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Impact on physical, social, and family functioning of patients with metachromatic leukodystrophy and their family members in Japan: A qualitative study

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ABSTRACT

Metachromatic leukodystrophy is a rare autosomal recessive disease. There are three forms of this disease, all of which result in cognitive and motor dysfunctions. Although enzyme replacement and gene therapies have been developed, they are not expected to be effective in patients with advanced diseases. Therefore, it is important to focus on treatment effects and patients' quality of life; however, qualitative findings on the experiences of patients and their families have not been adequately reported. Interviews were conducted with the family members of patients with metachromatic leukodystrophy in Japan. Verbatim transcripts were analyzed using a qualitative content analysis approach. We interviewed the mothers of five patients. Verbatim interview transcripts were classified into 81 codes. The codes were then aggregated into 15 categories and 3 themes: challenges of life for the patients, challenges in the healthcare system, and challenges of family function. Disease progression greatly affects patients' lives. Moreover, social systems supporting patients and their families are inadequate, especially as the disease progresses. Family members face life restrictions and role changes because of the patient's diagnosis. Patients with metachromatic leukodystrophy and their families require comprehensive support.

1. Introduction

Metachromatic leukodystrophy (MLD) is an inherited lysosomal storage disease caused by an autosomal recessive mutation in the *ARSA* gene [1]. Demyelination due to sulfatide accumulation in the central and peripheral nervous systems can cause ataxia, tetraparesis, mental regression, and other neurological symptoms [1,2]. MLD is a rare disease, with a reported prevalence of 1.09 to 1.85 per 100,000 live births [3–5]. According to a survey conducted between 2013 and 2016, the estimated number of patients was 83 in Japan [6].

There are three subtypes of MLD depending on the disease onset: a late-infantile type (< 30 months old), a juvenile type (2.5–16 years old), and an adult type (> 16 years old) [1]. Patients with infantile type exhibit early abnormal gross motor function [7]. Patients with late infantile type had symptoms at an average age of 1.5 years and were diagnosed at 2.6 years [8]. Language and cognitive functions begin to decline at approximately 30 months of age when spontaneous speech is no longer possible [9]. Peripheral neuropathy and dysphagia appear, and supportive care is needed; unfortunately, death occurs within a few years of onset [1].

Even though the juvenile type progresses more slowly than the infantile type, ataxia and mild pyramidal syndrome develop, leading to the loss of motor function eventually [1]. Patients with juvenile type developed symptoms at an average age of 8.7 years and were diagnosed at 11.6 years [8]. In the juvenile type, reading, writing, and calculating skills begin to decline after age 7, and speech becomes difficult at a median age of approximately 13 years [9]. The juvenile type may be further divided into an early juvenile type and a late juvenile type, suggesting differences in the onset of main symptoms [10].

The adult type begins with memory deficits and emotional instability. Its progression is slower than that in infantile or juvenile types, and death occurs over decades [1].

Hematopoietic stem cell transplantation (HSCT) has been applied to patients at an early stage, while gene therapy has only been approved in

Abbreviations: ERT, Enzyme replacement therapy; HSCT, Hematopoietic stem cell transplantation; MLD, Metachromatic leukodystrophy; QOL, Quality of life.

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the EU and USA for the treatment of MLD at an early stage [1]. Enzyme replacement therapy (ERT) via intraspinal administration is currently under clinical trials [11]. However, large proteins are restricted to the brain-blood barrier, and intravenous ERT is not expected to effectively treat central nervous system symptoms [12]. HSCT is associated with a risk of complications and is expected to be most effective before symptom onset. HSCT for the patients before the onset has a positive impact on improved survival and reduced cognitive decline compared to the natural progression [13]. Conversely, complications within one year after transplantation can lead to death in patients undergoing HSCT after the neurological onset [13]. Gene therapy has been suggested to be effective in maintaining cognitive and motor development and slowing demyelination in patients with infantile and juvenile types of MLD [14]. However, gene therapy requires treatment before disease onset. Therefore, patients who have already developed MLD are provided supportive care, such as tube feeding and ventilators, as well as symptomatic therapy for neurological symptoms or palliative care. In Japan, attempts are being made to support the lives of children with profound intellectual and multiple disabilities and their families through the use of social services, such as home ventilators and day services.

When considering supportive care for patients with MLD, it is important to focus on the patient's quality of life (QOL) besides developing treatments. It is also necessary to focus on the burden on the caregivers responsible for patient care. Currently, quantitative research on the quality of life and burden on patients with MLD and their families is limited. A study on caregivers of patients with MLD suggested that they are more likely to be anxious and depressed than the general population [15]. Owing to the small number of patients, quantitative research in this area is limited, and it is important to understand the unmet needs of patients and their families through qualitative findings based on interpretivism.

Qualitative research on the experiences of patients with MLD has not been conducted because of their age and cognitive impairments. However, there have been several reports on the parents or caregivers of patients [16]. Parents faced delays in diagnosis because of the rarity and rapid progression of the disease [17]. It also revealed how caregivers felt about the patient's condition before diagnosis [18]. Moreover, Eichler et al. reported that caregivers experience psychological and social burdens [19]. Brown et al. study developed a measure of physical activity in juvenile patients with MLD and suggested that disease progression affects various activities of daily living [20]. Other papers presented parents' experiences of the challenges of accessing insurance for children with rare diseases, including MLD [21].

To the best of our knowledge, no study has comprehensively collected the experiences of patients with MLD and their families from diagnosis to long-term care, nor have they identified issues in the implementation of medical care at home or the relationships with supporters. Particularly, gene therapy or enzyme replacement therapy for the central nervous system for MLD has not yet been approved in Japan, making a radical cure difficult. HSCT is applied in cases diagnosed at an early stage, but it is necessary to deal with the difficulties of managing complications and the gradual progression of symptoms. Thereby, patients with MLD and their families require various types of care and support [6]. While healthcare providers need to have a perspective on maintaining and improving QOL, there is insufficient information on factors that affect QOL. Therefore, we conducted interviews to reveal the experiences of family members of patients with MLD and to consider support in their daily lives.

2. Material and methods

2.1. Study design

The study design is a qualitative descriptive study based on an interpretive perspective [22,23]. Throughout the study, rigor was ensured using an inductive approach in qualitative content analysis [24].

2.2. Participants

This study participants' recruitment was conducted through the Japanese MLD Patient Association and the outpatient department, followed by one of the authors (NS). The target population consisted of family members of patients with MLD aged >18 years old. Family members in this study were recruited to include parents, siblings, and grandparents who lived with patients.

Participants were informed of the purpose of the study verbally and in writing; if they were willing to consider cooperating, they were asked to fill out a web questionnaire via a QR code provided in the recruitment flyer. The web questionnaire asked for the participant's name, relationship with the patient, and contact information that was used to schedule the interview. A research explanation document, consent form, and consent withdrawal form were sent, and the consent form was returned by mail.

2.3. Data collection

Data were collected through semi-structured in-person or online interviews. The interviews were conducted between March and August 2022 in Japanese language. The interviews were recorded with the participants' consent. The first author conducted all the interviews. Questions were answered according to the interview guide (see Appendix). Because MLD is a rare disease and the number of participants was very limited, data collection did not aim to saturate the information but to secure as many participants as possible.

2.4. Data analysis

Verbatim transcripts were created from the recorded interviews and entered into NVivo (version 1.7.1) for analysis. Verbatim transcripts were analyzed using qualitative content analysis [24]. First, the first and second authors carefully read the verbatim transcripts. Verbatim transcripts were coded by the first author. The second author reviewed the code list and verbatim transcripts, and the first and second authors discussed the revisions. The code lists were aggregated into categories and themes based on content similarity. The integration process was discussed with the first and second authors, and the final classification was confirmed by all authors. The first and second authors have experience in conducting qualitative research using a content analysis approach.

2.5. Trustworthiness

The reliability of this study was examined in terms of credibility, dependability, authenticity, and transferability [24]. A literature review was conducted for confirmability, and the researcher's experiences and preconceptions were described. The interviewers were careful not to induce responses in the interviews, and the participants were given adequate time to respond. To ensure dependability, data were collected and analyzed consistently using a qualitative content analysis approach. Information on the classification, from code to theme, is provided in Table 1. The analytical process was as follows: to ensure authenticity, at least one participant quote was cited for each identified theme or category. Consequently, information was added to the parentheses to indicate the intent of the extracted sentences. The verbatim Japanese transcripts were translated into English by a translation company. Participants' information was presented in a non-personally identifiable manner. The inclusion criteria and recruitment methods were also described and discussed for transferability.

Table 1
Characteristics of participants and patients.

No	Participants		Patients				Interview time
	Relationship with patients	Age	Age	Sex	Age of diagnosis	Phenotype	
1	Mother	52 years	20 years	Female	5 years	juvenile	58 min
2	Mother	46 years	16 years	Female	2 years	late-infantile	1h8min
3	Mother	30 years	6 years	Male	2 years	late-infantile	50 min
4	Mother	Unknown	11 years	Male	2 years	late-infantile	1h4min
5	Mother	Unknown	20 years	Female	2 years	late-infantile	1h2m

2.6. Influence of the researcher on the research

The first author is a nurse with no experience in caring for patients with MLD but has cared for patients with adrenoleukodystrophy, a phenotype similar to that of MLD, and for patients with Fabry disease, Gaucher disease, and lysosomal storage diseases. The first author also had experience in caring for children with profound intellectual and multiple disabilities, as would be the case if the symptoms of MLD were to progress. This may have been advantageous for obtaining information on the challenges and difficulties faced by patients with MLD and their families. However, this may have led participants to make the content of the interviews relevant to nursing and caregiving.

The last author is a pediatric neurologist specializing in lysosomal storage disorders, including MLD. The last author provided supervision from a medical perspective throughout the process, from the study design to analysis.

2.7. Ethical considerations

This study was approved by the Research Ethics Committee of Osaka Aoyama University (No.0217). Written and oral explanations were provided to the participants, and informed consent was obtained. The participants were informed that their cooperation in the research was voluntary, that they could withdraw their consent, that their personal information would be protected, and that the data would be properly stored and destroyed. Participants received 1000 yen as a reward for their cooperation. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Because MLD is a rare disease, only minimal information on the characteristics of the participants is presented in this paper to avoid identification of the participants.

3. Results

3.1. Characteristics of the participants

We recruited family members of patients with MLD to cooperate in the research, and five mothers were contacted and interviewed. Mothers' ages ranged from 30s to 50s. Patient ages ranged from 6 to 20 years, with a mean age of 14.6 years, and three were girls. Four patients were diagnosed at age 2 and one at age 5. The phenotypes of the participants' children were late infantile in four participants and juvenile in one participant (Table 1).

3.2. Interview overview

All interviews were conducted without interruption, and the average interview duration was 60 min.

Verbatim interview transcripts were classified into 81 codes. The codes were aggregated into 15 categories and 3 themes based on content similarity. The three themes were challenges of life for the patients, challenges in the healthcare system, and challenges of family function (Tables 2–4).

Table 2
Theme 1: Challenges of life for patients, categories, and participant's voice.

Category	Participant's voice
Disease progression	"After a while, talking becomes a struggle, and a little later, walking turns into a challenge. A bit later, even eating gets tough. And then, well, even using the bathroom becomes a real hassle. It is like tumbling down a hill, you know, or more like suddenly the illness just nosedives, like falling off a cliff." (No.1, mother of juvenile type patient)
Complication progression	"And then, uh, the tension in my body was just, like, crazy strong, and umm, my hand would just, you know, shoot out in front of me, both of them, just like that, extended out, bam, like this. Uh, like, when I try to do something, too much force gets applied, and my hand just ends up staying out there, like boom, left extended." (No.1, mother of juvenile type patient)
	"Well, [they would be like], 'Hey, it is becoming tough for you to walk,' and then they would suggest wearing a leg brace, or you know, some kind of support. So they would go ahead and make this brace and put it on foot, and then, well, oh, they would come up with stuff to help with walking, like support and all that jazz." (No.1, mother of juvenile type patient)
Coordination of life support	"Yeah, well, I noticed that taking baths was harder and harder. But you know, I was not in trouble with the other stuff, to be honest." (No.3, mother of late-infantile type patient)
Patient communication	"And, well, this person, um, they really express themselves fully, yes, like raising or lowering their pulse. It is not like just saying there is phlegm stuck or something, but it is like they have looked into it, and they know that a certain sound happens when they do this, and then, lo and behold, [their] mother comes. Yeah, it is like they have set up a saturation monitor instead of using their voice, which is kind of creative." (No.2, mother of late-infantile type patient)
Interaction with the outside world	"Ultimately, all the helpers and nurses interacting with this person are adults, right? So, spending time with individuals from the same generation is super important, you know, because the way they communicate is just totally different." (No.2, mother of late-infantile type patient)
School-related issues	"Yes, that is right. I mean, when I say they are going to school, [they] put on this really nice face, and, uh, I figured it must be a bit tough for them, but I am all like, 'Let me do this!' And, um, well, when they come back, they are all happy and stuff. So, yeah, I kind of got this feeling that they were genuinely glad they went." (No.4, mother of late-infantile type patient)
	"Yes, that is right. It is extreme, but, well, once the respirator is on, well, um, our school, um, it became home [schooling]." (No.4, mother of late-infantile type patient)

3.3. Theme 1: Challenges of life for the patients

This theme comprised six categories: disease progression, complication progression, coordination of life support, patient communication, interactions with the outside world, and school-related issues (Table 2).

The parents were concerned about disease progression, especially the rapid progression after onset, and the patient's inability to do the

Table 3
Theme 2: Challenges in the health care system, categories, and participant's voice.

Category	Participant's voice
Diagnostic process	"We had various developmental tests and functional training at the rehabilitation center, but, well, um, uh, the intelligence was a bit lower than the normal, um, age. They were not able to do what they were able to do before. Um, the pathological factors were really strong; at least, that is what the doctor told me. So, yeah, I got this pretty strong recommendation to get some proper check-ups done at the hospital, you know." (No.1, mother of juvenile type patient) "I was like, 'Hey, let us head over to the pediatrician and, uh, well, get the tests done.' So, we were all set for the examination, but then, well, they were slowly not able to walk." (No.4, mother of late-infantile type patient)
Expectations for treatment	"Um, we went to Australia and started a clinical trial from there." (No. 4, mother of late-infantile type patient) "And I was like, 'I cannot make it.' After watching various videos of mucopolysaccharidosis, I wondered if there were any helpers in the United States. It was like, seriously? In the United States, the two [of us], me and them? No way. I mean, I had this idea that I wanted to help them heal, but after seeing all that, they said, no, they could not do it." (No. 2, mother of late-infantile type patient) "It is kind of like, [I] want it to heal, but it cannot heal, yeah. The treatment medicine, too, you know, [I] would like to see if there is any change once I start using it. It is probably like, you know, even when using it, it will take time no matter what. Rather than that, um, how to improve the quality of life, how to spend time in a fun way, why not think about that, is the thought." (No.2, mother of late-infantile type patient)
Relationships with medical personnel	"I trusted the doctor's polite exchanges, and [they] would say, "Oh, let us go to XXX University now." (No.2, mother of late-infantile type patient)
Lack of social resources	"There were two young individuals at the nearest hospital. Yeah. And it was not even a neurologist. And, well, they could probably exchange cannulae, but during various consultations, it was just like, you just had to have [the medical staff] learn something." (No.2, mother of late-infantile type patient) "Well, yeah, coming this far, it had to be done, but "what will happen?" was the thought; it would be difficult. Ultimately, there were many former nurses, like the moms of little ones, yeah. So, well, [she is] one nurse mom, and I am a kindergarten teacher, so [I] could take care of her. "(No.2, mother of late-infantile type patient)
Transition challenges	"After all, well, it is a part that anybody would, well, get anxious about, and things like after I died first and stuff." (No.5, mother of late-infantile type patient) "Especially, well, once [one is] alone, for me, for example, if something happens, then there would be nobody to look after [them], and it would be a problem, and once you start thinking of that, I thought about dropping [them] off and using [the facility] fully." (No.3, mother of late-infantile type patient)

things they used to be able to do. As the disease progresses, muscle tone, dystonia, scoliosis, and joint contractures appear. Muscle tension is difficult to control, even with Botox injections or by adjusting body position.

Another complication with the progression of the disease is joint contracture, which results in an inability to bend the joint and dislocation of the hip joint. In this situation, the parents tried to use orthotics to help the patients perform as many activities as possible.

Thus, as the patient's activities of daily living (ADLs) declined, the parents used various lifestyle supports. Besides helping patients bathe and transfer to home, they also use day rehabilitation and day services to enrich their lives. However, this also implies that the patient's growing body made it difficult for the parents to care for the patient alone.

Table 4
Theme 3: Challenges of family function, categories, and participant's voice.

Category	Participant's voice
Increased care	"Yes. It depends on the situation, but when there is a lot [of respiration], it is very frequent, but on average, it is kind of like once every day, oh, but every hour, maybe." (No.4, mother of late-infantile type patient) "It was just really challenging to have [them] take the medicine by mouth or eat food. And well, ever since the gastric fistula was formed, the difficulty of eating or, just the difficulty of having [them] take medicine was just, really, well, sometimes it improved, um, and sometimes reduced, and, yes, I am really glad the surgery was done. Yes, I was beginning to think a bit about the gastric fistula; yeah, it should have been done earlier." (No.1, mother of juvenile type patient)
Impact on family life	"When, well, placing this kid in the car, and moving [them] to the vehicle, and moving, well, preparing the things, then moving to the car, that took a lot of time. When having them sit and then moving, [they] would start coughing up phlegm or something." (No.4, mother of late-infantile type patient) "I am caring for the younger sister so well; the older sister has a hard time. And, well, when the younger brother was born, well, YYY [patient] took a lot of work. So the younger brother was often neglected, and well, thinking about it now, those sorts of things happened when they were young. That kind of thing between the siblings." (No.5, mother of late-infantile type patient) "Yes, I fully use the service. Don't you think it is better when [the parent] works?" (No.3, mother of late-infantile type patient)
Family relationships	"[My] husband will inject almost every morning and afternoon. And we take turns, like an assembly line. So, my husband thickens it and puts it in this person. Then I would make and take breakfast; we kept taking turns. And I also prepare lunch, and my husband eats first, and I eat while ZZZ [patient] eats. Something like that. Since it is like that, we are working together as a couple." (No.2, mother of late-infantile type patient)
Impact on reproductive health	"There is an older brother, but, well, umm, [they] said that there is a disease called a congenital metabolic disorder, um, a genetic factor, present. So, in the future, um, well, it might be unrelated to finding work, but when getting married, um, if there was that kind of sibling, kind of, um, like, then even things that are going well, um, will not go well. That kind of worry was present [in my husband]." (No.1, mother of juvenile type patient)

Furthermore, communication with the patient was one of the parental concerns. The patients' spontaneous expression decreased. As conversations and facial expressions that were possible in the past disappeared, parents tried to understand the patient's feelings based on monitor readings and heart rate fluctuations.

Even as the number of things they could do gradually decreased, the parents believed that interacting with others outside the family was important. Although going out was difficult, attending kindergarten before the onset of the disease and socializing with other children and parents with the same disease improved the patient's QOL.

Schooling was especially important as it allowed them to engage with their peers, and parents found that the patients looked forward to going to school. However, parents also spoke of school-related issues. Patients requiring medical care, such as a ventilator, needed to be accompanied by their parents or were forced to change to home-visiting education, which reduced their opportunities to interact with their peers.

3.4. Theme 2: Challenges in the healthcare system

This theme consisted of five categories: diagnostic processes, expectations of treatment, relationships with medical personnel, lack of social resources, and transition challenges (Table 3).

During the diagnostic process, patients with MLD and their parents began to engage in medical care. Parents who noticed developmental delays and an unsteady gait were told that a close examination at the hospital was necessary. The doctor at the hospital worked closely with the specialist to obtain the diagnosis without delay. However, the disease progressed while they were undergoing tests and waiting for the results.

Parents of diagnosed patients were expected and anxious about the treatment of the disease. Immediately after receiving the diagnosis, parents sought clinical trials and other treatment options to help the patients. Some families went with patients and their mothers outside Japan for clinical trials conducted elsewhere, whereas others gave up on the idea of going outside Japan because it would be too difficult. Conversely, in patients with disease progression, parents were more focused on improving their QOL than on treatment.

Patients and parents also developed relationships with various healthcare professionals during treatment and support. Parents felt that the honesty of medical personnel and the sharing of professional knowledge were beneficial. However, few physicians and nurses had experience in caring for patients with MLD, and medical facilities specializing in this field were not located near where they lived.

Another challenge was the lack of support facilities besides human resources in rural areas. In some cases, especially for patients with advanced symptoms and severe disabilities, no facilities would accept them, and parents sometimes set up their own facilities.

The challenges of transitioning to adulthood to receive institutional services were discussed. Parents had to deal with the greater physical burden and find a facility in advance where they could stay after their patient's death. This category did not focus on parental burden but rather expressed concern about the future use of the facility.

3.5. Theme 3: Challenges of family function

This theme consisted of four categories: increased care, impact on family life, family relationships, and impact on reproductive health. Parents were concerned about the future caregivers of the patients as they aged (Table 4).

Disease progression was burdensome for the parents. Increased suctioning, tube feeding, and voiding care had a significant impact on family life. However, it was not only the increased burden but also learning the correct technique and the introduction of gastric lavage that lowered the burden of care.

The family's lifestyle, which includes going out, working, and friendships, was limited because someone had to be in charge of patient care. The family included not only the parents but also the patient's siblings and grandparents. Conversely, the mother, who was primarily responsible for care, wanted to work and attempted to return to work while taking advantage of various forms of support.

Additionally, family members coordinated and handled their roles in life, thus requiring help with the care of the patient. The mothers spoke about the relationships between family members. Parents took turns providing care and felt that it was important to exchange information with each other.

Finally, the hereditary disease MLD also affects the reproductive health of the families. Particularly, parents were concerned about the impact of their siblings' test results on their marriage.

4. Discussion

To the best of our knowledge, this is the first report to reveal the experiences of parents of patients with MLD in Japan. Although a few similar studies have been reported overseas, it is significant that we were able to clarify the findings in Japan, as there is an increase in the number of surviving children with profound intellectual and multiple disabilities. The aggregated findings encompassed three aspects: patient QOL, the healthcare system, and family support. This highlighted items to comprehensively assess the lives of patients with MLD and their families and to consider support that can lead to improved QOL.

4.1. Support for patients

MLD is a progressive disease that results in a gradual decline in physical and cognitive functions to varying degrees depending on the patient and disease type [1]. This was noted in interviews with mothers, which revealed changes and challenges in their lives due to disease progression and a decline in ADLs. The decline in physical function associated with the progression of the disease is weekly or monthly and requires assistance by caregivers [20]. Parents see patients who gradually lose the ability to walk, eat, and excrete [19]. Complications such as scoliosis and muscle strain also have a significant impact on patients' lives. Mothers also had a role in coordinating to ensure that appropriate support was provided for the changing patient's condition.

A mother was also concerned about communication difficulties due to cognitive and physical function decline. Patient cohort studies have reported that patients gradually lose language function as their symptoms progress, especially in the late infantile type [9]. Caregivers believe it is worthwhile to slow the decline in the physical function of children with MLD through treatments such as ERT [25]. In the participant's narrative, a mother believed that the low heart rate and oxygen saturation on the monitor and alarm sounds were forms of expression of the patient. Therefore, when supporting patients with MLD, careful consideration is required to adjust care according to disease progression and to detect minor changes in facial expressions and muscle tone in patients who have lost the ability to speak.

One of the strengths of this study is its ability to reveal the social experiences of patients with MLD after disease progression. A mother mentioned concerns about the patient's relationships with others. Studies on Krabbe disease, a leukodystrophy similar to MLD, have shown a negative impact of the severe type with infantile onset on communication and school attendance [26]. Moreover, the burden of getting patients out of the house increases as their disability progresses, and they require suction and ventilators. In some cases, schools were unable to accommodate children with medical care needs, as the participants in this study described. However, even for children with severe disabilities, interactions with children of the same age and with others outside the family are important for QOL. Just as general QOL measures for children include school and friendships [27], social enrichment should also be considered when assessing the QOL of patients with MLD.

4.2. Improvement of the healthcare system

Early diagnosis is important, as it is preferable to treat patients with MLD as early as possible, including HSCT [1]. The earliest method for identifying patients is newborn screening. One study reported that parents had a positive view of early diagnosis of MLD through newborn screening [17]. Many of the participants in this study were referred to specialists relatively early after disease onset and were able to receive an early diagnosis. However, waiting for a diagnosis can be stressful for parents [28]. In addition to presenting a medical diagnosis and the availability of treatment, medical staff must be willing to listen to the family's psychological perceptions and struggles and support them in their lives. A good relationship with a healthcare provider may ease parental anxiety [28]. HSCT, ERT, and gene therapy should start treatment for MLD [12]. Family members traveled abroad with the patient to receive treatment that had not been approved in Japan. Healthcare and the government need to close the healthcare gap so patients can benefit from newly developed therapies.

By contrast, in patients with disease progression, parents believed that maintaining daily QOL was more important than treatment. Participants also mentioned the paucity of social resources. The lack of access to specialized hospitals and medical personnel in a region makes it more difficult to receive a diagnosis [29]. Also, parents felt there was a

lack of services tailored to their children's needs, such as rehabilitation and home nursing services [28]. Patients with MLD with an advanced disease require a variety of support. It is necessary to develop basic medical facilities and train medical personnel with the knowledge of MLD so that patients and their families can receive appropriate services without feeling any differences in their place of residence.

Reports on medical costs for patients with leukodystrophy indicate that the average cost per patient is 24,495 USD/year, which is even higher if hospitalization is required for HSCT or other treatments [30]. In addition, the cost of hospitalization for patients with leukodystrophy is said to be 2–15 times that of general pediatric patients; therefore, early diagnosis and appropriate treatment are meaningful not only to the patients themselves but also to society as a whole [31].

4.3. Support for family members

With the progression of MLD, families are required to take on a variety of care responsibilities, which they find burdensome. Participants also spoke about the increasing burden of daily care. The most common care for patients with MLD includes positioning adjustment, suctioning, tube feeding, voiding, and seizure care [32]. Results from a survey of Japanese late infantile patients also showed that 60% used enteral nutrition and 13.3% used an invasive ventilator [6]. Therefore, there is a need for education to enable families to acquire appropriate techniques for care and support to reduce their burden so that they can continue to provide care.

Family life is restricted because of patient care. In this regard, the mother spoke of the difficulty of traveling with the patient and of the mother's employment. Parents of children with severe disabilities complain about the difficulty of finding work and are frustrated [33]. Family outings and friendships may also be affected, and healthcare providers should focus on the QOL of both the family and the patient. Cooperation between husbands and wives is important in the care of children with disabilities. It has been suggested that, when caring for children with PIMD in Japan, it is important for fathers to participate in the care of their children and for couples to cooperate with each other [34]. As patients are diagnosed and require care, support is needed to re-coordinate family functions as the patient is diagnosed and requires care [35,36]. Therefore, it is important to have a system in place to ensure that healthcare providers are listened about their family problems as outpatients, and that information about social resources to reduce the burden of care is appropriately provided.

We also need to look at siblings and parents. Parents' focus on caring for patients with MLD may lead to less attention being paid to their siblings. It has been suggested that the siblings of children with disabilities may experience distress in their relationships with friends [37]. While in some families siblings take on the role of care providers, some parents worry that they might be patients or carriers of the disease and that the impact would extend to future marriages. This was expressed in the participant's narrative as anxiety about sibling marriage and the possibility of being a carrier of a hereditary disease. Therefore, it is important to collaborate with genetic counselors to test and diagnose parents and siblings. It may also be necessary to understand the concerns of siblings and coordinate their support as individuals.

4.4. Limitation

Given the effects of MLD on cognitive function, it is difficult to study these patients. Because only mothers were included in this study, it was impossible to collect information on the experiences of fathers, siblings, or other family members. To identify events in a patient's life, it is advisable also to investigate the experiences of those around the patient, such as family members other than the mother, medical personnel, and educational personnel. We also asked family members to cooperate in the study through their mothers, but none of them indicated a willingness to cooperate. Moreover, due to the rarity of MLD, the number of study participants was quite limited, making it difficult to recruit new families.

Eighty percent of the patients in this study had the late infantile form. This may have biased the responses to the research toward those related to the burden of care. Additionally, the children in this study were either late-infant or juvenile patients, and we were unable to collect information on adult patients and their families. As differences in experience according to disease type and age are important considerations, it is desirable to increase the number of participants and accumulate information on the experiences of patients and their families.

It is believed that the number of participants was small and that information saturation had not yet been reached. However, this is unavoidable because MLD is a rare disease. To overcome this challenge, the number of participants can be secured through international collaboration, or sufficient information can be obtained through multiple or longitudinal qualitative research.

5. Conclusions

The experiences of parents of Japanese patients with MLD were evident. Patients experienced challenges in diagnosis, treatment, daily life, and social life and needed support as the disease progressed. Furthermore, the medical system for proper diagnosis and support is challenging, and resources are lacking to support patients with MLD, especially after the disorder becomes more severe. Finally, healthcare providers are expected to help coordinate the roles of family members responsible for patient care. Note that while family members are the patients' caregivers, they may also be carriers of genetic mutations.

Ethical considerations

This study was approved by the Research Ethics Committee of Osaka Aoyama University (No.0217). Written and oral explanations were provided to the participants, and informed consent was obtained. The participants were informed that their cooperation in the research was voluntary, that they could withdraw their consent, that their personal information would be protected, and that the data would be properly stored and destroyed. Participants received 1000 yen as a reward for their cooperation. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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CRediT authorship contribution statement

Yuta Koto: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Project administration, Funding acquisition. **Wakana Yamashita:** Validation, Formal analysis, Writing – review & editing. **Norio Sakai:** Conceptualization, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

YK has received research grants and honoraria from Takeda Pharmaceutical Company, Ltd.. NS received research grants and honoraria for lectures from Takeda Pharmaceutical Company, Ltd.. WY declares no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Interview guide

Background of participants
Age, gender, relationships to patients

Background of patients
What is the age at which the patient was diagnosed?
What is the course of the patient's symptoms to date?
What treatment has the patient received so far?

Main question
As a family, what are some of the things that you think are affected by disease in your and patient's daily life? Please tell me even if it's in the past.

Subsidiary question[a]
Have there been times when you think symptoms have made life difficult for patients and their families?
What impact has this had on the patient's student life?
What impact has this had on your employment?
Do you experience any difficulties in your relationships with friends or colleagues?
What impact did this have on your marriage and childbirth?
How does the treatment method affect your life?

[a] Subsidiary questions were asked as appropriate if the participant seemed reluctant to answer the main question or if the interviewee thought that only brief answers had been given and sufficient data had not been obtained.

Appendix B. Category and code classification for Theme 1: Challenges of life for patients

Categories	Codes
Disease progression	Rapid progression
	Gradual loss of ability to do the things patients used to be able to do
	Anxiety about disease progression
	Progression that does not stop even after transplantation
	Seizures
	Difficulty in managing body temperature
Complication progression	Muscle tone
	Scoliosis
	Joint contractures and dislocations
	Dystonia
Coordination of life support	Daily living care
	Bathing assistance
	Use of day service
	Use of short stay
	Use of residential facilities
	Use of day rehabilitation
Patient communication	Decreased vision
	Sensitivity to touch
	Hearing sensitivity
	Loss of responsiveness
	Children's own way of expressing themself
	What makes patient's happy
Interaction with the outside world	Interaction with others
	Behavioral restrictions due to tracheostomy
	Interaction with patient groups and close friends
	Sharing information via video
School-related issues	Relationship with school
	Burden of commuting to school
	Visiting education

Appendix C. Category and code classification for Theme 2: Challenges in the healthcare system

Categories	Codes
Diagnostic process	Developmental delay
	Unsteady gait
	Examination for definitive diagnosis
	Smooth diagnosis
	Disease notification
	Progression between onset and diagnosis
	Expectations for newborn screening
Expectations for treatment	Seek treatment options
	Clinical trials
	Adjustment of internal medication
	Prioritizing the quality of life over treatment
Relationships with medical personnel	Relationship with physicians
	Relationship with nurses
	Relationship with supporters
	Cooperation with consultation support specialists
	Lack of medical professionals with expertise
Lack of social resources	Lack of facilities that can take care of patients
	Not being accepted due to progression
	Issues in rural areas
	Home nursing and medical care
	Parents making facilities
	Complexity of administrative procedures
Transition challenges	Transition to adult department
	Seeing doctor other than a pediatrician
	Anxiety about aging and death of parents

Appendix D. Category and code classification for Theme 3: Challenges of family function

Categories	Codes
Increased care	Oral intake
	Tube feeding
	Pulmonary aspiration
	Suction
	Tracheotomy
	Tracheal obstruction
	Use of ventilator
	Central intravenous nutrition
	Excretion care
	Responding to epileptic seizures
	Burden of hospital visit
Impact on family life	Care is burdensome for parents
	Family lifestyle changes
	Burden of going out
	Parents' inability to go out
	Limitations on parent's employment
	Parent's friendships
	Mother and child sharing a room during hospitalization
	Cooperation of grandparents
	Adjustment of housing environment
	Burden on siblings
Family relationships	Relationship with family
	Sharing information within the family
	Dissatisfaction with father
Impact on reproductive health	Family planning
	Siblings get tested
	Sibling marriage

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