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Experiences of Patients and Families Living with Krabbe Disease

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Abstract

The challenges faced by patients with Krabbe disease remain unelucidated. This study aimed to identify these challenges and facilitate the development of methods for assessing the quality of life. This qualitative descriptive study used in-person or online semistructured interviews from March to December 2022 using a qualitative content analysis approach. Data were collected from one patient each for the late infantile, juvenile, and adult types of Krabbe disease. In total, 249 codes were extracted from the verbatim transcripts and integrated into 40 subcategories and eight categories. The categories were integrated into three themes: the impact of symptoms on daily life, challenges for healthcare systems, and challenges faced by family members. Patients experienced physical symptoms, social life challenges, and medical care difficulties. Additionally, families felt burdened caring for these patients. In conclusion, support systems for patients and their families during treatment and in their living environments should be developed to aid in managing these challenges. Moreover, a comprehensive scale that accurately reflects the social challenges faced by these patients and their families is needed.

Keywords

caregiver burden, delayed diagnosis, interviews as topic, Krabbe disease, quality of life

Introduction

Krabbe disease (OMIM#245200) is an autosomal recessive genetic disorder caused by galactocerebrosidase deficiency.[1] Galactolipid accumulation causes inflammatory reactions and progressive demyelination of the central and peripheral nervous systems. The infantile type accounts for approximately 80% of the cases of Krabbe disease.[2] Krabbe disease is classified into four types: early infantile, late infantile, juvenile, and adult. It is rare, with an unknown exact prevalence; however, the prevalence of the early infantile type is 1 in 394 000 live births.[3] A nationwide survey in Japan reported 15 patients.[4]

The early infantile form develops before 12 months, presenting with developmental delays, irritability, and feeding difficulties.[5,6] It progresses rapidly and has a poor prognosis.[6] Progression is slower in the late infantile form than in the early form; however, it may lead to muscle tone loss, visual impairment, and neurodevelopmental decline.[5] The juvenile form affects individuals aged 3 to 18 years, whereas the adult form occurs at ages ≥18 years. Most patients with these two forms of the disease survive until ≥16 years.[7] Symptoms in patients with the juvenile type include changes in gait, hemiparesis, stiffness, poor feeding, and visual loss.[8] Patients with adult-onset disease experience prolonged survival.[8] Case reports have described patients with headaches as the initial symptom diagnosed using imaging studies.[9]

Hematopoietic stem cell transplantation effectively treats Krabbe disease.[10] However, it may be ineffective unless performed early during the disease course. Therefore, Krabbe disease has been incorporated into newborn screening for early detection and treatment.[10] Additionally, early hematopoietic stem cell transplantation does not completely halt disease progression, and the challenges of donor matching and graft-to-host disease encourage the development of

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safer treatment methods.[11] Gene therapy holds promise but is not currently suitable for human application.[11]

Therefore, in supporting patients with Krabbe disease, patients' quality of life should be considered as the disease progresses. Few studies have investigated the quality of life of patients with Krabbe disease. Langan et al[12] developed a scale based on prior literature to assess patients' quality of life with Krabbe disease[12] and demonstrated that patients with the early infantile type had a lower quality of life than those with the late onset of the disease. Furthermore, patients with hematopoietic stem cell transplantation had a high quality of life).[12] However, the scale was based on medical findings and not on the hermeneutics of patient and family experiences. Conducting qualitative studies on patients and their families is crucial for developing detailed quality-of-life measures as a patient-reported outcome.[13] Krabbe disease is a very rare disease, and it may be difficult to collect qualitative data. However, due to its rarity, accumulating qualitative data that are in line with the lives of each patient rather than quantitative data could provide useful data for considering support and developing scales.

A systematic review indicated that qualitative studies on patients with Krabbe disease and their families remain lacking.[14] Therefore, in our novel study, we interviewed family members of patients with Krabbe disease to provide basic findings for assessing the quality of life of patients and their families.

Material and Methods

Study Design and Participants

To describe the experiences of patients and their families, this study was conducted using a qualitative descriptive research design, which employed an inductive content analysis approach.[15] We included patients with Krabbe disease and their parents in Japan from the Japanese Krabbe Disease Patient Association and the outpatient department. We distributed explanatory documents through the patient association and asked for their participation. In addition, explanatory documents were distributed to patients who visited the outpatient clinic of the fourth author, who specializes in the treatment of Krabbe disease. We included patients at least 18 years old who could speak conversational Japanese. Patients who have intellectual or physical disabilities and are unable to give written consent were replaced by their parents as interview participants.

Interview

Interviews were conducted either in person or online in Japanese using a semistructured interview method with an interview guide (Supplemental Material 1) from March to December 2022 and were recorded with the consent of the participants. The interview guide was created under the supervision of a Krabbe disease specialist based on the results of the development of a QOL scale for patients with Fabry disease,[16] a lysosomal storage disorder, and research of children with severe multiple disabilities.[17] The interviewer was either the first or the third author. Participants 1 and 2 are a married couple, and the face-to-face interview was simultaneously conducted. The interview was conducted in a private room in the hospital after the patient's outpatient consultation, where privacy was observed. In addition, interviews with participants 3 and 4 were conducted online on the participant's preferred date and time.

Analysis

Classification and naming were performed primarily by the first and second authors. The recorded interviews were transcribed verbatim and read multiple times to ensure a complete understanding of the content. Codes were created using simplified verbatim recording and aggregated into subcategories, categories, and themes based on content similarity. All authors were involved in consolidating categories and themes to ensure content validity. The analysis was carried out manually by the authors, but NVivo (version 1.7.1) was used to manage and organize the data. The participants' voices shown in the results were translated from Japanese into English by a company specializing in translation.

Trustworthiness

We ensured rigor in accordance with the trustworthiness of the qualitative content analysis approach.[15] For credibility, this article described the details of how to recruit participants, conduct interviews, and use qualitative content analysis to code and create themes. The researcher's experience and preconceptions that may have affected the process and results of the research are described in detail in the following section. For dependability, the first and second authors repeatedly discussed the process of condensation and coding the verbatim record according to the content analysis method. The fourth author also confirmed the composition of the categories. The overall results are presented in Tables 1 and 2. The results ensured authenticity by including at least one quote for each category. For transferability, information about the participants was provided to the maximum extent without requiring the individual's identification. In addition, through the introduction and discussion, we also described the social environment in which the participants were placed.

This paper was written according to the Standards for Reporting Qualitative Research checklist.[18]

Influence of the Researcher on the Research

The first and third authors who conducted the interviews had no previous direct involvement with patients with Krabbe disease. However, the first author had experience in nursing care for patients with lysosomal diseases, which

Table 1. Characteristics of Participants.

No	Participants	Age	Patient gender	Patient age	Phenotype	Age of diagnosis	Interview time
1	Mother	57 years	Man	21 years	Late infantile	1 year and 9 months	53 min
2	Father	52 years					
3	Patient		Woman	46 years	Juvenile	29 years	1 h 3 min
4	Patient		Man	48 years	Adult	37 years	41 min

are characteristic of Krabbe disease, and conducted interviews. The third author is a graduate student in a genetic counseling course specializing in genetic nursing. Therefore, the experiences of these interviewers may have influenced the progression and content of the interviews. However, in this study, the influence was positive in eliciting more specific stories, with an understanding of the disease progression and the limitations on their lives.

Ethical Consideration

This study was approved by the Research Ethics Committee of Osaka Aoyama University (approval no. 0217; approval date: February 26, 2021) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from the participants.

Results

Overview

Interviews were conducted with four participants, two of whom were parents of a patient with late infantile type Krabbe disease, and they were interviewed simultaneously. The remaining participants included one juvenile and one adult with Krabbe disease (Table 1).

In total, 249 codes were extracted from the verbatim transcripts and integrated into 40 subcategories and 8 categories. The categories were integrated into 3 themes: the impact of symptoms on daily life, challenges for healthcare systems, and challenges faced by family members (Table 2).

Impact of Symptoms on Daily Life

Impact of disease symptoms. Patients and their parents were concerned about Krabbe disease symptom onset and prognosis, which is a progressive condition. When symptoms manifested in childhood, patients were often diagnosed with developmental delays. As symptoms gradually progressed, patients became more concerned about their prognosis but were willing to work through it.

> "From this serious infant-type child, it was really kind of complex, and it was difficult to process all these different things in my head. When I first saw that, I got really depressed, wondering if I'd also really become like that, but looking back until now, it's not like it progressed that much. I was able to process it like that, and I stopped getting so depressed about it." No. 3 juvenile-type patient

Challenges in daily life. Challenges in walking considerably impacted the patients' lives. The risk of falls increased, necessitating the use of canes and braces.

> "When I am walking normally, I'd have these times when I lose my balance and I try not to fall over." No. 4 adult type patient

The difficulty of going out restricted patients' lives. They were frustrated by their reliance on caregivers and services to go outside.

> "I have gone to some barrier-free facilities and met with people. However, it has become a bit difficult. It's probably not possible now. Thinking that having a helper arrange everything and accompany me, having him/her do everything. It would become like that, right now, it's somewhat really hard." No. 3 juvenile-type patient

Issues in social life. Symptom progression affected patients' social lives. They felt restricted and needed consideration at school during childhood and work during adulthood.

> "Yes. It became harder to go out, so I had them decide that I'd work indoors." No. 4 adult type patient

However, patients and parents gained information and discovered prospects through interactions with other patients, particularly during patient association activities.

> "When I met that person, that person's child was about 6 years old, and my child was about 2 years old. I hoped that that kind of thing wouldn't happen, and there was hope to live. Well, by the hospital doctors, what shall I say? That can't be obtained, what shall I say, that, the hope to live." No. 1 mother of late infantile type patient

Challenges for Healthcare Systems

Challenges in the medical system. From symptom onset through disease progression, patients and their families require support from medical and welfare services. Given the rarity of the disease, patients experienced difficulties in diagnosis.

Table 2. Classification of Themes, Categories, and Subcategories.

Theme	Category	Subcategory	Code
Impact of symptoms on daily life			116
	Impact of disease symptoms		34
		Disease progression	5
		Developmental delay	3
		Progression of muscle symptoms	6
		Shoulder dislocation	3
		Visual impairment	10
		Anxiety about disease progression	7
	Challenges in daily life		50
		Walking problems	15
		Tremor and spasm	4
		Impact on bicycling and driving	4
		Challenges in going out	14
		Challenges in excretion	7
		Difficulties in life	6
	Issues in social life		32
		Challenges in school life	3
		Friendship	1
		Impact on work	7
		Financial burden	5
		Interaction with other patients	10
		Challenges of patient association activities	6
Challenges for health care systems			106
	Challenges in medical system		55
		Difficulty in diagnosis	16
		Distress as rare disease	4
		Follow-up system in medical facilities	12
		Use of genetic counseling	3
		Change in frequency of medical visits	7
		Lack of rehabilitation facilities	4
		Bone marrow transplant	5
		Expectations for new treatment	4
	Challenges for the welfare system		33
		Lack of information on support	6
		Challenges in coordinating support	8
		Use of home nursing and helpers	6
		Use of short stay	6
		Medical care	4
		Self-training	3
	Relationship with supporters		18
		Trust in healthcare providers	5
		Distrust of healthcare providers	10
		Dissatisfaction with supporters of the opposite sex	3
Challenges faced by family members			27
	Family burdens		12
		Burden on parents	2
		Aging of caregivers	4
		Siblings assume caregiving	6
	Patient and family relationships		15
		Notification of diagnosis to family members	6
		Relationships with family members	9

> "I suddenly felt like I really couldn't walk, and around that time, I started going around 2 or 3 hospitals. However, they determined it as cerebral palsy, and I was left without really knowing anything." No. 3 juvenile-type patient

After diagnosis, the patients and their families were offered bone marrow transplants and follow-ups with genetic counseling. However, adult patients were distressed by the choice of transplantation, which only halts the disease progression and does not cure or fundamentally treat advanced symptoms.

> "Yes, it won't heal but it'll stop the progression." No. 3 juvenile-type patient

Challenges for the welfare system. When wanting to use appropriate welfare services, patients and parents had to search for them independently because of the lack of information about services or supporters who could coordinate on their behalf.

> "Essentially, uh, there's this service, there's this service, there's this service, like, they wouldn't say that service at the front desk, first of all. They wouldn't tell me. So, I gotta go look for it." No. 2 father of late infantile-type patient.

Patients required the help of home nurses and helpers in various aspects of their lives. However, assistance was unavailable on certain days and times because of scheduling conflicts with the supporters.

> "So I would like the helper to come at least around 9 pm or so, but. Around here, there's so few helpers who would be willing to accept coming in to help after 6 pm." No. 3 juvenile type patient

Relationship with supporters. Patients sometimes struggle in their relationships with medical personnel and their supporters. Parents of pediatric patients found it distressing to ask medical personnel about comfortable positions for their children.

> "It's kind of like, even if in trouble, kind of like, uhhh, is it different that they wouldn't understand. Right now, this position is uncomfortable, but would they even understand that, is the kind of one-sided anxiety, and uhh, it's hard to rely on people, yeah. S- so that's the ma- main, uh, how to say it." No. 1 mother of late infantile type patient

Challenges Faced by Family Members

Family burdens. Krabbe disease affected both the patients and their family members. The parents and siblings of pediatric patients were caregivers at home; however, they felt home care was a significant burden.

> "Recently, there are these times where his sister would, uh, well, in during breaks in work, if she's around, that she would watch over. Well, uh, she has lots of experience, so, well, she might be better than us in responding to a certain extent. Saying it's 'better' is, there is a part that she can do it." No. 2 father of late infantile-type patient.

> "Yeah. For the others, there's just nobody in. It feels like it's pretty difficult." No. 2 father of late infantile-type patient.

Additionally, patients with advanced neurological conditions needed continuous care. For older/aging parents, the future seemed increasingly uncertain as they could not take concrete measures.

> "So, yeah. We're kind of old, old, like, I feel it every year, getting older and losing physical strength. I do get wo-, concerned, but. So, ki- kind of, thinking about what, I have to think what's next, but it's not yet at all, yeah. At zero." No. 1 mother of late-infantile-type patient

Patient and family relationships. It can be difficult for patients to explain the characteristics of the hereditary disease Krabbe disease to their family. Some patients were worried about whether or not to tell their families, but even if they did, they had experienced that their families did not fully understand their condition.

> "My mother doesn't understand at all. And, well, what should I say, she didn't really understand what Krabbe disease was, even though I gave her copies of the various things the doctors had given me." No. 3 juvenile type patient

Discussion

To our knowledge, this study is the first to use qualitative research methods to determine the experiences of patients and their parents with Krabbe disease. As recommended by the qualitative systematic review of patients with leukodystrophy,[14] it is important that the experiences of patients with Krabbe disease have been clarified. This research will lead to the accumulation of knowledge about the experiences of people with Krabbe disease and will help us to examine the effects of symptoms and social environments. Krabbe disease affects the lives of patients and their families and the social healthcare system. Additionally, the burden of caregiving by the family must be considered.

Despite the limited number of participants, the study findings may be used to develop a scale to assess the subjective health and quality of life of patients with Krabbe disease. Although a specific scale has already been published,[12] our findings include issues in the social lives of patients and their families. Hence, a scale that better reflects patients' real lives could be developed. These themes are similar in structure to research on metachromatic leukodystrophy in Japan.[19] This may lead to the development of a scale that integrates similar diseases.

Impact of Symptoms on Daily Life

Data were collected from three types of patients: infants, juveniles, and adults. The patients and families who were diagnosed sought knowledge about the disease and were pessimistic about their future. The age at onset of Krabbe disease varies widely depending on the disease type.[7] Therefore, appropriate information on the progression and treatment of each disease type must be provided. However, as Krabbe disease is ultra-rare, sufficient information regarding the specific progression of its symptoms and life challenges remains lacking. Including Krabbe disease in newborn mass screenings for early detection has also been considered.[10] Therefore, the early detection of patients with not only the infantile form but also the juvenile and adult forms and the accumulation of data on natural history may lead to the provision of appropriate information to patients.

Physical care and support are crucial as the disease progresses. In Krabbe disease, spasticity and contracture of the musculoskeletal system develop.[1] Patients had difficulty walking, interfering with their ability to go out and work. A qualitative systematic review of inherited metabolic leukodystrophies, including Krabbe disease, suggested that loss of walking and life functions is a significant factor leading to difficulties in life.[14] Attempts are being made to assess the activities of daily living, such as toileting, changing, and eating, in patients with juvenile metachromatic leukodystrophy.[(20)] Therefore, physicians and nurses should understand the progression of symptoms and the difficulty in daily living. Additionally, they should support patients in adjusting to their own lives.

Challenges for Healthcare Systems

The participants voiced problems concerning their current challenges with the Japanese healthcare environment. A delayed diagnosis is challenging. Juvenile-type patients may suffer from symptoms since childhood but are not correctly diagnosed. Furthermore, delays are observed in diagnosing other lysosomal diseases.[21] Although consulting a specialist for a proper diagnosis is essential, only a few physicians or medical facilities specialize in Krabbe disease because it is rare. Early detection via newborn screening allows many patients to undergo transplantation.[22] In false-positive cases of Krabbe disease detected through newborn screening, parents undergo emotional stress; however, they understand the importance of screening.[23] In addition to promoting screening for early diagnosis of Krabbe disease, specialists, nurses, and genetic counselors must collaborate to support parents who receive the results.

Furthermore, fundamental treatments for Krabbe disease other than early detection or hematopoietic stem cell transplantation remain unavailable.[1] Supportive daily care for patients with advanced symptoms improves their quality of life. Participants experienced situations where appropriate social services were unavailable and became frustrated. Although caseworkers for older adults are widespread, contact persons to consult for services for patients who are children or adolescents and need care are lacking. A lack of support service integration has also been reported in studies on parents of patients with metachromatic

leukodystrophy and adrenoleukodystrophy, which have symptoms similar to Krabbe disease.[24,25] Therefore, outpatient nurses are expected to play a role by being knowledgeable about the disease and social services.

This study showed that patients with Krabbe disease and their families struggled with their supporters, as they needed to interact with multiple supporters. To examine communication with healthcare providers, one study reported how patients and parents perceived and verbally expressed symptoms.[26] The naming of categories and subcategories in this study is based on the statements of patients with Krabbe disease and their families and aids in understanding the lives of patients.

Challenges Faced by Family Members

Family caregiving is a significant challenge for patients with infantile Krabbe disease. In patients with metachromatic leukodystrophy, frequent hospital visits, hospitalizations, and daily care reduce the quality of life of caregivers and limit their ability to work.[27] For healthy siblings, living with a patient in need of care is perceived as a burden, responsibility, or disadvantage.[28] Therefore, care is needed for the patients' and family members' physical and emotional needs to support patients with Krabbe disease.

Improvements in supportive care have allowed patients with infantile forms to reach adulthood; however, maintaining the standard of care is challenging for aging parents, who are the primary caregivers. Parents of children with disabilities are concerned about their aging and care for their children after their deaths.[29,30] This leads to the possibility of siblings becoming substitute caregivers.[29,30] Therefore, supporters, including nurses, should discuss prospects with family members and seek ways to satisfy them to adjust their functions and roles.

Recommendations for Healthcare Practice

This research has shown the physical symptoms and difficulties experienced by people with Krabbe disease. In clinical practice, doctors and nurses need to anticipate the difficulties patients face and create support plans, not just based on test data, so these data will be very useful. On the other hand, patients may have issues in their relationship with healthcare, from diagnosis to support for their daily lives. It is desirable for medical professionals to work with specialists such as genetic counselors to provide support for patients. Furthermore, because it is a hereditary disease and it places a burden on caregivers, it is also important to support family members. Understanding the support systems surrounding patients and the issues faced by their families will improve the QOL of patients with Krabbe disease.

Limitations

This study is based on qualitative data from a limited number of patients and does not cover all sex or disease types. In addition, the accounts of late-infantile-type patients are based on their parents' experiences. In addition, the fact that the interviewers had never been involved in the treatment or care of patients with Krabbe disease, may have affected the amount of data we were able to extract. To increase the transferability, the background and information of the participants are important, but because it is a rare disease, there are restrictions on the data that can be disclosed so that the patients cannot be identified. Nevertheless, our results are valuable. Future research should increase the sample size and collect longitudinal patient and family experiences to enrich the data.

Conclusions

Patients experience challenges with their physical symptoms, social life, and relationships with medical care providers. Furthermore, providing care to patients with Krabbe disease was burdensome for their families. Therefore, physicians and nurses should assess and develop support systems for patients and families during treatment and in their living environments to aid in the management of these challenges. The findings emphasize a need for a comprehensive scale that accurately reflects issues faced in the social lives of such patients and their families.

Authors' Note

Data Availability Statement: Because of the sensitive nature of this research and the potential for identification of the participants due to the rare disease, participants were assured that raw data would be kept confidential and would not be shared. *Statement of Human and Animal Rights:* The study was conducted in accordance with the Research Ethics Committee of Osaka Aoyama University (approval no. 0217; approval date: February 26, 2021) approved protocols and Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. This article does not contain any studies with animal subjects. *Statement of Informed Consent:* Written and oral explanations were provided to the participants, and written informed consent was obtained. Consent also included that the information would be published as a paper, with consideration given to not identifying individuals. The participants were informed that their cooperation was voluntary and that they could withdraw their consent. Furthermore, their personal information would be protected, and the data would be stored appropriately and destroyed. Participants received 1000 yen as a reward for their cooperation.

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Author Contributions

Yuta Koto: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, project administration, and funding acquisition. Wakana Yamashita: Validation, Formal analysis, Writing – review and editing. Kumiko Kitamura: Investigation, Writing – review and editing. Norio Sakai: Conceptualization, Resources, Writing – review and editing, Supervision. All authors have read and approved the final version of this manuscript.

Declaration of Conflicting Interests

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Ethical Approval

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Supplemental Material

Supplemental material for this article is available online.

References

1. Escolar ML, West T, Dallavecchia A, Poe MD, LaPoint K. Clinical management of Krabbe disease. *J Neurosci Res*. 2016;94:1118-25. doi:10.1002/jnr.23891
2. Krieg SI, Krägeloh-Mann I, Groeschel S, et al. Natural history of Krabbe disease—a nationwide study in Germany using clinical and MRI data. *Orphanet J Rare Dis*. 2020;15:243. doi:10.1186/s13023-020-01489-3
3. Orsini JJ. Newborn screening for Krabbe disease: perceived and current ethical issues. *Dev Med Child Neurol*. 2019;61:1354. doi:10.1111/dmcn.14265
4. Koto Y, Sakai N, Lee Y, et al. Prevalence of patients with lysosomal storage disorders and peroxisomal disorders: a nationwide survey in Japan. *Mol Genet Metab*. 2021;133:277-88. doi:10.1016/j.ymgme.2021.05.004
5. Bascou N, DeRenzo A, Poe MD, Escolar ML. A prospective natural history study of Krabbe disease in a patient cohort with onset between 6 months and 3 years of life. *Orphanet J Rare Dis*. 2018;13:126. doi:10.1186/s13023-018-0872-96
6. Beltran-Quintero ML, Bascou NA, Poe MD, et al. Early progression of Krabbe disease in patients with symptom onset between 0 and 5 months. *Orphanet J Rare Dis*. 2019;14:46. doi:10.1186/s13023-019-1018-4
7. Komatsuzaki S, Zielonka M, Mountford WK, et al. Clinical characteristics of 248 patients with Krabbe disease: quantitative natural history modeling based on published cases. *Genet Med*. 2019;21:2208-15. doi:10.1038/s41436-019-0480-7
8. Duffner PK, Barczykowski A, Kay DM, et al. Later onset phenotypes of Krabbe disease: results of the world-wide registry. *Pediatr Neurol*. 2012;46:298-306. doi:10.1016/j.pediatrneurol.2012.02.023
9. Paiva ARB, Fonseca Neto RE, Afonso CL, Freua F, Nóbrega PR, Kok F. Incidental magnetic resonance imaging findings leading to an unusual diagnosis: adult onset Krabbe disease. *Eur J Neurol*. 2022;29:1859-62. doi:10.1111/ene.15298
10. Kwon JM, Matern D, Kurtzberg J, et al. Consensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. *Orphanet J Rare Dis*. 2018;13:30. doi:10.1186/s13023-018-0766-x
11. Bradbury AM, Bongarzone ER, Sands MS. Krabbe disease: new hope for an old disease. *Neurosci Lett*. 2021;752:135841. doi:10.1016/j.neulet.2021.135841
12. Langan TJ, Barczykowski A, Jalal K, et al. Survey of quality of life, phenotypic expression, and response to treatment in Krabbe leukodystrophy. *JIMD Rep*. 2019;47:47-54. doi:10.1002/jmd2.12033
13. Mokkink LB, de Vet HCW, Prinsen CAC, et al. COSMIN risk of bias checklist for systematic reviews of patient-reported outcome measures. *Qual Life Res*. 2018;27:1171-9. doi:10.1007/s11136-017-1765-4
14. Koto Y, Ueki S, Yamakawa M, Sakai N. Experiences of patients with metachromatic leukodystrophy, adrenoleukodystrophy, or Krabbe disease and the experiences of their family members: a qualitative systematic review. *JBI Evid Synth*. 2024;22:1262-302. doi:10.11124/JBIES-23-00303
15. Kyngäs H, Kääriäinen M, Elo S. The trustworthiness of content analysis. In: Kyngäs H, Mikkonen K, Kääriäinen M, eds. *The application of content analysis in nursing science research*. 1st ed. Springer; 2020:41-8. doi:10.1007/978-3-030-30199-6.
16. Koto Y, Yamashita W, Lee Y, Hadano N, Kokubu C, Sakai N. Development and validation of a disease-specific quality of life scale for adult patients with Fabry disease in Japan. *J Patient Rep Outcomes*. 2022;6:115. doi:10.1186/s41687-022-00525-z
17. Koto Y, Tomozawa M, Sato T, Niinomi K, Sakai N, Nagai T. Supporters' experiences of sensory characteristics of children with profound intellectual and multiple disabilities in after-school daycare centres: a qualitative study. *Nurs Open*. 2023;10:7826-38. doi:10.1002/nop2.2031
18. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med*. 2014;89:1245-51. doi:10.1097/acm.0000000000000388

19. Koto Y, Yamashita W, Sakai N. Impact on physical, social, and family functioning of patients with metachromatic leukodystrophy and their family members in Japan: a qualitative study. *Mol Genet Metab Rep*. 2024;38:101059. doi:10.1016/j.ymgmr.2024.101059
20. Brown TM, Martin S, Fehnel SE, Deal LS. Development of the impact of juvenile metachromatic leukodystrophy on physical activities scale. *J Patient Rep Outcomes*. 2017;2:15. doi:10.1186/s41687-018-0041-x
21. Koto Y, Ueki S, Yamakawa M, Sakai N. Experiences of patients with lysosomal storage disorders who are receiving enzyme-replacement therapy and the experiences of their family members: a qualitative systematic review. *JBI Evid Synth*. 2022;20:1474-510. doi:10.11124/JBIES-21-00074
22. Blackwell K, Gelb MH, Grantham A, Spencer N, Webb C, West T. Family attitudes regarding newborn screening for Krabbe disease: results from a survey of leukodystrophy registries. *Int J Neonatal Screen*. 2020;6:66. doi:10.3390/ijns6030066
23. Peterson L, Siemon A, Olewiler L, McBride KL, Allain DC. A qualitative assessment of parental experiences with false-positive newborn screening for Krabbe disease. *J Genet Couns*. 2022;31:252-60. doi:10.1002/jgc4.1480
24. Lee TY, Li CC, Liaw JJ. The lived experience of Taiwanese mothers of a child diagnosed with adrenoleukodystrophy. *J Health Psychol*. 2014;19:195-206. doi:10.1177/1359105312467388
25. Yazdani PA, St-Jean ML, Matovic S, et al. The experience of parents of children with genetically determined leukoencephalopathies with the health care system: a qualitative study. *J Child Neurol*. 2023;38:329-35. doi:10.1177/08830738231176672
26. Eichler F, Sevin C, Barth M, et al. Understanding caregiver descriptions of initial signs and symptoms to improve diagnosis of metachromatic leukodystrophy. *Orphanet J Rare Dis*. 2022;17:370. doi:10.1186/s13023-022-02518-z
27. Sevin C, Barth M, Wilds A, et al. An international study of caregiver-reported burden and quality of life in metachromatic leukodystrophy. *Orphanet J Rare Dis*. 2022;17:329. doi:10.1186/s13023-022-02501-8
28. Ammann-Schnell L, Groeschel S, Kehrer C, Frölich S, Krägeloh-Mann I. The impact of severe rare chronic neurological disease in childhood on the quality of life of families-a study on MLD and PCH2. *Orphanet J Rare Dis*. 2021;16:211. doi:10.1186/s13023-021-01828-y
29. Kruithof K, IJzerman L, Nieuwenhuijse A, et al. Siblings' and parents' perspectives on the future care for their family member with profound intellectual and multiple disabilities: a qualitative study. *J Intellect Dev Disabil*. 2021;46:351-61. doi:10.3109/13668250.2021.1892261
30. Kruithof K, Olsman E, Nieuwenhuijse A, Willems D. I hope i'll outlive him': a qualitative study of parents' concerns about being outlived by their child with profound intellectual and multiple disabilities. *J Intellect Dev Disabil*. 2022;47:107-17. doi:10.3109/13668250.2021.1920377