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Clinical and genetic study of ataxia with vitamin E deficiency: A case report

Zhang LW *et al*. Ataxia with vitamin E deficiency

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Abstract

BACKGROUND

Ataxia with vitamin E deficiency (AVED) is a type of autosomal recessive cerebellar ataxia. Clinical manifestations include progressive cerebellar ataxia and movement disorders. α-tocopherol transfer protein (*TTPA*) gene mutations cause the disease.

CASE SUMMARY

We report the case of a 32-year-old woman who presented with progressive cerebellar ataxia, dysarthria, dystonic tremors, and a remarkably decreased serum vitamin E concentration. Brain magnetic resonance images showed that her brainstem and cerebellum were within normal limits. Acquired causes of ataxia were excluded. Whole exome sequencing subsequently identified a novel homozygous variant (c.473T>C, p.F158S) of the *TPPA* gene. Bioinformatic analysis predicted that F185S is harmful to protein function. After supplementing the patient with vitamin E 400 mg three times per day for 2 years, her symptoms remained stable.

CONCLUSION

We identified an AVED patient caused by novel mutation in *TTPA* gene. Our findings widen the known *TTPA* gene mutation spectrum.

Key Words: Ataxia with vitamin E deficiency; *TTPA* gene; Tremor; Case report

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Core Tip: Ataxia with vitamin E deficiency (AVED) can present as progressive chronic cerebellar ataxia and involuntary movement disorder. Vitamin E supplementation should be initiated as early as possible to stop disease progression.

INTRODUCTION

Ataxia with vitamin E deficiency (AVED) is a type of autosomal recessive cerebellar ataxia (ARCA). The most prominent symptoms include cerebellar ataxia, areflexia, peripheral neuropathy, and movement disorder[1,2]. AVED patients may also exhibit retinitis pigmentosa, cardiomyopathy, and scoliosis[3,4]. AVED is caused by mutations in the *TTPA* gene, which encodes the α-tocopherol transfer protein (α-TTP), which in turn binds α-tocopherol and transports vitamin E from hepatocytes to circulating lipoproteins[5]. Vitamin E supplementation may prevent the worsening of the condition of patients with AVED.

To date, the known incidence rate of AVED in China has been low[6]. Here, we report the clinical, biochemical, and genetic investigation of a Chinese patient with AVED due to homozygous mutations in the *TTPA* gene. This patient exhibited progressive cerebellar ataxia, dysarthria, and head titubation with markedly low levels of serum vitamin E. After treatment with vitamin E 400 mg three times per day for 2 years, the patient's neurological symptoms were stabilized.

CASE PRESENTATION

Chief complaints

A 32-year-old woman was admitted to the hospital because of progressive cerebellar ataxia and involuntary head tremors.

History of present illness

When the patient was 14 years old, she began exhibiting an unsteady gait, which worsened to become wide-based and staggering. She also developed slurring of speech and clumsiness of the hands. At 18 years of age, she began having involuntary dystonic head tremors too.

History of past illness

She had no specific intestinal lesions indicative of malabsorption. Past medical history was unremarkable.

Personal and family history

Her parents are cousins. There is no family history of similar neurological disorders.

Physical examination

Neurological examination revealed normal cognitive state, dysarthria, overt head tremor, bilateral dysmetria on nose-finger and heel-shin tests, and wide-based ataxic gait with inability to walk in tandem. Kayser-Fleischer Rings were absent, vision and hearing ability were normal. Motor and sensory examinations yielded normal results apart from areflexia. Romberg's sign and bilateral Babinski sign were positive, Pes cavus. Obvious overt head dystonic tremor, bilateral dysmetria on finger-to- nose and heel-to-shin tests, and wide-based gait and unable to walk in tandem. Scale for the assessment and rating of ataxia (SARA) score was 11 [gait 2, stance 2, sitting 0, speech 1, finger chase 1.0 (left 1, right 1), nose-finger test 2.0 (left 2, right 2), fast alternating hand movements 1.0 (left 1, right 1), and heel-shin slide 2.0 (left 2, right 2)].

Laboratory examinations

Routine blood tests, including liver function, autoimmune antibodies, thyroid function, blood smear for acanthocytosis, and plasma levels of vitamins (B1, B2, B6, B9, B12, A, D, E), copper and ceruloplasmin were normal. Cerebrospinal fluid was normal including inflammatory, immunological, and infectious indices. Electromyography, nerve conduction velocity, and brainstem auditory evoked potential were all normal. Initial DNA analyses using capillary electrophoresis of polymerase chain reaction products excluded Friedrich's ataxia, spinocerebellar ataxia (1,2,3,6,7,8,10,12,17) and dentatorubral-pallidoluysian atrophy. The plasma level of total vitamin E detected *via* high performance liquid chromatography was 0.59 μg/mL (normal: 10.8 ± 3.3 mg/L[7]).

Imaging examinations

Brain magnetic resonance imaging (MRI) showed no obvious atrophy of brainstem and cerebellum (Figure 1).

Further diagnostic work-up

Genomic DNA was extracted from peripheral leukocytes of the patient and all available family members, who gave written informed consent, according to the standard protocol approved by the China-Japan Friendship Hospital. DNA of the proband was subjected to whole exome sequencing (WES) using the Ion Torrent AmpliSeq Exome RDY kit (BGI Tech, Hong Kong). Variant call files were analyzed with Ingenuity Variant Analysis (Qiagen, Redwood City, CA, United States) using an autosomal recessive model. Clean reads were aligned on the human assembly GRCh37 by Burrow-Wheeler aligner. Small insertions/deletions and single nucleotide variants were called by genomic analysis toolkit and annotated by ANNOVAR. Several filtration steps to obtain putative pathogenic variants were processed. The functional effects of protein variants were predicted by Sorting Intolerant From Tolerant (SIFT), PolyPhen2 and MutationTaster. Disease association databases (*e.g.*, HGMD, OMIM and ClinVar) and genetic variation databases (*e.g.*, 1000 Genomes Project, ESP6500 and ExAC) were used in the filtering process too. Potential pathogenic variants were validated by

conventional Sanger sequencing, and her family members were included for segregation analysis. We used the transcript sequence (OMIM*600415, NM_000370.3) of the *TTPA* gene and discovered homozygous variants(c.473C>T, p.Phe185Ser) in the proband. Sanger sequencing confirmed this result and revealed that her parents and the younger sister are heterozygous carriers for 473C>T (Figure 2). This mutation was predicted to be harmful (SIFT: tolerated, Polyphen2: possibly damaging, MutationTaster: disease causing). The 158 phenylalanine residue affected by the mutation were highly conserved in evolution (Figure 3).

FINAL DIAGNOSIS

The final diagnosis of the presented case was AVED due to *TTPA* homozygous missense mutation (c.473C>T, p.Phe185Ser) (GRCh37/hg19).

TREATMENT

After we detected decreased plasma levels of total vitamin E, supplementation with vitamin E 400 mg three times per day was immediately administered. The patient also kept physical exercises for rehabilitation therapy.

OUTCOME AND FOLLOW-UP

After 2 years of vitamin E supplementation therapy, the symptoms of this patient showed neither improvement nor deterioration. On her last follow-up visit, her SARA score was 11 [gait 2, stance 2, sitting 0, speech 1, finger chase 1.5 (left 2, right 1), nose-finger test 1.5 (left 2, right 1), fast alternating hand movements 1.0 (left 1, right 1), and heel-shin slide 2.0 (left 2, right 2)].

DISCUSSION

By WES we identified homozygous mutations of *TTPA* gene (c.473C>T, p.Phe185Ser) in a Chinese family with ARCA, and we have excluded common causes of ataxia. AVED was first reported by Burck *et al*[8]. It usually manifests as a mild disease course and is

rarely reported in China. The presentation of AVED is highly heterogeneous, with onset usually in childhood[9], some cases have manifested in infancy and in adulthood[1]. Clinical phenotypes include progressive gait ataxia, movement disorders, areflexia, dysarthria, epilepsy, pyramidal signs, impaired proprioception and vibration sense and sensory neuropathy[9-11]. Apart from cerebellar ataxia, our patient exhibited obvious head tremor. Head titubation, seen in 37% to 73% of patients, and cervical dystonia are distinguishing motor features of AVED[1,3,12]. Non-neurological symptoms, such as retinitis pigmentosa, macular degeneration and cardiomyopathy[13,14], were not found in our patient. Laboratory examination often reveals markedly low serum vitamin E concentration in AVED[1]. The patient's MRI showed no obvious cerebellar atrophy in our patient, absence of cerebellar atrophy is common in AVED patients[15].

To date, various mutations of *TTPA* gene had been reported[16], the genotype-phenotype correlations were not found to be strong in AVED, and c.744delA was the most frequent mutation, often originated in the Mediterranean region[9]. Moreover, 744delA could increase the risk of early age onset, severe disease course, and cardiomyopathy[12]. c.473C>T(p.F185S), which was detected in our patient, has not been reported previously. Her symptoms began in adolescence, and she is still able to walk 18 years after the onset of disease.. F185S is located in CRAL_TRIO domain, and its predicted function is to combine with α-tocopherol[18]. Bioinformatic analysis predicted this novel mutation would lead to the damage of protein function.

AVED is a treatable form of hereditary ataxia, early and sustained vitamin E supplementation could result in a remarkably clinical response or stabilization in AVED patients[1,19,20]. In patients with ataxia, a prompt investigation for vitamin E deficiency is recommended[19,20]. AVED patients require lifelong vitamin E supplementation at 300-2400 mg/d to maintain adequate plasma levels of vitamin E[1,8,14]. Our patient received 1200 mg/d of vitamin E for two years and her symptoms showed no deterioration.

CONCLUSION

We identified a Chinese AVED female patient caused by a novel mutation in *TTPA* gene. This finding widens the known *TTPA* gene mutation spectrum.

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