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Pantothenate kinase-associated neurodegeneration with novel mutations: A case report

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Abstract

A 32-year-old male with pantothenate kinase-associated neurodegeneration (PKAN) disease who had two heterozygous mutations in the *PANK2* gene presented with dystonic storm. The MRI T2WI showed the "eye of the tiger" sign, which combined the abnormal low signal in the globus pallidus due to accumulation of iron and the longitudinal strip of high signal due to gliosis. The patient underwent bilateral globus pallidus internus deep brain stimulation (GPi-DBS) implantation surgery under general anesthesia with marked improvement. Genetic test showed c.1550T>G and c.377G>C heterozygous mutations in the *PANK2* gene. To our knowledge, this is the first report of a PKAN patient with the novel mutations in the *PANK2* gene.

INTRODUCTION

Pantothenate kinase-associated neurodegeneration (PKAN) syndrome is a rare, autosomal-recessive neurodegenerative disease caused by mutations in the *PANK2* gene affecting approximately 1-3 per million population.[1] PKAN is characterized by iron deposition and demyelination in the globus pallidus manifesting as progressive dystonia and spasticity clinically.

CASE REPORT

The patient was a 32-year-old Han Chinese male presenting with emaciation and increased muscle tone throughout the body. He had been born via normal vaginal delivery after an uncomplicated full-term pregnancy. The onset of the patient's symptoms began at age 5 years, when he had difficulty staying focused and paying attention. At age 7 years, the patient came to our hospital and was diagnosed with retinitis pigmentosa in both eyes with night blindness. At age 10 years, he had a wide-based gait and was prone to accidental falling, accompanied by sleeping problems. At age 19 years, he was bedridden, and was unable to speak and feed himself. Baclofen 20 mg/day was started to reduce the spasticity and the dose was increased to 40 mg/day gradually. Unfortunately, his symptoms was did not improve. At age 30 years, the patient was unsteady when he tried to sit, had stiffness in the neck and extremities, dysarthria, difficulty in opening his eyes (the ophthalmic examination did not reveal any ocular problems), and coughing while drinking water. The oral examination showed that the patient's lingual dystonia was accompanied by clenching of the teeth. Limb examination revealed the patient had increased deep tendon reflexes, ataxia and severe generalized dystonia, with marked bilateral clonus, blepharospasm and antecollis. The patient could not supernate his forearms and write but could grasp objects. The patient could perform the finger-to-nose test using the left hand, but could not do the same with the right hand. The patient had severe contraction of both calf muscles and inversion of both feet, resulting in equinovarus position both lower extremities, but no pathological reflex. Overall the symptoms on the left side were milder than that on the right. MRI T2WI showed bilaterally symmetrical, hyperintense signal in the anterior medial globus pallidus surrounded by hypointense signal. This combination of axial cranial MRI results was consistent with the "eye of the tiger" sign (Figure 1a). Based on the physical examination and MRI findings, PKAN disease was suspected. Sanger's sequencing analysis was performed and it revealed two heterozygous mutation in the *PANK2* gene at the c.1550T>G (p.V517G) and c.377G>C (p.G126A) splice sites which have not been previously reported in the literature (Figure 2). Gene sequencing confirmed that the patient had PKAN. The patient failed to respond to medications for PKAN. Due to patient's severe disability and the intractability of the dystonia, our hospital's medical ethics committee approved deep

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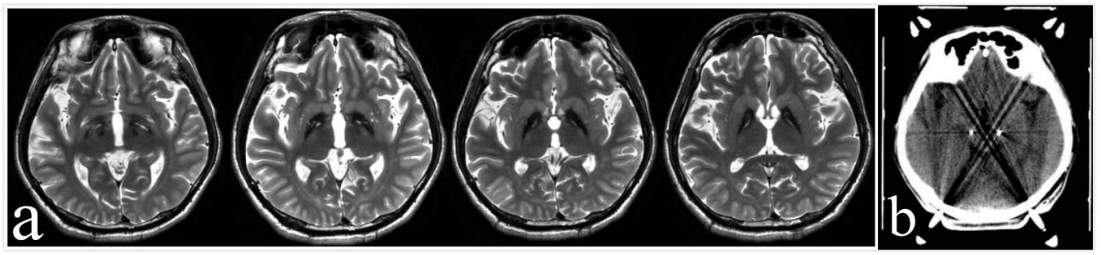

Figure 1. (a) The MRI T2WI shows the "eye of the tiger" sign, with combination of low signal in the globus pallidus due to accumulation of iron and the longitudinal strip of high signal due to gliosis. (b) The implant site of permanent DBS electrodes (Medtronic Inc., USA) is shown on CT.

brain stimulation (DBS) as a treatment option.

The patient underwent bilateral globus pallidus internus DBS (GPi-DBS) implantation surgery under general anesthesia (Figure 1b). The neurostimulator was switched on 2 weeks following the surgery. The parameters were set to achieve optimal control of the dystonia without side effects. During the visits after initial DBS implantation, we activated the DBS according to standard settings, based on the feedback from patient: R (3.0V, 135Hz, 70ms) and L (2.85V, 135Hz, 70ms) at the middle two contact points located in the globus pallidus. After one month of chronic DBS, the patient reported that he could open his mouth half-way, open his eyes more easily, and muscle tension in his limbs was also reduced. On pre-DBS, the patient scored 114 on the motor section and 28 on the disability section of Burke-Fahn-Marsden dystonia rating scale (BFMDRS).[2] At 3 months, 6 months, 1 year and 3 years after stimulation, both the motor and disability scores of the BFMDRS significantly improved at 41 and 18, 40 and 18, 47 and 19 respectively.

DISCUSSION

To our knowledge, this is the first report of a PKAN patient with two heterozygous mutations at the c.1550T>G (p.V517G) and c.377G>C (p.G126A) splice sites in the *PANK2* gene.

The globus pallidus internus is a common DBS target for the treatment of dystonia. Current GPi-DBS therapies focus on managing the dystonia to improve the patient's neurological disability. But to determine an optimal implant site to provide better benefit, more clinical trials are required. DBS not only regulates the brain neural network affecting the electrical signal pathway, but also affects the secretion of neurotransmitters.

We searched all the case reports of PKAN undergoing DBS surgery in PubMed. We found 8 PKAN patients (include 4 GPi-DBS and 4 subthalamic nucleus-DBS) who had BFMDRS scores preoperative and multiple occasions postoperative.[3-7] The follow-up BFMDRS scores of these 8 patients and our case were plotted into line charts (Figure 3). Their postoperative mean improvement rates of BFMDRS were 55.79%, 59.42%, 61.93%, 46.85% and 41.33% at 3, 6, 12, 24 and 36 months respectively. According to this line chart, we speculate that the process of DBS regulating the brain neural network is completed within 1 year and it is possible to estimate the level of long-term treatment effect by the means of patients' BFMDRS scores at 6 months after stimulation.

In conclusion, our patient's outcome suggests that GPi DBS can be an effective therapeutic alternative for medically intractable dystonic storm and generalized dystonia in PKAN patients.

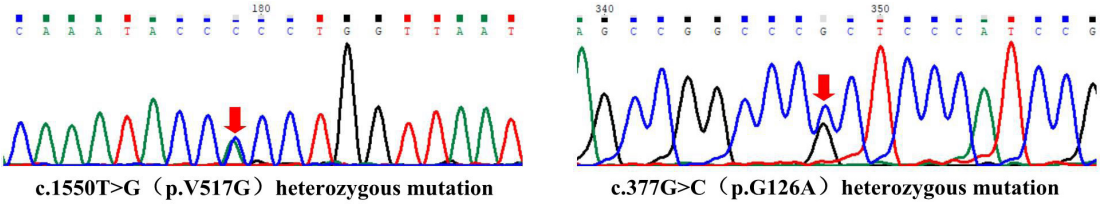

Figure 2. The mutation at the c.1550T>G (p.V517G) splice site observed is a rare variation with a frequency of 0.00005437, based on the gnomAD database for East Asian populations. Bioinformatics software SIFT and Polyphen2 were used to predict the variations that were potentially deleterious or damaging. The mutation at the c.377G>C (p.G126A) splice site is a common benign mutation based on ACMG.

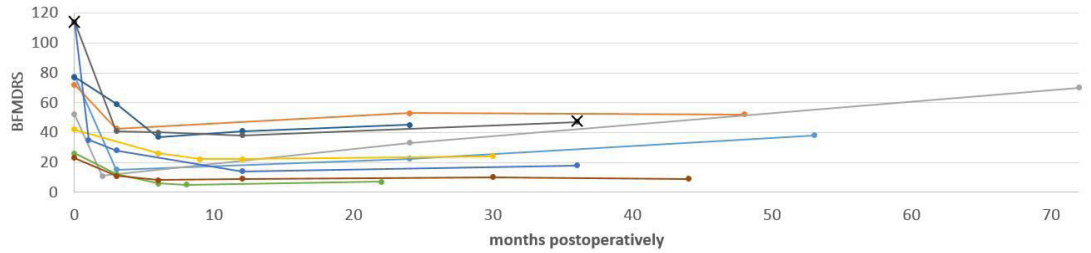

Figure 3. The DBS effect of the patient was nearly stable for 6 months after the surgery, and the score was observed to be slightly fluctuating 1 to 3 year after the surgery. The head and tail of the current patient's line were marked with "X".

Our patient also had novel c.1550T>G and c.377G>C heterozygous mutations.

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DISCLOSURE

Conflict of interest: None

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