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Original article

Characteristics of Japanese patients with X-linked adrenoleukodystrophy and concerns of their families from the 1st registry system

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Abstract

Objective: Early diagnosis is critical in achieving the best outcome following hematopoietic stem cell transplantation (HSCT) for X-linked adrenoleukodystrophy (X-ALD). We used a questionnaire to gather detailed clinical information and information regarding the anxieties of patients' families using the registry system for X-ALD.

Methods: We and the patients' families established the registry system for X-ALD in Japan. We created a questionnaire and distributed it to the patients' families.

Results: Questionnaire data from 28 patients were collected. The median age at enrollment was 14.5 years. The most common type of X-ALD was the childhood cerebral form (22 patients, 78.6%). The median age at symptom onset was 7.4 years. Frequently reported initial observations were behavior or character changes (46.4%), gait disturbances (42.9%), strabismus (39.3%), reduced academic ability (32.1%), failing vision (21.4%), a positive family history (21.4%), clumsiness (17.9%), hearing disturbances (17.9%), convulsions (10.7%), and suspected psychiatric disorders (10.7%). The median duration from symptom onset to diagnosis was 12 months. The families of 12 patients (42.9%) with X-ALD who received HSCT were satisfied regardless of its effectiveness. Common concerns of patients' families were worries regarding heritability of X-ALD (78.6%), present symptoms (57.1%), frequent hospital visits (42.9%), problems at school or work (42.9%), economic issues (35.7%), and limited information regarding X-ALD (32.1%).

Conclusion: This is the first study clarifying the clinical characteristics of X-ALD and the concerns of patients' families using the registry system. Investigation of rare diseases using registry systems is very valuable for the understanding of such conditions.

Keywords: X-linked adrenoleukodystrophy; X-ALD family members; Registry system; Initial symptoms; Hematopoietic stem cell transplantation

1. Introduction

X-linked adrenoleukodystrophy (X-ALD, OMIM #300100) is a progressive neurodegenerative disorder.

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Mutation of the adenosine triphosphate binding cassette, subfamily D, member 1 (*ABCD1*) gene located on chromosome Xq28 [1] causes X-ALD and results in the accumulation of saturated very long-chain fatty acids in tissues and body fluids [2,3]. This in turn leads to demyelination in the central nervous system and adrenocortical insufficiency. The clinical features of X-ALD include various neurological disturbances, such as intellectual, behavioral, psychological, gait, visual, hearing, and swallowing disturbances. The incidence of X-ALD in men is estimated to be between 1:20,000 and 1:50,000 of the total population [3]. In Japan, it is estimated that the number of X-ALD patients is 200. There are eight distinct phenotypes of X-ALD, as follows: the childhood cerebral form (CCALD), adolescent form, adult form, olivo-ponto-cerebellar form (OPC) with cerebellar ataxia, adrenomyeloneuropathy (AMN), Addison's disease, heterozygote female form, and presymptomatic form. The most common phenotype is CCALD, and individuals with CCALD express the most severe neurological disturbances, including progressive intellectual, behavioral, visual, hearing, and gait disturbances until the age of 4–8 years. Patients with CCALD usually progress to a vegetative state within a few years after onset. Although several therapeutic approaches have been reported, hematopoietic stem cell transplantation (HSCT) has been the only effective therapy for individuals with X-ALD with neurological involvement [4–7]. Recently, the effectiveness of *ex vivo* gene therapy using CD34+ cells transduced with a lentiviral vector containing the *ABCD1* gene has been reported in patients with X-ALD [8]. To achieve the maximum clinical benefit, HSCT and gene therapy should be performed at very early stages of the disease. Thus, early diagnosis prior to the occurrence of irreversible pathogenic central nervous system changes is essential.

Logically, diagnosing X-ALD in the very early stages requires a full understanding of the initial symptoms, and such symptoms are usually recognized first by parents. An X-ALD family association has been established in Japan. However, there have not been any registry systems for patients with X-ALD.

To better understand the characteristics of patients with X-ALD and the concerns of their families, we and the X-ALD family association first generated a registry system for X-ALD and collected clinical information from patients' families. This registration system can also be used to elucidate the concerns of the families, which should not be ignored by medical providers. The aim of this study was to establish the usefulness of this registry system and to investigate the clinical characteristics, and particularly the initial symptoms, of X-ALD in Japanese patients. We also aimed to improve our understanding of the most common anxieties of patients with X-ALD and their families.

2. Subjects and methods

2.1. Registration system

We established the Japan Registration System for Metabolic & Inherited diseases (JaSMIn) for more than 50 inherited metabolic diseases, including X-ALD, in 2013. In 2014, a questionnaire in Japanese (Supplementary material in English) was created based on input from experts in inherited metabolic diseases, pediatricians, pediatric neurologists, neurologist, genetic counselors, and family members of patients with X-ALD. The questionnaire included questions regarding the patient's name, birth date, the doctor's name, the hospital name, initial observations, age of onset, age of diagnosis, current symptom list, list of therapeutics used, list of nursing procedures, effectiveness of HSCT, satisfaction level following HSCT, complications, gene analysis, familial medical history, school, work, activities of daily living, and concerns. We held numerous meetings to create the questionnaire and avoided using technical and medical terms in the questionnaire so that patients and their families could easily understand it. The questionnaire in its final form was distributed to 45 patients with X-ALD in the Japanese ALD Family Association (Association for the future of ALD patients, http://ald-family.com) via this new registration system. The questionnaire allowed us to gather precise data regarding the initial observation leading to a diagnosis of X-ALD in the patients, age of onset, duration from onset to diagnosis, satisfaction levels following HSCT, and the anxieties and concerns of the patients' families, excluding patient's names.

2.2. Ethical issues

This study was approved by the Institutional Review Board or Ethics Committee of the two participating hospitals/institutes (approval number from The Jikei University School of Medicine: [26-337]7843, approval number from the National Center for Child Health and Development: 619). We conformed to the Japanese confidentiality guidelines. Written consent was obtained from all patients, their parents or family.

3. Results

3.1. Demographics and characteristics of patients in the X-ALD registry

The characteristics of all included patients are summarized in the Table 1. Twenty-eight questionnaires were returned and analyzed. The most common form of X-ALD was CCLAD (n = 22, 78.6%), followed by the presymptomatic form (n = 2, 7.1%), adolescent form (n = 1, 3.6%), adult form (n = 1, 3.6%), OPC with

Table 1
Demographics and characteristics of the X-ALD registry patients. X-ALD: X-linked adrenoleukodystrophy, CCALD: childhood cerebral form, OPC: olivo-ponto-cerebellar from, AMN: adrenomyeloneuropathy, HSCT: haematopoietic stem cell transplantation. Date of this investigation: 04/23/2014.

Disease type, Number of patients, n (%)	
{Total number of patients: 28}	
CCALD	22 (78.6)
Adolescent	1 (3.6)
Adult	1 (3.6)
OPC	1 (3.6)
AMN	1 (3.6)
Addison's	0 (0.0)
Heterozygote female	0 (0.0)
Presymtomatic	2 (7.1)
Age at enrollment, n (%)	
{Median age at enrollment: 14.5 years (range 7–63)}	
0–9 years	5 (17.9)
10–19 years	17 (60.7)
20–29 years	4 (14.3)
30–39 years	0 (0.0)
40–49 years	1 (3.6)
50–59 years	0 (0.0)
60–69 years	1 (3.6)
Age of initial X-ALD symptoms, n (%)	
{Median age of symptom onset: 7.9 years (range 2–41)}	
Presymptomatic	2 (7.1)
0–9 years	20 (71.4)
10–19 years	3 (10.7)
20–29 years	1 (3.6)
30–39 years	1 (3.6)
40–49 years	1 (3.6)
Duration between first X-ALD symptoms and diagnosis, n (%)	
{Median duration from onset to diagnosis: 1 year}	
Presymptomatic	3 (10.7)
<3 months	2 (7.1)
3–5 months	3 (10.7)
6–11 months	6 (21.4)
12–59 months	13 (46.4)
60 < months	1 (3.6)
Gene analysis, n (%)	
Mutation positive	19 (67.9)
Mutation negative	2 (7.1)
During analysis	3 (10.7)
No analysis	1 (3.6)
Unknown	1 (3.6)
No response	2 (7.1)
Treatments, n (%)	
Anti epileptic drugs	14 (50.0)
HSCT	12 (42.9)
Lorenzo's oil	9 (32.1)
Steroids	4 (14.3)
Impression of efficacy of HSCT, n (%)	
{Total number of patients receiving HSCT: 12}	
Improved	2 (16.7)
Deteriorated	5 (41.7)
Unchanged	2 (16.7)
Unknown	3 (25.0)
Daily living conditions, n (%)	
Needs support for all daily living activities	18 (64.3)
Needs help with some daily living activities	2 (7.1)
Can care for themselves with slight difficulties	3 (10.7)
Does not require any assistance for daily living activities	3 (10.7)

cerebellar ataxia (n = 1, 3.6%), and AMN with spinal cord disturbance (n = 1, 3.6%). No cases of Addison's disease with adrenal insufficiency (AI) or heterozygote female X-ALD were reported.

The median age of patients was 14.5 years (range, 7–63 years) at the time of enrollment. The peak age distribution at the time of enrollment was between 10 and 19 years. The median age of patients at the time of symptom onset was 7.9 years (range, 2–41 years), with the peak age of patients at the time of symptom onset being between 0 and 9 years. The median duration from the first onset of symptoms to a definitive diagnosis was 12 months, and only 14 cases (50%) were diagnosed within 12 months after symptom onset.

Gene analysis was performed in 24 patients (85.7%), and the *ABCD1* gene mutation was identified in 19 patients (67.9%). Eighteen patients (64.3%) had a positive family history of X-ALD.

Fourteen patients (50%) were being treated with antiepileptic drugs. Twelve patients (42.9%) underwent HSCT. Lorenzo's oil was administered to nine patients (32.1%), and four patients (14.3%) received steroid supplementation.

We made inquiries regarding the perceived efficacy of and satisfaction levels following HSCT in patients with X-ALD or their families. Of the 12 patients who received transplantation, the families of two patients (16.7%) were confident that the patient had improved, as brain magnetic resonance imaging (MRI) had revealed improvements. The families of another two patients (16.7%) felt that the patient's medical condition had stabilized, and the families of five patients (41.6%) felt that the patient had deteriorated after HSCT. However, despite disease progression, the families of all 12 patients who underwent HSCT, including the eight patients who required total medical assistance, did not regret HSCT.

Eighteen patients (64.3%) required support for all activities of daily living, two patients (7.1%) required help with some activities of daily living, four patients (14.3%) could care for themselves with slight difficulties, and three patients (10.7%) did not require any assistance for activities of daily living.

3.2. Initial symptoms of X-ALD

The initial signs at onset (Fig. 1a) included changes in behavior or character (46.4%), gait disturbances (42.9%), strabismus (39.3%), a decline in academic ability (32.1%), failing vision (21.4%), a positive familial history (21.4%), clumsiness (17.9%), hearing disturbances (17.9%), convulsions (10.7%), suspected psychiatric disorders (10.7%), pigmentation (3.6%), and AI (3.6%). Initial symptoms were most frequently recognized by patients' families (67.9%), followed by a school teacher,

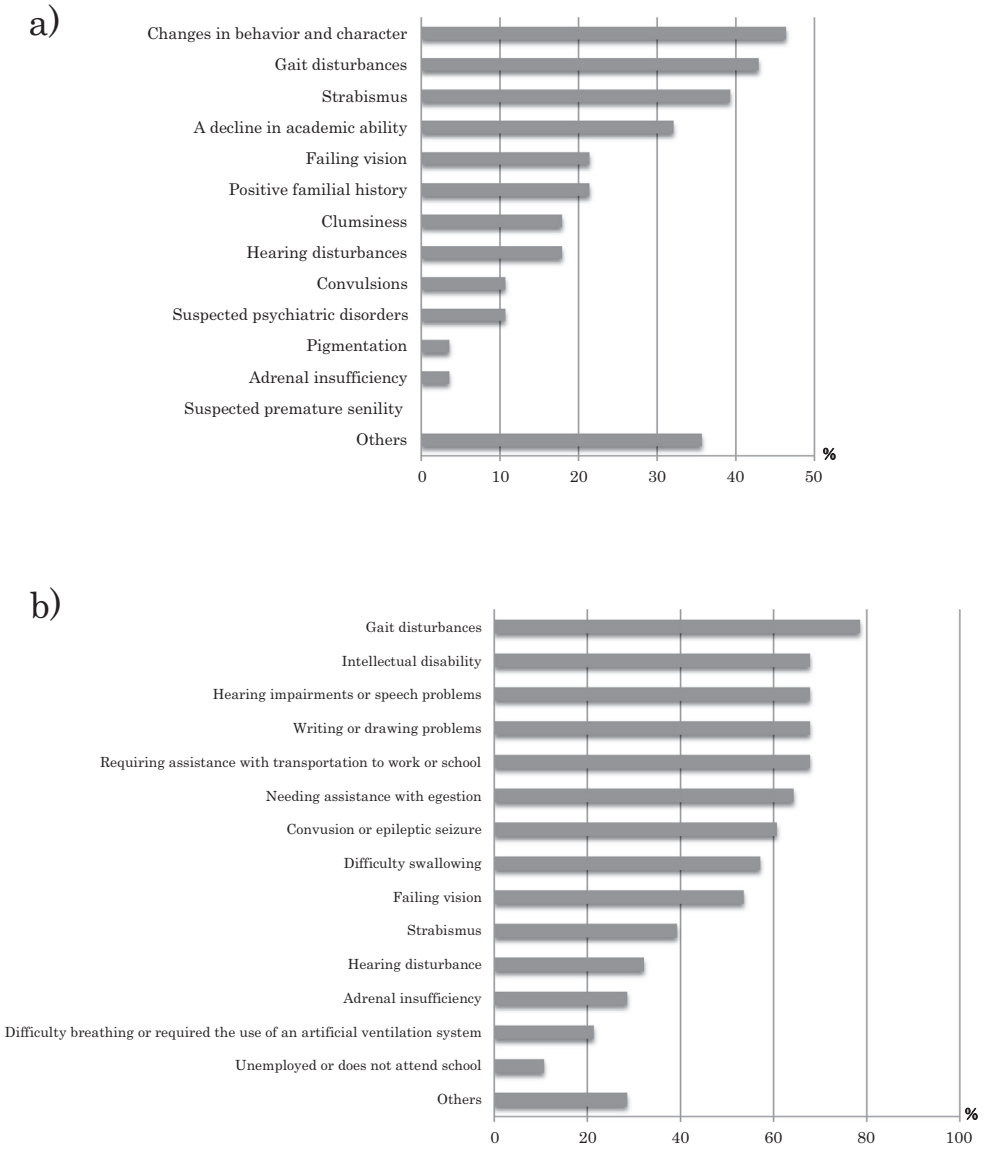

Fig. 1. Symptoms at the time of onset and enrollment of patients with X-ALD. (a) Initial symptoms of patients with X-ALD. (b) Symptoms at the time of enrollment. Both graphs show the percentages of patients with each symptom.

friend, colleague, primary doctor, or the patient him/herself (3.6% each).

3.3. Symptoms at the time of enrollment

The most frequent symptoms at the time of enrollment (Fig. 1b) were gait disturbances (78.6%), followed by intellectual disability, hearing impairments or speech problems, writing or drawing problems, needing assistance with transportation to work or school (67.9% each), requiring assistance with egestion (64.3%), convulsion or epileptic seizures (60.7%), difficulty swallowing (57.1%), and failing vision (53.6%). From onset to enrollment, the frequency of gait disturbances, failing vision, hearing loss, convulsions, and AI were elevated over time. This demonstrates the progressive nature of X-ALD. Interestingly, the frequency of strabismus was not affected by age.

3.4. Current issues and concerns

Patients and their families expressed their current concerns by answering nine questions, the results of which are shown in Fig. 2. The most frequent source of anxiety for patients and their families was heredity issues (78.6%). The second most frequent source of anxiety was the patient's present symptoms (57.1%). Frequent hospital visits (42.9%), problems at school or work (42.9%), economic issues (35.7%), and limited availability of information regarding the disease (32.1%) were also common concerns of patients and their families.

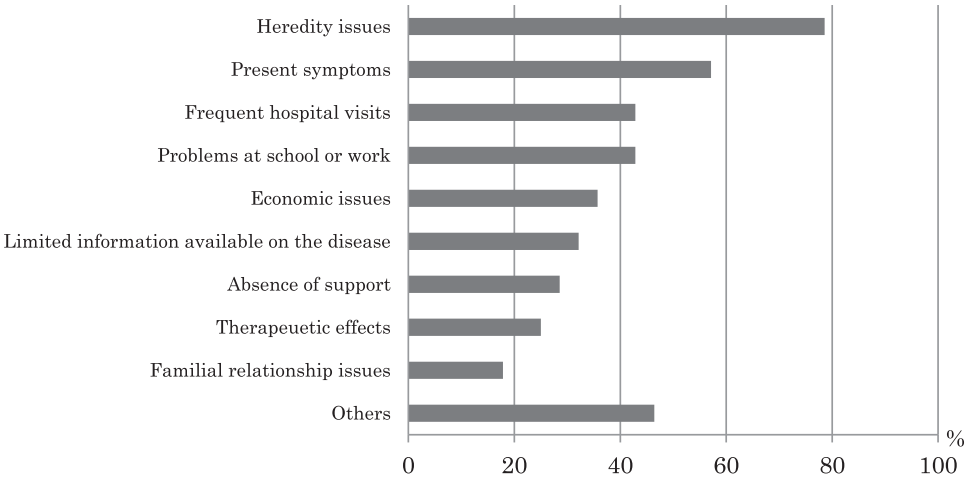

Fig. 2. Anxieties of patients and their families. The graph shows the percentages of patients and their families with each concern.

4. Discussion

Currently, the only effective treatment for X-ALD is HSCT. However, this treatment is only effective if it is performed at a very early stage of the disease. Once irreversible neurological damage has occurred, it is very difficult to improve or stabilize the disease course with HSCT. To ensure that patients experience the full benefits of HSCT, it is first essential to characterize the initial symptoms noticed by patients' families to obtain an early diagnosis. This was the aim of the current study.

The effectiveness of HSCT treatment for X-ALD is quite striking. For example, Mahmood et al. found that 94.7% of patients who received HSCT survived for more than 5 years from the first abnormal MRI, compared with only 54% of untreated patients [7]. However, as mentioned above, timing is key in HSCT treatment; in particular, Polgreen et al. found that patients who were diagnosed more than 12 months after symptom onset and received HSCT had higher MRI severity scores than did patients who received an early diagnosis and HSCT treatment [9]. Moreover, the authors found that the relative risk of death in the delayed diagnosis group was 3.9 times higher than the risk in the early diagnosis group. Interestingly, Shapiro et al. reported that 67% of patients who received HSCT returned to regular classes without additional support and maintained their verbal scores after HSCT [5]. However, patients with severe demyelination (MRI severity scores >10) at the time of HSCT have a rapid prognosis of neurological involvement and decreased survival rates [5,10–12]. The overall mortality for HSCT is ~20% among children with X-ALD, and many of the patients who receive HSCT die owing to disease progression and transplantation-related complications such as graft failure, opportunistic infection, and graft-versus-host diseases. Although fully matched donor cells can reduce the risk of these complications, it is very difficult to find a donor within a restricted time frame [11]. To overcome the HSCT-related complications, Cartier et al. genetically modified CD34+ cells using a lentiviral vector carrying the *ABCD1* gene and transplanted them into patients with X-ALD; their results confirmed that this *ex vivo* gene therapy was feasible [13]. Similarly, a phase 2–3 study (STARBEAM study) by Eichler et al. demonstrated the efficacy and safety of *ex vivo* gene therapy for human patients with CCALD by using autologous CD34+ cells that were transduced with a lentiviral vector containing the *ABCD1* gene [8]. Collectively, these results clearly indicate that early diagnosis is crucial for patients to experience the full benefits of HSCT and gene therapy.

Given the importance of early diagnosis for treatment, recognizing the initial symptoms of X-ALD is imperative. However, only a few reports [14–16] have described the clinical presentation of X-ALD and only one report [15] has discussed the initial symptoms in exact detail. Moreover, the clinical symptoms of genetic diseases sometimes differ between different ethnic groups. This further supports the value of the Japanese data we collected in the current study. Berger and Gärtner have reported that the most frequent symptoms indicative of CCALD were behavioral changes, intellectual deterioration, hearing problems, and vision disturbances [17]. Here, we found that frequent initial symptoms of CCALD were changes in behavior or character (46.4%), gait disturbances (42.9%), strabismus (39.3%), and intellectual deterioration (32.1%). Our observations are thus consistent with those of studies conducted outside Japan. Data from other countries suggests that AI is a common symptom in CCALD, and it has been estimated that 43% of patients with this condition present with sub-clinical AI, even in asymptomatic forms of the disease [18]. In our study, only 3.6% (n = 1) of patients had AI at the time of onset, while 28.6% of patients had AI at the time of

enrollment. In the study by Suzuki et al., which was performed in Japan, only one of 46 patients with CCALD had AI as the initial symptom [15]. These findings indicate that AI may be overlooked in Japanese patients with X-ALD. Alternatively, AI may have a lower incidence in Japanese patients with CCALD. Nonetheless, the initial symptoms of X-ALD are not specific. This leads to difficulties with early diagnosis of this disease. In 2013, a newborn screening system for X-ALD was established in New York in the U.S. and led to the identification of 45 patients during 3 years [19]. Newborn screening for X-ALD is also included in the Recommendation Uniform Screening Panel that was established in 2016, which may be employed in Japan in the near future.

One of limitations of this study is that the data were collected in a retrospective manner. Prospective longitudinal studies will be essential for elucidating not only the natural medical history and characteristics of X-ALD, but also to assess the effectiveness of treatment. Although the data were collected from patient's families and this was an effective method for uncovering the details of the initial symptoms, medical data, such as laboratory data, MRI findings, and physical examination findings, were not collected. Future studies wherein such data are obtained will be more valuable.

In conclusion, the JaSMIn registry system we developed allowed us to collect clinical information regarding the initial symptoms of X-ALD, as well as information regarding the related anxieties of patients' families. This registry system will help us to understand the clinical presentations of rare diseases such as X-ALD, and to identify unmet medical needs.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.07.007.

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