Globus Pallidus Internus Deep Brain Stimulation for Pantothenate Kinase-Associated Neurodegeneration Dystonia

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Pantothenate kinase-associated neurodegeneration (PKAN) represents an autosomal recessive hereditary disease with progressive pharmacologically intractable dystonia. In this report, after consultation to neurologist for dystonia, a PANK2 gene mutation in a 50 year-old woman was identified. She suffered from dystonia and dystonic pain which cause difficulty in activity of daily living. We performed bilateral internal globus pallidus stimulation (GPi DBS) and the benefit was evident. She showed marked improvement in dystonia and dystonic pain with a significant reduction in disability. This study shows the importance of cooperation with neurologist and the benefits of GPi DBS for the dystonia of PKAN patient. To conclude, bilateral pallidal stimulation is an effective and safe treatment for intractable dystonia in PKAN.

KEY WORDS: Deep brain stimulation · PKAN · PANK2 · Dystonia.

INTRODUCTION

A heterogeneous group of autosomal recessive disorders characterized by iron accumulation in the globus pallidus and substantia nigra is called neurodegeneration with brain iron accumulation (NBIA). This was formerly referred to as Hallervorden-Spatz syndrome.²³⁾ Swaiman, et al suggested that the diagnostic criteria for the disease include the occurrence of a progressive disorder with dystonia, rigidity, tremor, and bradykinesia or choreoathetosis.¹⁹⁾ Additionally, the eye-of-tiger sign should be observed on T2-weighted images. This sign refers to a marked low signal intensity in the globus pallidus completely surrounding a hyperintense central area in the anteromedial region on otherwise normal-appearing magnetic resonance (MR) images.¹⁰⁾ There are several subtypes of NBIA. Among them, pantothenate kinase-associated neurodegeneration (PKAN), which accounts for 50% of cases, is the most common¹²⁾ and is caused by mutations in the PANK2 gene.²³⁾ PKAN is categorized into two phenotypes according to the age of onset, presenting signs and symptoms, and the rate of progression.9) Classic PKAN presents with dystonia, dysarthria, and rigidity in childhood. In addition, PKAN has an unyieldingly severe progressive course, culminating in early death.¹²⁾ Atypical PKAN shows late onset and slow progression of impairments in motor functions. However, in atypical PKAN, more prominent psychiatric symptoms, including depression, emotional lability, impulsivity, and violent outbursts are exhibited.¹⁶⁾

The treatment of PKAN mainly focuses on treating dystonia. Thus, pharmacotherapy for PKAN is guided by therapeutic experience in the treatment of other forms of dystonia. Albright, et al prescribed oral or intrathecal anticholinergics or gamma-aminobutyric acid agonists for the treatment of dystonia.²⁾ Dressler, et al.⁷⁾ treated patients using botulinum toxin injections. Levodopa has also been used.⁶⁾ However, most of these pharmacological therapies are typically ineffective in PKAN.⁵⁾ Refractory dystonia after medical treatment has prompted early neurosurgical approaches for treatment.²⁰⁾ Stereotactic lesioning such as unilateral thalamotomy,¹⁴⁾ bilateral thalamotomy.²¹⁾ and bilateral pallidotomy⁴⁾ has improved the treatment of dystonia with PKAN. However, because of the high risk of severe irreversible side effects, the use of stereotactic lesioning has been replaced by deep brain stimulation (DBS), which is an effective and reversible therapeutic method for treating dystonia.²⁰⁾ There are two DBS targets in the treatment of refractory dystonia and they are the globus pallidus internus and subthalamic nucleus. Pallidal stimulation (GPi DBS) is performed in cases of PKAN

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with drug-resistant dystonia, with results ranging from excellent to very modest improvement.¹⁾⁵⁾⁸⁾¹³⁾¹⁵⁾¹⁷⁾²⁰⁾²²⁾ Sub-thalamic stimulation (STN DBS) also shows similar efficacy when compared to GPi DBS.¹⁸⁾ In the present study, we performed bilateral GPi DBS to treat intractable generalized dystonia in a patient with PKAN.

CASE REPORT

A 50 year-old-woman visited our hospital due to her dystonic pain. A year ago, the abnormal posture of her neck suddenly started causing her mild pain. The abnormal posture and pain progressively extended to her upper trunk. After 5 months, she visited a local neurosurgery clinic and underwent brain magnetic resonance imaging (MRI). The neurosurgeon diagnosed her with primary dystonia using the normal brain MRI. He prescribed the injection of botulinum toxin in the affected muscles. The botulinum toxin showed some improvements in the symptoms. However, the improvement only lasted for a week. Her dystonia consistently progressed. When she visited our hospital, she complained of cervical and upper trunk dystonia with pain in the neck, upper back, and both arms. Because of her symptoms, she experienced difficulty in performing daily living activities such as television watching. We decided to perform pharmacotherapy because she had never undergone pharmacotherapy before. Anticholinergics (Trihexyphenidyl) and gamma-aminobutyric acid agonists (baclofen, clonazepam) were therefore prescribed for the treatment of primary dystonia. Even though she took the medication for 2 months, her symptoms were not improved. We subsequently considered treatment with bilateral GPi DBS for medically refractory primary dystonia. Before the surgical treatment, she was referred to a neurologist for a precise examination of the status of her disease. A review of her MRI revealed the eve-of-tiger sign on T2-weight images (Fig. 1). From this finding, PKAN was suspected and PANK2 mutation was detected in the gene. Based on her symptoms, MRI findings, and the results after analyzing her gene, she was diagnosed as having PKAN. Due to her severe dystonic pain, we planned to perform GPi DBS for medically refractory dystonia from PKAN. She scored 38.5/120 on the motor section and 1/30 on the disability section of the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) prior to the DBS. After obtaining informed written consent, the surgical procedure was performed under monitored anesthesia care for



Fig. 1. Preoperative T2-weighted MR image of a patient with PKAN showing the characteristic "eye-of-tiger" appearance which represents an area of low signal intensity in the GP and an anteromedial area of high signal intensity due to iron deposition in the pallidum.

micro-electrode recording. Coordinates for the GPi were set according to standard coordinates but were modified based on preoperatively acquired 3T MR images. During the procedure, which involved the frame-based stereotactic technique, the neurophysiological target verification was made by simultaneous micro-electrode recording. After the verification of the bilateral coordinates, quadripolar DBS leads 3387 (Medtronic, Minneapolis, U.S.A.) were implanted on each side. Subsequently, internal pulse generator (IPG) Activa PC (Medtronic, Minneapolis, U.S.A.), which is dual-channel device capable of delivering bilateral stimulation was placed in the left subclavicular pocket and was subcutaneously connected to the DBS leads. The positioning of the electrodes in the GPi was verified with fusion images of postoperative CT and preoperative MRI (Fig. 2). After recovering from anesthesia, she still showed dystonia and complained of dystonic pain. However, there was no immediate surgical complication. Two weeks later, the DBS system was turned on. Each side had a different electrical setting. On the right side, Contact 0 was used as the cahthode and IPG to anode the electrical setting wasn a voltage of 1.5V, a frequency of 150Hz, and a pulse width of 150µs. On the left side, Contact 1 was used as the cathode and IPG to the



Fig. 2. Fusion image of postoperative CT and preoperative MR images of a patient with PKAN which demonstrates the appropriate placement of DBS electrodes in the bilateral GPi.

anode, the electrical setting was voltage of 2.5V, a frequency of 150Hz, and a pulse width of 150µs. Immediately after stimulation, she exhibited marked improvement in her dystonia and dystonic pain. The improvement her dystonia was objectively evaluated on the BFMDRS. Her BFMDRS score was 1.5/120 on the motor section and 0/30 on the disability section.

DISCUSSION

PKAN is a not well-known disease among neurosurgeons. Therefore, neurosurgeons easily misdiagnose PKAN as primary dystonia. The hallmark of PKAN is the eye-oftiger sign observed on T2-weighted MR images. Therefore, when the eye-of-tiger sign is observed during MRI in dystonia patients, PKAN should be considered as the first differential diagnosis.

After the identification of the pantothenate kinase-based pathogenesis of PKAN, there were efforts to find pharmacological treatments for the disease.²⁾⁶⁾⁷⁾ However, these treatments exerted only minimal effects on symptoms of patients.⁵⁾ As a result, the functional neurosurgical approach is currently the most important alternative for PKAN patients. Because DBS is less destructive and adaptable to each patient's needs, DBS is preferred to stereotactic surgery which includes thalamotomy and pallidotomy. There are reports on cases where DBS electrodes were implanted in patients with PKAN.^{1)8)13)15)17)20)22) In} most of these cases, when the DBS system was turned on, the symptoms of patients, including dystonia, markedly improved compared to the pre-DBS state. 1)8)13)15)17)20)22) There is currently no consensus on the target of DBS in patients with PKAN. The subthalamic nucleus, which is supported by theoretical assumption that describe the functional organization of basal-ganglia-thalamocortical circuits,³⁾¹¹⁾ is also considered a possible target of DBS in patients with PKAN. Schjerling, et al. reported that both STN DBS and GPi DBS have similar efficacies.¹⁸⁾ However, due to our lack of experience in performing STN DBS in secondary dystonia, we performed GPi DBS instead. In our case, the outcome of the GPi DBS was excellent, especially in the treatment of dystonia. This result is consistent with those of previous studies in which GPi DBS was implanted in patients with PKAN.¹⁾⁸⁾¹³⁾¹⁵⁾¹⁷⁾²⁰⁾²²⁾

CONCLUSION

DBS, particularly in the GPi, is a long-lasting and efficient treatment for dystonia with PKAN. Therefore, GPi DBS should be considered when pharmacotherapy fails. GPi DBS can reduce dystonia and painful spasm, and improve the performance of activities of daily living. Our study demonstrates a promising method for the treatment of dystonia with PKAN.

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