leading to late-onset KD, and summarize the clinical characteristics of previously reported late-onset KD patients with this mutation. Our experience highlights the challenge in diagnosing adult patients with spastic paraplegia and pes cavus, as muscle weakness and foot deformities may overlap with other conditions, such as CMT disease. Therefore, it is essential to consider late-onset KD as a potential diagnosis in such cases. When GALC activity and brain MRI results are inconclusive, genetic sequencing can be a valuable tool for accurate diagnosis.

Author Contributions

Conceptualization: Z.G., S.W. and C.Y. Funding acquisition: L.W., Z.G., S.W., and C.Y. Investigation: S.Y., Z.J., C.Y., W.J., L.J. and Z.T. Methodology: S.Y. and Z.J. Project administration: Z.G., S.W. and C.Y. Resources: H.L. and L.X. Supervision: Z.G., S.W. and C.Y. Visualization: S.Y. Writing – original draft: S.Y., Z.J., L.H.and L.X. Writing – review and editing: L.W., Z.G., S.W., and C.Y.

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We would like to express our gratitude to the patients and their family for the invaluable support and cooperation.

Ethics Statement

The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval number: SYSKY-2024-886-01).

Consent

Written informed consent was obtained from the patients for the publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The original contributions presented in the study are included in the article material. Further inquiries can be directed to the corresponding authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.