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Predominant Tremors at Onset in a Case of SCA42 from China: A Case Report and Literature Review

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Abstract

Spinocerebellar ataxia (SCA) is a kind of genetically inherited neurodegenerative disorders, mostly autosomal dominantly inherited. Spinocerebellar ataxia-42 (SCA42) is caused by heterozygous mutation in the calcium channel 1G (CACNA1G) gene. We presented a SCA42 patient with obviously resting tremor in the head, postural tremor in both upper limbs and ataxia. The patient's cerebral magnetic resonance imaging (MRI) showed cerebellar atrophy. A missense mutation in CACNA1G gene was found by whole-exome sequencing. The clinical features and MRI findings, as well as whole-exome sequencing made the diagnosis of SCA42.The patient was treated with valproic acid (Depakine 0.5g once daily) and nerve nutrition. At the 6-month follow-up visit, patient's tremor symptoms had relieved.

Keywords: SCA42; CACNA1G; Cerebellar atrophy; Spinocerebellar ataxia; Valproic acid

Introduction

Spinocerebellar ataxia (SCA) is a kind of genetically inherited neurodegenerative disorders, mostly autosomal dominantly(AD) inherited, and the prevalence range of SCA was 2.7 cases per100,000 individuals [1]. SCA3 is the most common subtype which may be accounted for 48% to 49% of total SCA patients in China, followed by SCA2, 1, 6 and 7. The clinical hallmarks of SCA are cerebellar ataxia, ophthalmoplegia, cognitive impairment and slurred speech [2]. The age of onset ranges from 30 to 40 years usually, but it can occur at any age of life. Spinocerebellar ataxia-42 (SCA42) is a kind of SCA subtype, caused by the variation of calcium channel 1G (CACNA1G) gene [3]. Currently known that due to the variation of c.5144G> A site, it affects the progress of arginine-to-histidine (p.Arg1715His) in the voltage sensor S4 segment of CaV3.1 t-type voltage-dependent calcium channels (VDCCs) [4]. In this case, we presented a heterozygous mutation SCA42□c.5144G>A:p. Arg 1715His□patient in China.

Case Presentation

A 24-year-old Han Chinese male was admitted to our hospital due to progressively aggravating resting tremor of the head and abnormal gait over the past 2 years. He began to experience mild tremors in the head and upper limbs since 2017, the symptom occurred once or twice per day and lasted 1-2 hours each time. After a few months, the frequency and duration of the symptoms gradually increased, and he began to experience abnormal gait and become unable to walk straight, especially at night. The tremor would be worse after the lack of sleep or emotional excitement. It was no consanguineous marriage between the patient's parents, and there were no similar symptoms in his parents. Physical examination of the patient showed that he had resting tremor in the head, postural tremor in both upper limbs, slight hyporeflexia in both lower limbs and ataxia. He cannot walk in a straight line, but his muscle power of lower limbs was normal. Besides, no disorders in the trunk, limbs' sensory disorders, nystagmus, and dysarthria, or pathologic signs were observed. Cerebral magnetic resonance imaging (MRI) showed cerebellar atrophy, as shown in Figure 1. The pedigree analysis of the complete family is shown in Figure 2. To consider the diagnosis of SCA, we conducted the exome sequencing analysis, as shown in Figure 3.

Heterozygous mutation (c.5144G>A:p.Arg1715His) was found in the patient and variants of the family were validated by Sanger sequencing. As shown in Figure 3, variants of the

parents (chr17:48694921 A) were wild-typed homozygous while variants of the patient were novel mutation (chr17:48694921 G). c.5144G>A was recommended to be classified as a pathogenic variant according to the ACMG (American College of Medical Genetics and Genomics) guideline assessment criteria. Based on clinical manifestations, MRI results, and exome sequencing analysis, the case was diagnosed as SCA42. The patient was treated with valproic acid (Depakine 0.5g once daily) to reduce motor symptoms. At the 4-month follow-up visit, his tremor symptoms had relieved to some extent.

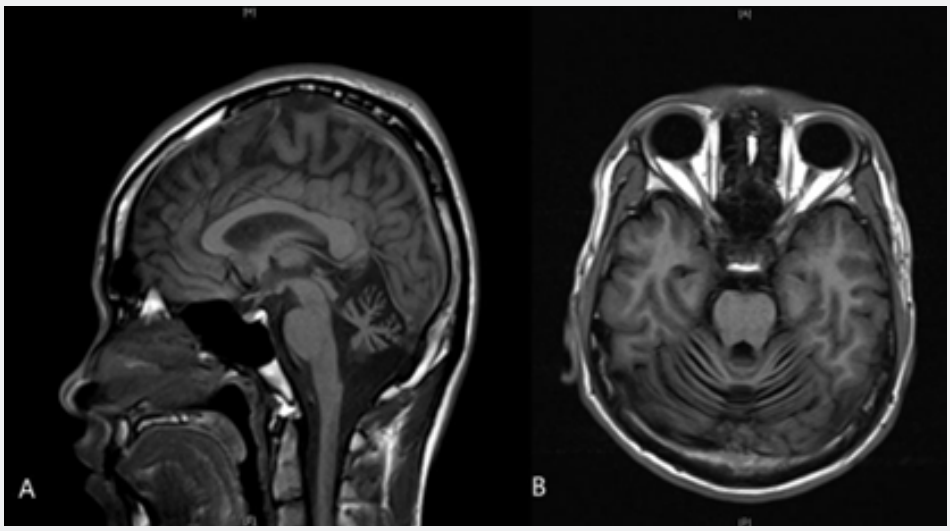

Figure 1: MRI scans showed cerebellar atrophy. Arrows indicate lesion site.

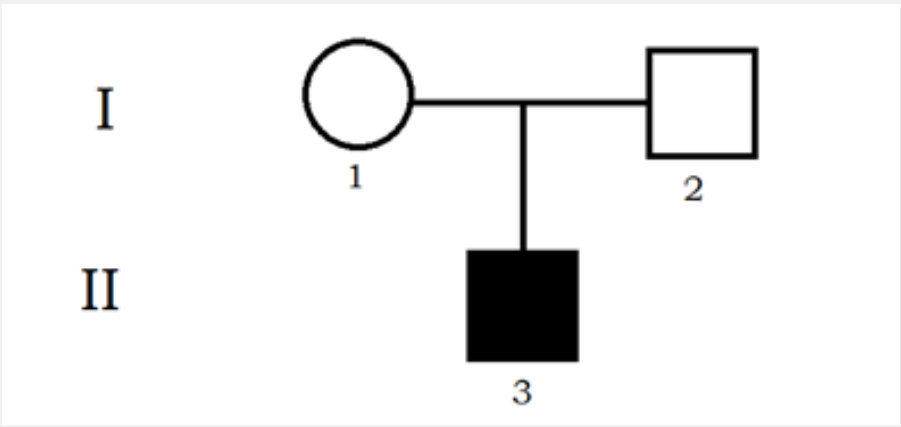

Figure 2: Pedigree analysis of the patient's family. Black circles (female) and squares (male) indicate family members affected with the disease, while open circles or squares indicate unaffected members.

Discussion

SCA, a class of autosomal dominantly inherited disease, progressive cerebellar ataxia and ocular motor abnormalities are the main clinical characters. SCA usually involves the spinal or cerebellar, but it doesn't mean SCA was only restricted to spinocerebellar systems. In addition, pontine nuclei, basal ganglia, retina, cerebral cortices even peripheral nerves also can be involved [5]. Currently, there are over 44 kinds of SCA due to the difference in pathogenic gene location. SCA42 was first reported by Coutelier M in 2015 as a kind of autosomal dominantly inherited SCA subtype, CACNA1G was regarded as the pathogenic gene [6]. Since then the disease caused by a missense mutation of the CACNA1G gene (c.5144G>A; p.Arg1715His) was only reported in French and Japan and there was no similar report in China [6,7,8]. In this study, we presented a heterozygous mutation SCA42 patient and there was no evidence that any of his family members had similar symptoms, so we considered this patient was an isolated single case caused by de novo point mutation.

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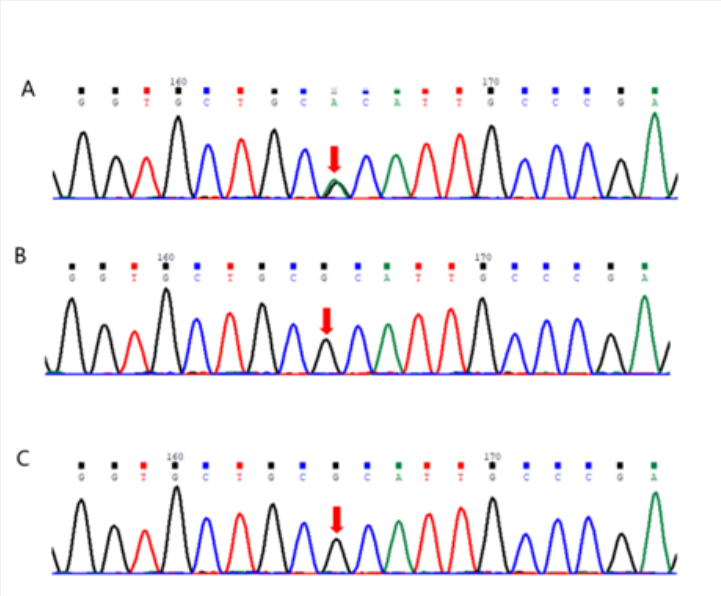

Figure 3: Sequencing analysis of the CACNA1G gene locus. Panel (A) shows the genetic profile of the patient (II-3). Panel (B) represents the genetic profile of the patient's father (I-1), while panel (C) represents the genetic profile of the patient's mother(I-2).

Unlike previous research reports, tremor is the prominent clinical manifestation in this patient. According to the current study, tremor is not a typical manifestation of SCA, and there were only three descriptions of tremor in the 38 case reports of SCA42 from French and Japanese families, and this report would be the fourth. At the same time, it is the first report of SCA42 caused by c.5144G>A mutation in China. There was accumulating evidence illustrate that the cerebellum was involved in the pathogenesis of tremors [9]. However the relationship between cerebellar degeneration and tremor remains unclear, and patients with tremors usually have more severe ataxia compared to those without tremors [10]. CACNA1G was regarded as the pathogenic gene of SCA42 which encoded the low-threshold voltage-dependent Ca channel Cav3.1. The function of this gene was to mediate calcium entry into excitable cells and it also involved in a variety of calcium-dependent processes, including muscle activity, release of hormones or neurotransmitters, and gene expression. It was highly expressed in Purkinje neurons, deep cerebellar nuclei and the inferior olive nucleus [11]. Studies have shown that Cav3.1 in the inferior olive nucleus was involved in the generation of tremors [12].

Currently, there is no effective treatment for SCA, the clinical symptomatic and supportive for the maintenance of function still the main method of treatment [13]. Some studies show some benefits of riluzole, valproic acid, varenicline and lithium carbonate, but no definite evidence of benefit was established [1]. Zonisamide was a kind of T-type calcium (Ca) channel inhibitor. It has been reported that low doses of Zonisamide can mitigate SCA42 [14]. Valproic Acid is a common pan-HDAC inhibitor drug used to treat bipolar and seizure disorders, in the research of Li-Fang Lei is a potential drug for the treatment of SCA3 [15]. According to the patient's clinical manifestation, we treated the patient with valproic acid (Depakene 0.5g once daily) and nerve nutrition. With the 6-month follow-up visit, the patient's tremor symptoms and abnormal gait had relieved. Our report may provide a new direction for diagnosing unexplained tremors in youth.

Declaration of Competing Interest

The authors declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Acknowledgment

We are grateful to the patient who was willing to share his medical data.

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