Neurology Asia 2017; 22(2) : 161 – 163

Hereditary spastic paraplegia with *SPG30* mutation: A report from North East China

[1]Chunkui Zhou, [2]Lijun Zhu, [1]Xinyuan Li, [1]Heqian Du, [1]Shanshan Dong, [1]Qun Liu, [1]Shaokuan Fang

[1]Department of Neurology, Neuroscience Centre, the First Teaching Hospital of Jilin University, Changchun; [2]The Third Teaching Hospital of Jilin University, Changchun, China

Abstract

Hereditary spastic paraplegia is a heterogeneous group of genetic neurodegenerative disorders of the nervous system. It is classified into four subtypes based on the mode of inheritance; and among them, most autosomal recessive hereditary spastic paraplegia cases are due to type *SPG11* and *SPG15* gene mutations. Autosomal recessive hereditary spastic paraplegia cases with *SPG30* gene mutation have never been reported in China. Herein, we present our experience with a case of hereditary spastic paraplegia with SPG30 gene mutation in our hospital from North East China. In this patient we detected a missense mutation of c.499 C>T (p.Arg167Cys) in gene *KIF1A*, a causative gene of type SPG30.

Key Words: Hereditary spastic paraplegia, SPG30, KIF1A

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a heterogeneous group of genetic neurodegenerative disorders that affects the nervous system. Clinically, the disease manifests as progressive spastic paraplegia. Pathologically, the disease is characterized by degeneration and/or demyelination of bilateral corticospinal tract.[1] HSP is classified into four subtypes based on the mode of inheritance: autosomal dominant HSP (AD-HSP), autosomal recessive HSP (AR-HSP), X-linked HSP (XL-HSP) and HSP with maternally inherited characteristics.[2] Most AR-HSP cases are due to type *SPG11* and *SPG15* gene mutations.[3,4] AR-HSP cases with SPG30 gene mutation have never been reported in China. Here, we present a HSP patient with SPG30 gene mutation presented to our Hospital in Jilin, North East China.

CASE REPORT

A 16-year-old Han male middle school student was referred to our hospital with a history of progressive gait difficulties over the past 4 years. Initially the patient had stiffness of the lower limbs and had to drag his feet while walking. At the onset of the illness, there was no muscle weakness. His parents did not have a consanguineous marriage. There was no other significant past medical history, such as trauma or surgery. There was also no family history of similar illness, or epilepsy.

On physical examination, the patient had normal mentation, the cranial nerve examination was also normal. There was no muscle atrophy, the muscle strength in his upper extremities was also normal (Medical Research Council --MRC grade V). The upper limbs muscle tone was normal, whereas hypertonia was observed in both lower limbs. Deep tendon reflexes of the upper and lower limbs were brisk. Ankle clonus could be elicited both sides. Babinski and Chaddock signs were bilaterally extensor. He could not walk on a straight line. Romberg's sign was negative. There were no deficits of superficial or deep sensation, and no ataxia. The brain stem evoked potential was normal; EMG results were suggestive of damage to sensory nerve fibers in both legs. No obvious abnormalities were observed on magnetic resonance imaging (MRI) study of brain and spinal cord.

High-throughput sequencing was performed to assess mutations of genes related to HSP. These included, *PLP1, ATL1, SPAST, CYP7B1, NIPA1, SPG7, KIAA0196, KIF5A, KIAA1840, RTN2, HSPD1, ZFYVE26, ERLIN2, KIF1A, REEP1, ZFYVE27, FA2H, PNPLA6, SLC33A1, GJC2, AP4B1, AP5Z1, AP4M1, AP4E1* and *AP4S1*. Suspected mutation sites were found in gene KIF1A, with c.499 C>T, p.Arg167Cys revealed by Sanger sequencing (Figure 1). Results were

Address correspondence to: Professor Shaokuan Fang, Department of Neurology, Neuroscience Centre, the First Teaching Hospital of Jilin University, No71 Xinmin street, Changchun, Jilin, 130021 China. E-mail: fang20063536@sina.com

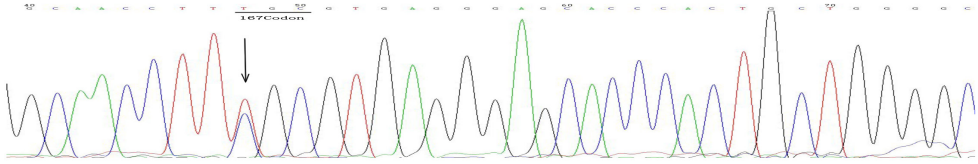

Figure 1. Genetic testing for potential mutation sites in gene KIF1A in our patient. Missense mutation of c.499 C>T (p.Arg167Cys) in gene KIF1A was detected from the patient.

analyzed in ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/), with a previous report on c.499 C>T, p.Arg167Cys in gene *KIF1A*, which was thought to be the possible cause of spastic paraplegia.[5]

The patient was diagnosed as HSP based on history, clinical findings and investigations. Oral baclofen therapy was prescribed at initial dosage of 5 mg tid. The muscle tone of lower limbs improved slightly. Physiotherapy was also given.

DISCUSSION

HSP is a rare hereditary neurodegenerative disease that can be categorized as simple or complex types according to the clinical manifestations.[1] HSP is marked by significant genetic heterogeneity. It is caused by the mutation of genes encoding proteins that maintain the functions of corticospinal tract in the spinal cord.[6] Mutation sites have been localized in nearly 60 genes.[7] Nineteen HSP genes are related to AD-HSP; 34 are related to AR-HSP; 5 to X-linked XL-HSP, and one gene is related to SP with maternally inherited characteristics.

In this patient we detected a missense mutation of c.499 C>T (p.Arg167Cys) in gene KIF1A, a causative gene of type *SPG30,* which is seen in AR-HSP. The characterization of this gene mutation remains poor. AR-HSP cases with *SPG30* gene mutation have never been reported in China. Klebe *et al*.[8] reported one pedigree of *SPG30* gene mutation in eastern France, whose family was originally from Algeria. A total of four family members were affected. Their clinical manifestations included spastic paraparesis, peripheral neuropathy and mild cerebellar symptoms. Computed tomography (CT) revealed cerebellar atrophy, which was probably the cause of the mild cerebellar symptoms. In another report, Lee *et al*. identified a *de novo* missense mutations in *KIFIA* in 13 patients. These mutations were present in the blood DNA of the probands but not in the parents. These heterozygous *KIFIA* mutations included c.499C>T(p.R167C).[9] The report also mentioned that de novo missense mutation in the motor domain of KIFIA causes a phenotype being more severe than recessive mutations in the same gene. The difference between our case and the case in the report is that our patient has a simple HSP phenotype.

The pathogenic gene for *SPG30* is located on chromosome 2q37.3, which is known to encode for protein kinesin 3.[5] Genetic testing of this patient revealed a missense mutation of c.499C>T for the 167th codon. However, genetic testing of samples from his parents and sister showed no mutation of this gene, which suggest de novo missense mutation of this HSP case of an unknown etiology. The patient was diagnosed as a case of pure HSP based on the clinical manifestations of spastic paraplegia, with normal brain stem evoked potential.

The pathogenesis of HSP remains unknown. Deranged myelin formation, mitochondrial respiratory chain dysfunction, axonal transport interruption, cytoskeleton damage and vesicular transport blockade are believed to contribute to the axonal degeneration.[10] No effective therapeutic modalities are currently available.

In our patient, the hypertonic lower limbs did not respond to baclofen therapy in the first month, which required an increase in its dosage. Physiotherapy was administered as supportive treatment. Currently available treatment modalities only provide symptomatic relief and improve the patient's quality of life with no effect on the clinical course of the disease. Gene therapy tailor-made for each of these diseases may be the future therapeutic option.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Harding AE. Classification of the hereditary ataxias and paraplegia. *Lancet* 1983; 1:1151-5.
2. Faber I, Servelhere KR, Martinez AR, D'Abreu A1, Lopes-Cendes I, França-Jr MC. Clinical features and management of hereditary spastic paraplegia. *Arq*

Neuropsiquiatr 2014; 72:219-26.
3. Varga RE, Khundadze M, Damme M, *et al*. In vivo evidence for lysosome depletion and impaired autophagic clearance in hereditary spastic paraplegia type SPG11. *PLoS Genet* 2015; 11:e1005454.
4. Renvoisé B, Chang J, Singh R, *et al*. Lysosomal abnormalities in hereditary spastic paraplegia types SPG15 and SPG11. *Ann Clin Transl Neurol* 2014; 1:379-89.
5. Lee JR, Srour M, Kim D, *et al*. De novo mutations in the motor domain of KIF1A cause cognitive impairment, spastic paraparesis, axonal neuropathy, and cerebellar atrophy. *Hum Mutat* 2015; 36:69-78.
6. Fink JK. Hereditary spastic paraplegia: clinicopathologic features and emerging molecular mechanisms. *Acta Neuropathol* 2013; 126:307-28.
7. Kaplan JC, Hamroun D. The 2014 version of the gene table of monogenic neuromuscular disorders (nuclear genome). *Neuromuscul Disord* 2013; 23: 1081-111.
8. Klebe S, Azzedine H, Durr A, *et al*. Autosomal recessive spastic paraplegia (SPG30) with mild ataxia and sensory neuropathy maps to chromosome 2q37.3. *Brain* 2006; 129:1456-62.
9. Lee JR, Srour M, Kim D, *et al*. De novo mutations in the motor domain of KIF1A cause cognitive impairment, spastic paraparesis, axonal neuropathy, and cerebellar atrophy. *Hum Mutat* 2015; 36:69-78.
10. Svenstrup K, Møller RS, Christensen J, Budtz-Jørgensen E, Gilling M, Nielsen JE. NIPA1 mutation in complex hereditary spastic paraplegia with epilepsy. *Eur J Neurol* 2011; 18:1197-9.