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Original article

Natural history of X-linked adrenoleukodystrophy in Japan

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Abstract

The natural history of X-linked adrenoleukodystrophy (ALD) was investigated, using a nation-wide retrospective study based on a questionnaire survey. The data on 145 patients, including 46 patients with the childhood cerebral form, 39 with adrenomyeloneuropathy (AMN), 33 with the adult cerebral form, 14 with the adolescent form and 13 with the olivo-ponto-cerebellar (OPC) form, were analyzed. Initial symptoms of the childhood cerebral form were intellectual ($n=16$) and visual ($n=11$) disturbances, whereas those of AMN were gait ($n=37$) and sensory ($n=3$) disturbances; the adult cerebral form, psychic ($n=19$) and gait ($n=11$) disturbances; the adolescent form, visual $n=5$) and gait ($n=4$) disturbances; and the OPC form, gait ($n=9$) disturbance. Patients with onset under the age of 8 years progressed more rapidly than those over 8 years old. Visual, hearing, gait and swallowing disturbances progressed more slowly in the older group. About half of AMN patients showed cerebral involvement about 10 years after onset. Patients with the OPC form also showed a similar progression. A Kaplan–Meier plot clarified the characteristic pattern of progression of neurological symptoms in each phenotype. These finding will improve the understanding of the natural history of X-linked ALD and will provide a basis for the evaluation of specific treatment for X-linked ALD.

Keywords: X-linked adrenoleukodystrophy; Natural history; Phenotype; Progression; Kaplan–Meier plot

1. Introduction

X-linked adrenoleukodystrophy (ALD) is a severe neurodegenerative disease with demyelination of the central nervous system, adrenal insufficiency, and accumulation of very-long chain saturated fatty acids (VLCFA) in tissues and body fluids. Patients manifest various neurological disturbances, including intellectual, psychological, visual, hearing, gait, swallowing, autonomic, and sensory disturbances [1]. The incidence of X-linked ALD has been estimated to be one in 20,000 to 200,000 males [2,3]. The pathogenic gene for ALD resides in the terminus of the long arm of X-chromosome (Xq28) [4], and the gene product, ALD protein, is located in the membrane of peroxisomes and was suggested to act as a transporter of VLCFA into peroxisomes [5]. Several therapeutic trials for X-linked ALD, including monounsaturated fatty acid supplementation [6], bone marrow transplantation [7,8], lovastatin [9], and 4-phenylbutyrate [10] have been investigated.

There are many clinical phenotypes such as the childhood cerebral form, the adolescent form, adrenomyeloneuropathy (AMN), the adult cerebral form, the olivo-pontcerebral (OPC) form, and Addison's disease only [1]. The childhood cerebral form is the most common phenotype and is characterized by the progression of intellectual, visual and gait disturbances during school age [11]. The prognosis of the childhood form is generally very poor and patients

Abbreviations: ALD, adrenoleukodystrophy; AMN, adrenomyeloneuropathy; VLCFA, very long chain fatty acid; OPC, olivo-ponto-cerebellar; BMT, bone marrow transplantation.

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usually die within a few years. AMN is known as an adult phenotype with slow progression of gait, sensory and autonomic disturbances. The adult cerebral form is more common in Japan than in Western countries [3], and is sometimes misdiagnosed as dementia or psychological disorders. The OPC form characterized by cerebellar ataxia and pyramidal tract involvement has been described predominantly from Japan [3,12].

Recently, we performed a retrospective nation-wide epidemiological survey of X-linked ALD in Japan during the 1990s [3]. In the present and previous studies we clarified the characteristic progression of neurological symptoms in each phenotype.

2. Materials and methods

A nationwide retrospective survey of X-linked ALD in Japan between 1990 and 1999 was performed. Questionnaires were sent to 4802 departments of internal medicine, neurology, pediatrics and psychiatry in hospitals with more than 200 beds, and to 77 children's hospitals or national sanatoria. A second survey requesting precise clinical data including phenotypes, onset, initial symptoms, progression of neurological symptoms and prognosis, was sent to 161 departments and hospitals that replied positively. The phenotypes and the onset of symptoms were judged by the attending doctors, or by the investigators based on the clinical data described in the questionnaire sheet. Data from patients who received bone marrow transplantation (BMT) were not included in this survey. A Student's *T*-test was performed to evaluate the differences between two groups.

3. Results

3.1. Initial symptoms

The common initial symptoms of 46 patients with the childhood cerebral form were intellectual ($n=16$) and visual ($n=11$) disturbances (Table 1). Psychic ($n=4$), hearing ($n=3$) and gait ($n=4$) disturbances were also seen. The common initial symptoms of 14 patients with the adolescent form were visual ($n=5$) and gait ($n=4$) disturbances, however, intellectual disturbance was not so common ($n=2$). Most of the 39 AMN patients manifested gait disturbance as the initial symptom ($n=37$), although a few patients had sensory or bladder disturbance. Over half of 33 patients with the adult cerebral form manifested symptoms mimicking psychic disorders ($n=19$). Gait disturbance ($n=11$) was also common in the adult form. Most of 13 OPC patients first manifested gait disturbance ($n=9$).

3.2. Progression of neurological symptoms

3.2.1. Childhood cerebral form

Earliest symptoms among patients with the childhood cerebral form were intellectual (0.2 years after the onset) and psychic disturbances (0.3 years). Visual disturbance appeared slightly later (0.5 years), and gait disturbance followed (0.7 years) (Table 2). A Kaplan–Meier plot of symptom-free patients clarified the progression of each neurological symptom (Fig. 1(A)). Patients free of intellectual disturbance deteriorated rapidly, and most patients manifested intellectual deterioration within one year. Progression of psychological disturbance was similar to that of intellectual disturbance (data not shown). Visual disturbance appeared a few months later and gait disturbance followed. About 75% of the patients manifested swallowing difficulty at the end of the second year. When we compared the progression of patients with earlier onset (less than 8 years old) with that of patients with later onset (over 8 years old), most of the disturbances appeared significantly later in the later-onset group, except for the intellectual disturbance (Table 3). Death was more common in the earlier-onset group compared to the later-onset group.

3.2.2. Adolescent form

The appearance of each symptom in the adolescent form was generally later than in the childhood cerebral form. Although gait disturbance appeared to manifest first (Table 2), visual disturbance was the most common initial symptom (Table 1). Intellectual disturbance appeared slower than that in the childhood cerebral form. About 30 and 70% of the patients were still free from intellectual

Table 1
Initial symptoms of ALD

Phenotype	Number of patients	Initial symptoms (*n*)							
		Intellectual	Psychic	Visual	Hearing	Gait	Sensory	Bladder	Adrenal
Childhood	46	16	4	11	3	4	–	–	1
Adolescent	14	2	2	5	1	4	1	–	1
AMN	39	–	–	–	–	37	3	1	–
Adult cerebral	33	5	19	3	1	11	1	2	1
OPC	13	1	–	–	–	9	1	–	2
Total	145	24	25	19	5	65	6	3	5

ALD, adrenoleukodystrophy; AMN, adrenomyeloneuropathy; OPC, olivo-ponto-cerebellar form.