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Case study

Deep brain stimulation as a mode of treatment of early onset pantothenate kinase-associated neurodegeneration

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ABSTRACT

We report a case of a young girl with early onset pantothenate kinase-kssociated neurodegeneration (PKAN) whose initial clinical manifestation was ataxia at the age of 2.5 years. Subsequently the patient presented to us with refractory severe dystonia resulting in essentially complete loss of motor control. She had a mutation in PANK2 gene consisting of an aminoacid change of Alanine to Valine in exon 5 (A382V). After Globus Pallidus deep brain stimulation (DBS) at the age of 11 years, the patient regained useful motor function and speech with a marked decrease in the severity of the dystonia. The patient's condition gradually returned to her pre-DBS status when the device had to be removed 3 months later due to infection. Our case is the sixth case with classical PKAN that was treated by Globus Pallidus stimulation, the fifth one to have a favorable response to it and the only one in whom response was proven by the inadvertent removal of the DBS device due to infection. In addition, our case had a novel mutation and novel clinical features (onset with ataxia, occurrence of early seizure activity) on top of her other symptoms that were otherwise typical of early onset disease.

1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a rare progressive disorder that causes Parkinsonism, dystonia, cognitive decline, and other neurological deficits. Many patients with NBIA have mutations in the gene encoding pantothenate kinase 2 (PANK2) and are considered to have pantothenate kinase-associated neurodegeneration (PKAN).[1] Medically refractory dystonia due to causes other than NBIA was previously subject to ablative stereotaxic surgery such as pallidotomy. With the use of high-frequency deep brain stimulation (DBS) many patients with previously refractory generalized dystonia show marked improvement in their symptoms with less permanent neurological deficits.[2] To our knowledge, there have been, so far, very few cases reported of NBIA that have been treated with DBS.[3,4] In this article we

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report the fifth case in which DBS was useful in clinical PKAN and the first in whom a favorable response was proven by the inadvertent removal of the device due to infection.

2. Case report

Our patient D.H. is a 11-year-old female product of uncomplicated full-term pregnancy to consanguineous, first cousin parents from a normal vaginal delivery. Her symptoms started at 3 years of age when she developed unsteady wide based gait, ataxia and difficulty in maintaining equilibrium, "walking like a drunk", which made her subject to many episodes of falls and multiple fractures. In the next few years she developed progressive muscle stiffness which started in the right upper extremity and progressed further to include the left upper extremity and later the trunk and the lower extremities. Her gait continued to be unsteady; the patient also concurrently developed a progressive decrease in vision. The stiffness then increased in the neck and orofacial muscles with difficulty in swallowing foods together with slow and slurred articulation. At the age of 8 years she had an episode of a reported single generalized tonic clonic seizure. She was treated with Phenytoin for few months, and then Phenytoin was discontinued. When she presented to us at the age of 9 years an ophthalmoscopic examination was positive for "beaten" bronze maculae, retinal pigment epithelial changes and attenuated blood vessels consistent with the picture of retinitis pigmentosa. Visual acuity was 20/100. On physical exam she was also not able to walk more than a few steps due to her stiffness and ataxia, had upper and lower extremity increased tone with abnormal posturing and +2 deep tendon reflexes, but had otherwise an unremarkable exam. MRI of the brain showed the classical "eye of the tiger" sign. The patient failed multiple repeated medication trials with the following drugs: Levodopa/Carbidopa, Phenytoin, Baclofen, Clonazepam, Trihexyphenidl, and Diazepam. Despite this and despite physiotherapy the patient continued to deteriorate with severe diffuse increase in tone and increasingly worsening continuous dystonia associated with disabling pain. She soon became unable to sit without support and was completely bedridden. Her younger sister, who is 2 years younger, started experiencing similar symptoms at the age of 6 years. The PANK2 gene 7 coding exons were screened. These showed a mutation in the homozygous state in the PANK2 gene 1145 C>T (A382V) in exon 5 resulting in an Alanine to Valine change at the amino acid position 382. Upon admission, at the age of 10 years, the patient was awake, conscious, but completely averbal and bedridden having continuous dystonic involuntary posturing of her four limbs, trunk, and neck with superimposed intermittent severe painful dystonic spasms. She was able to speak only a few single words with maximal effort and with very severe dysarthria. When asked to move her extremities she usually could not do that. Occasionally, she would be able to move them only 1–2 cm. Often dystonic spasms, which were precipitated by attempts of movement, prevented her from moving her limbs. The patient was not able to walk or to sit and was not able to handle, grasp or even reach for objects. Also, her feet were deformed bilaterally in a fixed equinovalgus position. Because of her marked generalized stiffness and rigidity, her motor power could not be assessed. She also had hyperreflexia (+3), severe muscle wasting, and was incontinent of urine and of stools, apparently due to her severe motor disability.

The patient at the age of 11 years underwent insertion of a "Kinetra" battery, the only DBS battery available in our country, for the DBS in the Globus Pallidus Internus. The stereotactic Leksell frame was applied to the head of the patient. A CT scan of the brain was done with the stereotactic frame on. After that, the images were transferred to the Stealth Station where the CT scan was fused with the MRI of brain that was acquired few days before for the purpose of targeting. After the fusion of the images, the target was identified on the system. We targeted the posteroventrolateral part of the GPi bilaterally. The coordinates of the targets in relationship of the mid point of the AC–PC were as follows: On the right side laterality 14.59 AP 5.64, verticality −2.06; on the left side laterality −14.5 AP 5.10, verticality −0.43. Using the coordinates previously calculated on the Stealth Station, the DBS electrode was inserted. Intra-op C-arm X-ray was used for the verification of the position of the tip of the electrode. The tip of the electrode was exactly at the center of the target.

It was adjusted within 14 days of surgery in the following manner:

- *Channel* 1: Case positive. Electrodes 0 and 1: negative, electrodes 2 and 3: off. Amplitude = 0.5 mV, frequency = 185 Hz, pulse width = 120 Ms.
- *Channel* 2: Case positive. Electrodes 4 and 5: negative, electrodes 6 and 7: off.
- Amplitude = 0.5 mV, frequency = 185 Hz, pulse width = 120 Ms.

The patient was followed up postinsertion of the electrodes and 2 weeks later the patient was less rigid, was able to stand unassisted alone for few seconds, follow commands like "raise your arm" and "point to your dad". She was able to vocalize many words, but was still dysarthric. She was able upon request to give her name, her parent's names and to answer simple questions such as "what do you want to eat". She also had better voluntary movement of the extremities. The battery was further readjusted to the amplitude of 1 mV bilaterally. The patient subsequently started to respond better to physiotherapy and 2 weeks later, the parents noted further improvement characterized subjectively by them, as "more than 70% improvement" as compared to her initial presurgical situation. By that time, she was able to sit unassisted, to apply force against resistance, to hold objects in her hands and to transfer them from one hand to the other as well as to resist forces. She also was able to execute new movements in response to commands like shaking hands, moving arms and legs that she was able to do with relative ease and minimal rigidity. She also had further decrease in muscle tone in the extremities that was by that time only mildly increased. She also no longer had her previous disabling painful dystonic spasms. So according to Barry–Albright dystonia scale[5] and to Functional Independence Measure (WeeFIM) for children,[6] our patient improved from a score of 24/36 to 8/36 and from 1/7 to