



FULL LENGTH ARTICLE

A novel *ABCD1* G1202A mutation in a Chinese patient with pure adrenomyeloneuropathy and literature review

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Abstract Adrenomyeloneuropathy (AMN) is a kind of varied disease caused by *ABCD1* gene mutation and characterized by very-long-chain fatty acids (VLCFA) accumulation. It is diagnosed by clinical features, high VLCFAs levels and *ABCD1* gene mutation. AMN is rarely reported in Chinese population. In this study, we report the genetic and clinical features of a Chinese pure AMN patient. Meanwhile, we conducted a literature review of AMN cases to summarize the characteristics of AMN. We report a rare Chinese pure AMN case with slowly progressive weakness of the lower extremities, caused by a novel c.1202G > A mutation in *ABCD1* gene. The literature review indicates that spastic paraplegia is the mainly clinical manifestation in patients with AMN. VLCFAs and *ABCD1* gene test should be performed in patients with spastic paraplegia of the lower limbs to diagnose AMN.

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Introduction

X-linked adrenoleukodystrophy (X-ALD) is a recessively inherited peroxisomal disease characterized by abnormal accumulation of VLCFAs in plasma and tissues, such as brain white matter, spinal cord and adrenal cortex. It is caused by mutations in *ABCD1* gene leading to abnormal peroxisomal β -oxidation, which results in the harmful buildup of VLCFAs.^{1,2} The prominent manifestations of ALD in male patients are adrenal insufficiency and cerebral demyelination, typically observed in childhood. Adrenal insufficiency is much rarer in females. Adrenomyeloneuropathy (AMN) is a varied phenotype of X-ALD, which is characterized by slowly progressive weakness of the lower limb in males. Additionally, other symptoms including peripheral neuropathy, cerebral disease and adrenal insufficiency could be also observed.^{3,4} Few of heterozygous women develop AMN-like syndrome.^{1,2} X-ALD or AMN is diagnosed by clinical features, increased plasma VLCFAs and *ABCD1* gene mutation. The treatments for AMN patients mainly focus on dietary constraints and supplemental treatment, such as limiting dietary intake of fatty acids (Lorenzo's oil), glucocorticoid supplementation and haematopoietic stem cell transplantation (HSCT).^{5,6}

Here, we report a 29-year-old man presenting progressive weakness of lower limb. Spinal MRI showed thoracolumbar spinal cord atrophy. Increased VLCFAs and a homozygous mutation of c.1202G > A in *ABCD1* gene were also observed.

Case report

A 29-year-old Chinese man was born out of non-consanguineous marriage with normal childbirth and developmental history. He experienced progressive lower limb weakness since 8 years of age. The symptom of weakness occurred after one kilometer walking and could be relieved with rest. Two years later, he became difficult to climb 4 floors and needed a rest to alleviate fatigue. Meanwhile he suffered from constipation with having bowel movements every three or four days. There were no diarrhea, urination and sexual dysfunction complaints. As his

symptom of lower extremities weakness increased gradually, he had to walk with crutches four years later. Then he went to local hospital, however there was no special treatment was given. Six years later, the patient became difficult to walk independently and needed a wheelchair. Eventually, the patient was enrolled at the Department of Neurology, Xinhua Hospital, affiliated to Shanghai Jiaotong University School of Medicine. His complaint is that he couldn't stand and walk, independently.

Neurological examination showed spasticity, weakness and hyperactive tendon reflexes in the lower limb (muscular strength was 3/5, muscular tension was strengthened and tendon reflexes were ++++). In addition, his ankle clonus, knee clonus and Babinski sign were positive bilaterally. Due to spasticity and weakness of the lower limb, he couldn't complete bilateral heel-knee-shin tests and walk on the ground. There was bilateral pinprick impairment below the 4th thoracic cord symmetrically. The abdominal reflex and cremasteric reflex reduced bilaterally. There were no abnormal findings in the upper limb and cranial nerves. The meningeal irritation sign and finger-to-nose test were negative. Intellectual and memory functions were within the normal range (MMSE = 28, MoCA = 29). Physical examinations showed the respiratory, cardiovascular and abdominal examinations were normal.

The thoracolumbar spinal MRI showed severe spinal cord atrophy. No abnormal signals and disc herniation were seen in T1 MRI of the spinal cord on mid-sagittal plane (Fig. 1). The brain MRI was normal in signal intensity and morphology (The image was not showed here).

In electrophysiological studies, we found that latent period of every wave and interspike intervals delayed in somatosensory evoked potential, visual evoked potential and brainstem auditory evoked potential. There was no obviously abnormal findings in electromyography, motor nerve conduction velocities and sensory nerve conduction velocities and electroencephalography.

In laboratory findings, the concentration of very long chain fatty acids (VLCFAs) in plasma were increased (the tetracosanoic acid (C22:0) 35.12 μ mol/L, normal range 31.88–71.49 μ mol/L; the hexacosanoic acid (C24:0) 65.51 μ mol/L, normal range 24.97–61.04 μ mol/L; the hexacosanoic acid (C26:0) 2.49 μ mol/L, normal range

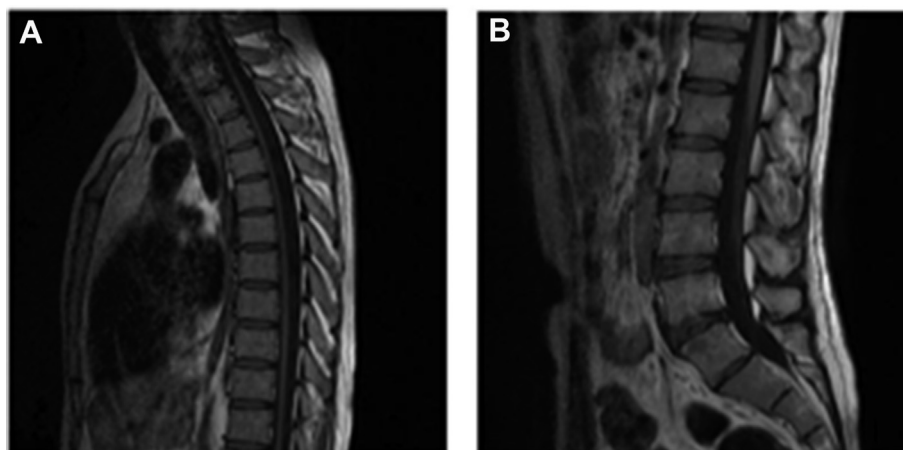


Figure 1 The spinal MRI of patient. There is severe spinal cord atrophy, but no abnormal signals and disc herniation were seen in T1 MRI of the spinal cord on mid-sagittal plane (A–B).

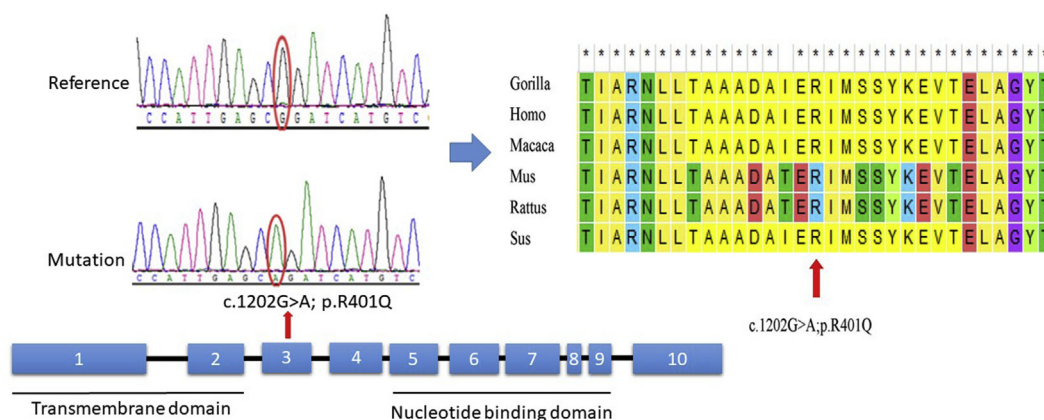


Figure 2 ABCD1 gene mutation in patient. A mutation of c.1202G > A in exon 3 in ABCD1 gene, which resulted in the 401 amino acid changing from arginine to glutamine.

0.22–0.77 $\mu\text{mol/L}$; the ratio C24:0/C22:0 1.865, normal range 0.697–0.963; the ratio C26:0/C22:0 0.07, normal range 0.005–0.015). Other tests including blood routine test, liver function, kidney function, blood glucose, electrolytes, tuberculosis, syphilis and HIV were normal.

The mutation of c.1202G > A in exon 3 in ABCD1 gene was detected in the patient (Fig. 2), which resulted in the 401 amino acid changing from arginine to glutamine. This ABCD1 gene mutation was not be found in other family members. This mutation was not include in 1000 Genomes and ExAC database. ABCD1 c.1202G > A mutation is reported as “pathogenic” in ClinVar database. The number 401 arginine acid is highly conserved across different species (Fig. 2). This mutation is predicted to be “disease causing” by Mutation Taster, “High impact” by Mutation assessor, “Probably damaging” by Polyphen2. The clinical interpretation of the c.1202G > A mutation generated by the CLNSIG is “Pathogenic”.

Literature review of patients with AMN reported in China

Literature review of AMN cases was conducted by searching for all cases published from 1975 to 2019, with the keyword “Adrenomyeloneuropathy” and “ABCD1 gene”. The databases included PubMed, Medline, VIP database and Chinese Biology Medicine. Only studies published in English or Chinese were included. All relevant papers were read carefully. We reviewed 18 papers including 32 cases with AMN: the clinical features of these patients were summarized in Table 1.^{7–24}

We summarized the reported cases worldwide, which describe the details of genotypes and phenotypes of AMN patients. The clinical features of genotype and phenotype of AMN patients with ABCD1 mutation were described in Table 1. We found the mutation occurs most frequently in the exon 1 of the ABCD1 gene (37.5%). Most of them are missense mutations (84.38%). Most patients are male, except for one female patient. The age of onset was between 8–44 years, and the course of disease was between 1–28 years. Most onset symptoms were lower limbs

weakness and gait disorder. Adrenal insufficiency could be observed in 14 patients (43.75%). The disease was characterized by spastic paraplegia of lower limbs. In addition, the 7 patient had complaint of sexual dysfunction. Our patient had constipation without sexual dysfunction. There were 14 patients with positive family history. Our patient had no family history and suffered from progressive weakness of the lower extremities at the age of 21 years. However, we can’t speculate any significant correlation between genotype and phenotype. In addition, lack of detailed records of treatment outcomes and long-term follow-up, we can’t conclude the characteristics of AMN patients with glucocorticoid responsive difference, treatment effects, disease progression and prognosis. This requires multi-center, large sample, long-term research to conclude the correlation between genotype and phenotype in the future.

Discussion

We report a young male presented progressive lower limb weakness. In addition to thoracolumbar spinal atrophy in MRI, we found increased plasma VLCFAs and ABCD1 c.1202G > A gene mutation in our case.

The incidence of X-ALD has been reported to be 1:21,000 in males and 1:14,000 in females.²⁵ And most patients are misdiagnosed as other diseases such as multiple sclerosis and hereditary spastic paraparesis, especially for heterozygous female carriers. The clinical phenotypes of X-ALD vary greatly among males than female patients, and can be classified into the following categories: childhood cerebral ALD, adolescent cerebral ALD, adolescent cerebral ALD, AMN, Addison-only, preclinical type and asymptomatic ALD.²⁶ According to the affected sites and imaging features, AMN can be further classified: firstly, Cerebral AMN: The patient presents spinal symptoms accompanied by leukodystrophy and cognitive dysfunction. Secondly, Pure AMN: patients have the only or prominent spinal cord symptoms with progressive weakness of the legs, accompanied by autonomic nerve and sensory impairment. The MRI shows atrophy in thoracolumbar spinal cord and no obvious abnormality in head.^{27,28} According to the clinical

Table 1 The clinical features of genotype and phenotype of adrenomyeloneuropathy patients with *ABCD1* mutation.

Population	Genotype			Phenotype								
	Exon	Nucleotide change	Type	Sex/Age (years)	Onset age (years)	Spastic paraparesis	Sensory deficit	Sexual dysfunction	Cerebral involvement	Change of skin/hair	Adrenal insufficiency	Family history
Dutch ⁷	1	c.1 A > G	Missense	M/27	25	+	+	—	NA	NA	+	—
German ⁸	1	c.1 A > G	Missense	M/37	NA	+	+	NA	—	NA	—	—
American ⁹	1	c.143_155del 13insAG	Frameshift	M/19	17	+	+	NA	+	NA -	—	—
Chinese ¹⁰	1	c.231G > A	Missense	M/40	30	+	+	—	+	+	NA	+
Korean ¹¹	1	c.225_242del	Deletion	M/20	18	+	+	NA	+	NA	NA	—
Korean ¹¹	1	c.277_296dup20	Frameshift	M/37	35	+	+	NA	+	NA	—	+
Chinese ¹²	1	c.290 A > C	Missense	M/21	8	+	NA	NA	—	+	+	—
Chinese ¹³	1	c.346G > A	Missense	M/45	38	+	+	+	—	+	+	±
Korean ¹¹	1	c.421G > A	Missense	M/30	23	+	+	NA	—	NA	NA	—
Korean ¹¹	1	c.479 T > C	Missense	M/25	23	+	+	NA	—	NA	NA	—
Greece ¹⁴	1	c.668C > A	Missense	M/23	14	+	—	NA	NA	+	+	—
Canadian ¹⁵	1	c.881C > T	Missense	F/19	47	+	+	NA	—	NA	—	—
Korean ¹¹	IVS1	c.901-1G > A	Frameshift	M/38	36	+	+	NA	+	NA	+	+
Chinese ¹⁶	2	c.946C > T	Missense	M/29	17	+	—	NA	—	—	—	—
Italy ¹⁷	2	c.1028G > T	Missense	M/46	NA	+	NA	NA	+	NA	+	+
Chinese ¹⁸	3	c.1144 A > C	Missense	M/18	16	+	—	NA	—	—	—	+
Chinese ¹³	3	c.1166G > A	Missense	M/40	31	+	+	—	—	+	—	—
Korean ¹¹	3	c.1166G > A	Missense	M/57	55	+	+	NA	—	NA	—	—
Chinese (this paper)	3	c.1202G > A	Missense	M/29	8	+	—	—	—	—	—	—
German ¹⁹	6	c.1544C > T	Missense	M/36	18	+	+	NA	—	NA	—	±
Japanese ²⁰	6	c.1598 A > G	Missense	M/29	1	+	—	NA	—	NA	+	—
Korean ¹¹	7	c.1661G > A	Missense	M/24	23	+	+	NA	+	NA	+	—
Korean ¹¹	7	c.1679C > T	Missense	M/19	18	+	+	NA	—	NA	NA	—
Korean ¹¹	7	c.1679C > T	Missense	M/38	30	+	+	NA	+	NA	+	—
Chinese ¹³	8	c.1817C > T	Missense	M/31	26	+	—	+	—	+	+	±
Chinese ¹³	8	c.1843dup	Frameshift	M/41	29	+	+	+	+	+	+	—
Chinese ¹³	8	c.1849C > T	Missense	M/30	21	+	+	+	—	+	+	—
Chinese ²¹	IVS8	c.1866—1 ins ACCCCAG	Insertion mutation	M/45	25	+	—	+	+	NA	+	—
Chinese ²²	9	c.1923A > C	Missense	M/29	27	+	—	+	NA	+	NA	+
Korean ¹¹	9	c.1970_72del	In-frame deletion	M/38	32	+	+	NA	—	NA	+	—
German ²³	10	c.2035T > C	Missense	M/52	40	+	NA	NA	—	NA	—	±
Danish ²⁴	10	c.2005C > T	Missense	M/55	44	+	+	+	—	NA	NA	—

M, male; F, female; NA, not available.

and imaging features, our patient should be diagnosed as pure AMN, which is a rare subtype of AMN reported in China.

The prominent biochemical abnormality of AMN is an excess of VLCFAs. The concentration of VLCFAs is mainly determined by the level of C22:0, C24:0, C26:0, C26:0/C22:0 and C24:0/C22:0, especially the latter 3 items are more sensitive. However, there is no significant correlation between the level of VLCFAs and the phenotype of the disease.²⁹

Additionally, the pathophysiology of AMN is caused by *ABCD1* gene mutation. The *ABCD1* gene, which contains 10 exons and covers 21 Kb, is located at Xq28. The product of *ABCD1* gene, ALD protein (ALDP), is predicted to be responsible for the transport of VLCFAs across the peroxisome membrane. The gene mutation leads to ALDP dysfunction and abnormal peroxisomal β -oxidation. The impaired β -oxidation of VLCFAs and consequent accumulation in various tissues affects the function of adrenal gland, the nervous system and gonads.^{14,30} The genetic examination in our study identified a novel *ABCD1* gene mutation c.1202G > A in our patient, which resulted in the 401 amino acid changing from arginine to glutamine.

AMN is a slowly progressive non-inflammatory distal axonopathy involving spinal cord and peripheral nerves. Nerve conduction studies usually show axonal sensorimotor polyneuropathy. In addition, evoked potentials often reveal functional abnormalities of the central nervous system conduction, even before any changes in MRI are evident. About half of the pure AMN patients clinically develop cerebral AMN. Evoked potentials are helpful to detect functional impairment of intracranial corticospinal tract, probably demyelination, in pure AMN patients.³¹ SEP, VEP and BAEP reveal that latent period of every wave and delayed interspike intervals in our patient. We speculate our patient has functional impairment in intracranial corticospinal tract, and maybe develop cerebral AMN in the future. It need a long time follow-up.

The treatments for AMN patients mainly focus on dietary constrains and symptomatic therapy. Previous studies have shown that limiting dietary intake of fatty acids is beneficial for patients. Lorenzo's oil, a 4:1 mixture of glyceryl trioleate and glyceryl trierucate, has been used to reduce the saturated VLCFAs level in the plasma of AMN patients. It may have preventive effects on AMN patients without neurological symptoms, but fail to improve neurological symptoms that have occurred.⁵ Treatment of AMN with glucocorticoid supplementation is used in patients with primary adrenal insufficiency. Hematopoietic stem cell therapy (HSCT) is clearly confirmed to delay or avert disease progression, but it is mainly used in patients with mild neurological symptoms, and is ineffective in patients with severe white matter damage.⁶ Our patient was treated with low-fat diet treatment. After one-year follow-up, the symptom of lower limbs weakness was not improved.

In conclusion, we report a rare Chinese pure AMN case with *ABCD1* c.1202G > A gene mutation, accompanied with slowly progressive weakness of the lower extremities and increased plasma VLCFAs. The literature review indicates that spastic paraplegia is the mainly clinical manifestation in patients with AMN. Therefore, VLCFAs or *ABCD1* gene test should be performed in patients with spastic paraplegia of the lower limbs to diagnose AMN.

Ethics statement

Written informed consent was obtained from the participant for the study and the publication. This study was performed with the approval of the Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao tong University School of Medicine (XHEC-C-2016-150-19).

Authors contribution

YZ and ZGL conceived the project and designed the study. GYZ, WHC, LS, XHT, ZP and ZGL contributed to participant recruitment, data collection and data analysis. YZ, and GYZ wrote the paper together.

Conflict of Interests

The authors declare no conflict of interests.

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