Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6094-20
Intern Med 60: 1283-1286, 2021
http://internmed.jp

【 CASE REPORT 】

Adult Krabbe Disease That Was Successfully Treated with Intravenous Immunoglobulin

Ryosuke Fukazawa[1], Hiroki Takeuchi[2], Nobuyuki Oka[2], Toko Shibuya[3], Norio Sakai[4] and Akihiro Fujii[1]

Abstract:

Krabbe disease involves the accumulation of neurotoxic metabolites due to lysosomal galactocerebrosidase enzyme deficiency, which results in widespread demyelination of central and peripheral nerves. Generally, Krabbe disease presents as spastic paraplegia with a slow progressive course; however, some cases may show clinical symptoms similar to those of chronic inflammatory demyelinating polyneuropathy (CIDP). No previously reported studies have investigated the efficacy of intravenous immunoglobulin (IVIg) for treating Krabbe disease, and reporting a case involving IVIg treatment may be informative in the clinical setting. A 14-year-old girl who developed Guillain-Barré syndrome-like limb weakness was administered IVIg, and her limb weakness improved. At 16 years old, she developed abnormal sensory perception and weakness of both upper limbs. A nerve conduction study revealed demyelination, which led us to suspect CIDP. IVIg was administered, and her symptoms gradually improved. A nerve biopsy, enzyme activity, and genetic test results indicated adult Krabbe disease. In some cases, IVIg may be an effective treatment for Krabbe disease.

Key words: adult Krabbe disease, demyelinating neuropathy, IVIg, immunotherapy, CIDP

(Intern Med 60: 1283-1286, 2021)
(DOI: 10.2169/internalmedicine.6094-20)

Introduction

Krabbe disease involves the accumulation of neurotoxic metabolites from lysosomal galactocerebrosidase enzyme deficiency, resulting in the widespread demyelination of central and peripheral nerves. Krabbe disease has several clinical types, but many cases follow a slow progressive course.

We herein report a case of Krabbe disease that presented with unusual symptoms due to demyelination and thus prompted differentiation from chronic inflammatory demyelinating polyneuropathy (CIDP). We also describe the effectiveness of administering intravenous immunoglobulin (IVIg) for improving the disease symptoms. The use of IVIg for managing Krabbe disease has not been previously reported.

Case Report

A 14-year-old girl with no history of infection developed distal extremity weakness and numbness in an acute course. A cerebrospinal fluid (CSF) examination revealed protein cell dissociation (protein 67 mg/dL, cell number 6/μL), and a nerve conduction study (NCS) revealed demyelination (extended distal latency in the left median nerve 5.2 ms, reduced F wave in the left median nerve 38%), prompting suspicion of Guillain-Barré syndrome (GBS). She had no significant medical or family history and no motor developmental delay.

The patient was hospitalized and given IVIg treatment [0.4 g/(kg×d) for 5 d], which caused her symptoms to improve, at which time she was discharged. Following her discharge, she had no subsequent complications. Her anti-ganglioside antibody test was negative. Two weeks later, an

[1]Department of Neurology, Saiseikai Shiga Hospital, Japan, [2]Department of Neurology, National Hospital Organization Minami Kyoto Hospital, Japan, [3]Department of Pediatrics, Osaka University Graduate School of Medicine, Japan and [4]Child Healthcare and Genetic Science Laboratory, Division of Health Sciences, Osaka University Graduate School of Medicine, Japan
Received: August 12, 2020; Accepted: October 1, 2020; Advance Publication by J-STAGE: November 16, 2020
Correspondence to Dr. Ryosuke Fukazawa, ryo8878@koto.kpu-m.ac.jp

NCS was repeated and showed a trend toward improvement (extended distal latency in the left median nerve 4.7 ms, reduced F wave in the left median nerve 69%). However, at 16 years old, she developed abnormal sensory perception and weakness in both hands, which progressively extended to both lower limbs to an extent that the patient required handrails to climb stairs by the 8th day and visited the neurology department on the 14th day following symptom onset.

There were no abnormalities in the patient's vital signs, nor did she display general physical abnormalities. Her consciousness was clear, but slight cognitive impairment was observed. The third edition of the Wechsler Adult Intelligence Scale (WAIS-III) revealed a 78 verbal IQ, 80 performance IQ, and 77 full-scale IQ. Her grip strength was 5 kg/5 kg, and her muscle tone was normal. Muscle weakness was symmetrical (manual muscle test: grade 4/4 shoulder abduction strength and grade 3/3 elbow flexor and extensor muscle, long toe extensor muscle, ankle flexor, and extensor muscle strength), and her deep tendon reflex (DTR) was normal. There was no decrease in superficial or deep sensation, although abnormal sensory perception at the extremities occurred. Romberg's and Gowers' signs were negative and positive, respectively. The Overall Neuropathy Limitations Scale (ONLS) was 3 on the upper limbs and 3 on the lower limbs. The Modified Rankin Scale (mRS) was 4.

Her blood count and other biochemical test results were unremarkable, and antinuclear antibody, anti-ganglioside antibody, and ANCA-related antibodies were negative. A CSF examination revealed increased protein (51 mg/dL) levels but no increase in cell number. An NCS revealed extended distal latency (left median nerve 4.9 ms), conduction block (right tibial nerve; ankle CMAP 9.6 mV, popliteal fossa CMAP 0.3 mV), and prolonged duration (right peroneal nerve 8.0 ms). These features met the European Federation of Neurological Society/Peripheral Nerve Society's guidelines for the management of CIDP (definite; partial motor conduction block in the right tibial nerve and other demyelinating parameters in the left median nerve and right peroneal nerve) (1). Head magnetic resonance imaging (MRI) revealed enhanced T2-weighted imaging (T2WI) in the deep white matter at the dorsal horn of both sides of the ventricle near the corpus callosum (Fig. 1). In retrospect, this finding had also been present on head MRI performed at 14 years old. Cervical and lumbar spine MRI showed no nerve root swelling or contrast effect.

The recurrent disease course, protein cell dissociation in the CSF examination, and demyelination findings via NCS suggested CIDP. IVIg was administered as an initial treatment at 20 days post-symptom onset. However, there was minimal improvement in the subjective symptoms and grip strength, so IVIg was again administered at 43 days post-symptom onset. After this second IVIg administration, the subjective symptoms disappeared, and her grip strength gradually improved to 22/20 kg. The ONLS was 0 for the upper limbs and 0 for the lower limbs, and the mRS was 1. The NCS findings were not significantly different, and there was no marked decrease in the DTR, with deep white matter lesions still present on head MRI.

To determine whether or not a disease other than CIDP might have caused the symptoms, a nerve biopsy was performed, showing that nerve bundles with myelin were uniformly thin and consisted mainly of intermediate-diameter axons. There was no endoneural edema or onion bulb, as seen in CIDP. There was no evidence of vasculitis or cell invasion, which was indicative of myelination dysplasia (Fig. 2). Based on the slight cognitive impairment, white matter lesions, demyelinating peripheral neuropathy, and myelin dysplasia on a nerve biopsy, we suspected Krabbe disease and measured the enzymatic activity of galactocerebrosidase, which was found to be low (0.03 nmol/h/mg). In addition, a *GALC* gene analysis detected the presence of I82 M+I305V and G284D compound hetero mutations. Taken together, these findings indicated adult Krabbe disease. Since then, she has gone a year and a half without relapse.

Discussion

Krabbe disease causes demyelination of the central white matter and peripheral nerves due to lysosomal galactocerebrosidase enzyme deficiency, which results in the accumulation of neurotoxic galactosphingosine and psychosine. Krabbe disease is an autosomal recessive disorder, with a reported frequency of 1 in 100,000 to 200,000 (2). Clinical types of the disease are classified according to the patient's age at the disease onset as follows: early-infantile type (3-6 months old), late-infantile type (6 months-3 years old), adolescent type (3-10 years old), and adult type (10-35 years old). Early infantile, late infantile, adolescent, and adult types account for 41%, 20%, 10%, and 29% of total Japanese cases, respectively (3).

Two mutations, I82M+I305V and G284D, were identified within the present patient, and each was determined to have been inherited from a different parent (her father: I82M+I305V, her mother: G284D and I305V). Several genotype-phenotype correlations for Krabbe disease have been reported with respect to I82M+I305V, which is a relatively common mutation in Japanese patients with late-onset Krabbe disease (4). However, the G284D mutation has not previously been reported. The pathogenicity mutation score for the mutation was 'probably damaging' with a score of 1.000 using PolyPhen-2, 'disease-causing' using Mutation Taster, and 'deleterious' with a score of -0.6198 using PROVEAN. The allele frequency was 0.000004 using GnomAD and 0.0001 using ALFA. G284S has been reported as the cause of an adult-onset Krabbe disease case (5) that was treated using hematopoietic stem cell transplantation, which improved the clinical symptoms and galactocerebrosidase activity (6). The G284D mutation was assessed as likely pathogenic based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (7).

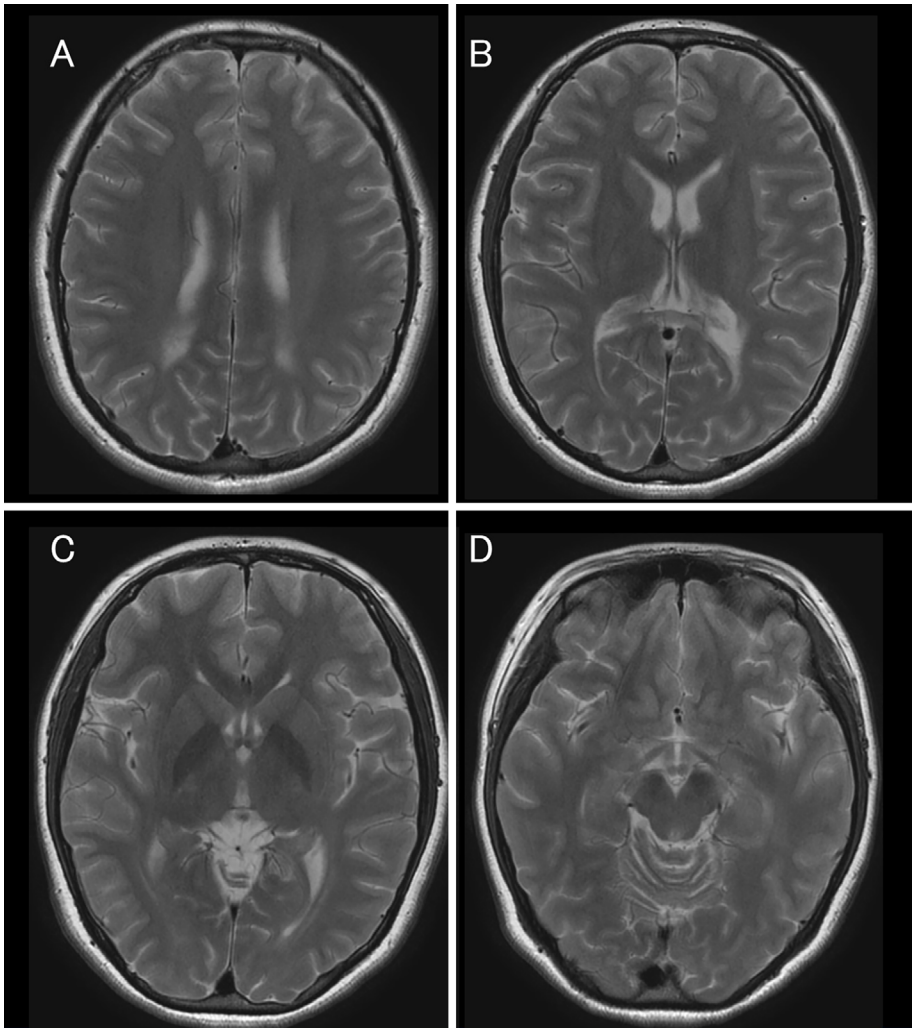

Figure 1. **Head magnetic resonance imaging. T2-weighted imaging. The sequence acquisition parameters were identical (standard fast spin echo sequence; TR=10,000 ms, TE=90 ms). A high signal is visualized in the deep white matter of the dorsal horn of both sides of the ventricle via the corpus callosum. TR: repetition time, TE: echo time**

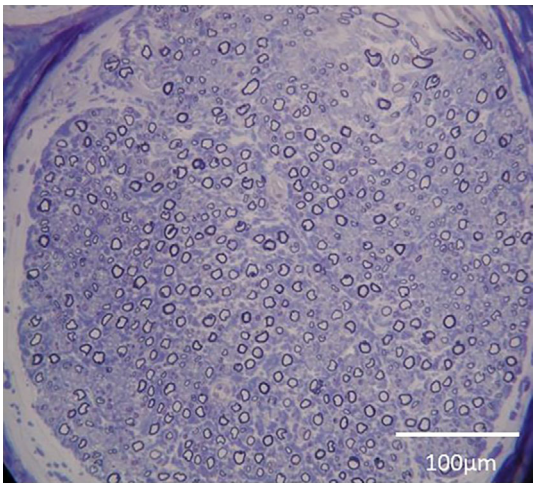

Figure 2. **Pathology of the left sural nerve biopsy. Toluidine Blue staining shows that all nerve bundles are uniformly thin with myelin and consist mainly of intermediate-diameter axons. There is no evidence of vasculitis or cell invasion. Bars 100 μm.**

A total of 96% of adult-onset patients have pyramidal disorders and spastic paraplegia or limb paralysis. Psychiatric symptoms often develop in adult-type disease after 9 years old, and gait disturbance, cognitive dysfunction, and visual impairment progress slowly over a period of 5-10 years. In the present case, spastic paraplegia was not noted. However, given that her DTR was maintained despite the presence of peripheral neuropathy, she might have possessed pyramidal dysfunction. In the CSF, moderate protein increases have been detected in 54% of cases. Head MRI shaw high signal intensity in the corticospinal tract (94%), the visual ray (89%), and atrophy or high signal intensity in the posterior corpus callosum (60%). In this case, the CSF protein levels were slightly increased, and head MRI showed high signal intensity at the back of the corpus callosum. Peripheral neuropathy occurs in 83%, 33%, and 59% of infantile, adolescent, and adult patients, respectively. Demyelinating disease accounts for 80% of the peripheral neuropathy pattern and some cases have reported similar findings to CIDP, such as conduction blocks and temporal dispersion (8).

A previous report described the efficacy of hematopoietic stem cell transplantation for treating early-stage adolescent and adult Krabbe disease with mild neurological symptoms (9). In addition, the effectiveness of enzyme replacement therapy and gene therapy using intrathecal injection has been reported in animal models (10). In this case, the symptoms of demyelination may have recurred and relapsed, or IVIg may have been only temporarily effective. However, there have been no previous reports describing the effectiveness of IVIg treatment for Krabbe disease. IVIg is recognized as an effective treatment of autoimmune diseases, such as CIDP or acute disseminated encephalomyelitis (ADEM).

Krabbe disease is slowly progressive; however, symptom variation has been reported in a few cases (11). Acute progression is very rare, but Mamada et al. reported a case of Krabbe disease that initially presented with acute hemiplegia (12). Metachromatic leukodystrophy (MLD) and Krabbe disease are disorders of the same metabolic pathway of sphingolipidosis, and both have similar underlying pathologies. A few cases of MLD have GBS-like symptoms, and some cases have been reported to show relapse and remission as a result of a partial response to immunotherapy using steroids and IVIg (13). In addition, anti-sulfatide antibodies associated with neuropathy were detected in the serum of adult-onset MLD siblings (14), suggesting that an immune mechanism is associated with the disorder.

In the Krabbe disease model twitcher mice, the expression of cytokines and chemokines increases as the disease progresses (15). Although the levels of psychosine were not measured in the present patient, increased concentrations of psychosine have been shown to be correlated with increased levels of inflammatory markers and amplified cytokine expression (16). However, while neuroinflammation in Krabbe disease is generally considered a late event, recent studies using two different mouse models of Krabbe disease have demonstrated significant astrocyte and microglia reactivation and cytokine elevation in advance of demyelination or oligodendrocyte loss (17). Therefore, it is possible that IVIg transiently neutralized the upregulated cytokines.

We herein report a case of Krabbe disease in which IVIg treatment was successful. However, due to demyelination, there was subsequent improvement and exacerbation of symptoms, which prompted a differential diagnosis of CIDP. Adult Krabbe disease has several clinical features and may follow a similar clinical course to CIDP. The presence of pyramidal signs should be examined, and if abnormal head MRI findings are observed, Krabbe disease should be considered. IVIg may be an effective treatment for Krabbe disease, but more studies will be necessary to confirm its effectiveness.

The authors state that they have no Conflict of Interest (COI).

References

1. Van Der Bergh PY, Hadden RD, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Eur J Neurol **17**: 356-363, 2010.
2. Suzuki Y. Globoid cell leucodystrophy (Krabbe's disease): deficiency of galactocerebroside beta-galactosidase. Proc Natl Acad Sci **66**: 302-309, 1970.
3. Wegener DA, Suzuki K, Suzuki Y, et al. Galactosylceramide lipidosis: globoid cell leukodystrophy (Krabbe disease). In: The Metabolic & Molecular Basis of Inherited Disease. 8th ed. Scriver R, Beaudet AL, Sly WS, et al., Eds. McGraw-Hill, New York, 2001: 3669-3694.
4. Hossain MA, Otomo T, Saito S, et al. Late-onset Krabbe disease is predominant in Japan and its mutant precursor protein undergoes more effective processing than the infantile-onset form. Gene **534**: 144-154, 2013.
5. Rita DG, Miguel AGS, Edi LS, et al. Molecular heterogeneity of late-onset forms of globoid-cell leukodystrophy. Am J Hum Genet **59**: 1233-1242, 1996.
6. Edwin HK, Srinivasa R, William K. Late-onset Krabbe disease (Globoid Cell Leukodystrophy): clinical and biochemical features of 15 cases. Dev Neurosci **13**: 232-239, 1991.
7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med **17**: 405-424, 2015.
8. Debs R, Froissart R, Aubourg P, Papeix C, Douillard C, Degos B. Krabbe disease in adults: phenotypic and genotypic update from a series of 11 cases and a review. J Inherit Metab Dis **36**: 859-868, 2013.
9. Sakai N. Pathogenesis of leukodystrophy for Krabbe disease: molecular mechanism and clinical treatment. Brain Dev **31**: 485-487, 2009.
10. Kondo Y, Wenger AD, Gallo V, Duncan ID. Galactocerebrosidase-deficient oligodendrocytes maintain stable central myelin by exogenous replacement of the missing enzyme mice. Proc Natl Acad Sci **102**: 18670-18675, 2005.
11. Goebel HH, Harzer K, Emst JP, Bohl J, Klein H. Late-onset globoid cell leukodystrophy: unusual ultrastructual pathology and subtotal β-galactocerebrosidase deficiency. J Child Neurol **5**: 299-307, 1990.
12. Mamada N, Nakamagoe K, Shioya A, et al. Adult-onset Krabbe disease presenting as acute hemiparesis and progressive demyelination detected by diffusion-weighted imaging. J Neurol Sci **367**: 326-328, 2016.
13. Rachana D, Biswaroop C, Sheffali G, et al. Leukodystrophy presenting as acute-onset polyradiculoneuropathy. Pediatr Neurol **50**: 616-618, 2014.
14. Iannaccone S, Nemni R, Fazio R, Quattrini A, Lacerenza M, Smirne S. Polyneuropathy with antibodies to sulphatide and decreased level of arylsulphatase A. J Neurol **240**: 260-261, 1993.
15. Eric RS, Jeanne MFP, Hope AS, et al. Innate immune activation in the pathogenesis of a murine model of globoid cell leukodystrophy. Am J Pathol **184**: 382-396, 2014.
16. Santambrogio S, Ricca A, Maderna C, et al. The galactocerebrosidase enzyme contributes to maintain a functional neurogenic niche during early post-natal CNS development. Hum Mol Genet **21**: 4732-4750, 2012.
17. Gregory BP, Magdalena AP. Neuroimmune mechanisms in Krabbe's disease. J Neurosci Res **94**: 1341-1348, 2016.