DBS Treatment in a 18-Year-Old Patient with Refractory Dystonia Due to DYT1 Mutation: a case report

Camilla Caetano Alves da Motta¹
Bruna Marques Lopes¹
Daniela Rumi Fujita¹
Pedro Henrique Simm Pires de Aguiar²
Nilton Alves Lara Junior³
Paulo Henrique Pires de Aguiar⁴

ABSTRACT

Purpose: To present a case of an infrequent refractory dystonia due to DYT1 gene mutation in an 18-year-old male patient that was later treated with Deep Brain Stimulation (DBS). Case presentation: Male 18-year-old patient, affected by torsion dystonia of the neck and upper limbs is reported. Genetic analysis identified a DYT1 gene superexpression mutation. Previous therapies had included physiotherapy, botulinum toxin injection, drugs such as primidone and clonazepam, but all with little improvement. The patient underwent two neurosurgeries in order to insert Deep Brain Stimulation (DBS) on his left and right internal Globus Pallidus (GPi). The electrodes inserted were Medtronic® 3389 and the generator was Activa RC rechargeable. The postoperative period of both procedures were successful, without any identified deficits. After a 2-year follow-up period, the patient presents a normal life compared to the average of his age, without any of the symptoms or complications that he had before. Conclusions: DYT1-dystonia is a disabling disease that can affect young patients but shows good prognosis with DBS therapy. The reported case presented an excellent outcome particularly because it involves a young patient with DYT1-related dystonia.

Keywords: DYT1; Dystonia; DBS

RESUMO

Objetivo: Apresentar um caso de uma infrequente distonia refratária por mutação no gene DYT1 em um menino jovem que foi tratado com estimulação cerebral profunda (DBS – da sigla em inglês). Relato do caso: Jovem de 18 anos do sexo masculino afetado por uma distonia de torção cervical do pescoço e membros superiores. A análise genética identificou uma mutação de superexpressão no gene DYT1. Terapias prévias incluíram fisioterapia, injeções de toxina botulínica, drogas como primidona e clonazepam, mas todas com pouca ou nenhuma melhora. O paciente foi submetido a duas neurocirurgias para inserção do DBS no lado esquerdo e direito do Globo Pálido interno (GPi). Os eletrodos inseridos foram da Medtronic® 3389 e o gerador foi Activa RC rechargeable. O pós-operatório de ambos os procedimentos foi de sucesso, sem nenhum déficit identificado. Após um seguimento de 2 anos, o paciente apresenta vida normal comparada à média de sua idade, sem nenhum sintoma ou complicação que apresentava antes. Conclusão: O caso apresentado mostrou excelente evolução por se tratar de jovem com distonia por DYT1. Esse tipo de distonia é uma doença que pode acometer jovens, mas tem bom prognóstico com a inserção do DBS.

Palavras-chave: DYT1; Distonia; DBS

¹ Medical student, Faculty of Medical Sciences of Santa Casa de São Paulo, São Paulo, SP, Brazil.
² Medical student, Faculty of Medicine, Pontifical Catholic University of São Paulo, São Paulo, SP, Brazil.
³ MD, PhD, Neurosurgeon, Department of Functional Neurosurgery, Santa Casa de Misericoírdia de São Paulo Hospital, São Paulo, SP, Brazil.
⁴ MD, PhD, Neurosurgeon, Department of Neurosurgery, Santa Paula Hospital; Professor, Faculty of Medical Sciences of Santa Casa de São Paulo; Professor, Medical School of ABC, São Paulo, SP, Brazil.

Received June 6, 2022
Corrected Aug 15, 2022
Accepted Aug 15, 2022
**INTRODUCTION**

Dystonia may be defined by abnormal involuntary movements or postures due to sustained or intermittent muscle contractions. It is a highly stigmatizing and disabling condition, just as other movement disorders. One of the most common aetiologies of early onset, dystonia — with symptoms beginning in childhood of adolescence — is due to the mutation in the DYT1 gene: up to 53% of all cases in non-Jewish populations and about 80% in Ashkenazi Jewish population, because of a founder mutation. The penetrance of this autosomal dominant gene is 30%, meaning that 70% of all gene carriers have no signs or symptoms of dystonia.

Typically, the clinical manifestation of this type of dystonia will begin at the average age of 13 years, involving more likely a limb or, less frequently, the trunk, cervical or cranial muscles. More than half of these cases will progress to a generalized dystonia, involving other limbs and/or the trunk.

The pathophysiology of DYT1-dystonia involves a GAG deletion in the coding region of the TOR1A gene located on chromosome 9, resulting in a disorder of anomalous regulation of transcription and neuronal circuit development. The mutant gene product — torsinA — has been found to be stocked intracellularly and interact abnormally with other proteins. Overall, the outcome of this mutation is a neurodevelopmental circuit disorder involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways.

The objective of this report is to present a case of a severe refractory dystonia due to DYT1 mutation in an 18-year-old boy, who was later treated with Deep Brain Stimulation (DBS). Also, the possible treatments for this disease will be discussed.

**CASE PRESENTATION**

Male patient, 18-year-old, affected by segmental cervical dystonia was reported. First, he exhibited symptoms when he was 15 years old and, within one year through the course of the disease, and he had a number of complications including severe pain, recurrent pneumonia and social isolation due to his condition. Physical examination revealed a bilateral torsion dystonia of the neck and proximal third of the upper limbs, with more prominent signs on his right side (Figure 1). His genetic analysis identified a DYT1 gene superexpression mutation. In previous medical care, he was oriented towards treatments such as physiotherapy, botulinum toxin injections, drugs such as primidone and clonazepam, but all with little improvement.

The attending neurosurgeon indicated a procedure to treat initially the symptoms of the right side, as it was the more severely affected. A Magnetic Resonance Imaging (MRI) of the patient’s head was done in order to make the surgical planning. The neurosurgery was performed in March 2018 to implant a DBS on the left internal globus pallidus (GPi) posteromedial area with general anesthesia. The generator was implanted on his right side, under the skin in the upper chest. The electrodes inserted were Medtronic® (Minneapolis - MN, EUA) 3389 and the generator was Activa RC rechargeable, with 0.5 mm spacing. The following programming was set: current of 3 mA, frequency of 130 Hz and pulse width of 90 μs. The procedure was successful and the patient was discharged from the hospital 4 days post-operative (PO) (Figure 2A).

After 10 months, in January 2019, the same procedure was performed in the right GPi, aiming to treat his dystonic tremors located in the left part of the body. The procedure was also successful, without any deficit, with the patient being discharged from the hospital at the PO day 2 (Figure 2B).

During a 2-year follow-up period, the patient presented a normal life compared to the average of his age, without any of the symptoms or complications he had before. He regularly attends to physiotherapy and fitness centers to maintain muscle training.

**DISCUSSION**

The patient presented a severe refractory dystonia due to DYT1 mutation. Regarding the recommended treatment for early onset dystonia, it aims mostly at relieving the symptoms. The first option of therapy are botulinum toxin injections, mainly if it is a focal or segmental dystonia. If refractory to this step or in case of a generalized dystonia, the next option are oral medications,
such as anticholinergics or benzodiazepines. Once more, if the disease is refractory to the previous therapies, a surgical treatment can be tempted: a system called Deep Brain Stimulation (DBS) consists in the insertion of an electrode in a specific part of the brain, in order to modulate the patterns of electrical activity.

Our patient went through clinical therapies including physiotherapy, botulinum injections and oral medications, but not only he still presented the dystonia symptoms of intermittent muscle contractions but also complications due to the disease: severe pain, recurrent pneumonia and social isolation. The respiratory disease most likely resulted from the decrease of the size of his thoracic cavity, due to the dystonic posture. As for the social isolation, it can be analyzed as a collateral effect of the severity of his disease: Junker et al. demonstrated significant correlations between Health-Related Quality of Life (HRQoL) subscales such as social functioning and emotional role functioning, and dystonia severity. Those complications exhibited by our patient are within the most common of this disease, including chronic pain, depression, anxiety, social stigma, and reduced self-esteem, all leading to an impaired HRQoL.

The adequate management of the disease is important to avoid the decreased well-being and that is the main idea brought...
by this report: young patients with refractory dystonia may have more lifetime with higher quality of life when there is an early approach of DBS, specially if there is a presumption of a DYT1 mutation.

Supporting this statement, Tsuboi et al. showed in a systematic review that patients with inherited isolated dystonia reported significant improvement in motor function and pain after DBS surgery, leading to an improved overall life satisfaction.

Our patient had important symptoms regarding physical and social spheres, but after the insertion of DBS bilaterally, he claimed to have an immeasurable improvement in both of the complaints.

As for the medical literature, the results from the last five years in PubMed database with the keywords “Dystonia”, “DBS” and “DYT1” are scarce, with 12 papers in the English language, seven from which correlate with this report. Mainly, their data showed that the surgical stimulation is efficacious and can potentially prevent disease progression in the long term, and also a great improvement in motor and disability scores post-operatively. From all dystonias, the one with the best prognosis is DYT1-related. Other positive predictive factors for good prognosis after DBS insertion are short disease duration and isolated idiopathic dystonia. One study even showed that 8% of their DYT1-dystonia cohort presented suboptimal response after DBS implantation (less than 30% of improvement over baseline), but still the long-term follow-up demonstrated beneficial effects of the stimulation, compared to before the procedure. All of these data are in line with our case report, showing significant improvement after DBS implantation in young patients with severe DYT1-dystonia.

CONCLUSION

DYT1-dystonia is a disabling disease that can affect young patients but it has good prognosis with DBS therapy. The reported case showed an excellent outcome particularly because it involves a young patient with DYT1-related dystonia.

Finally, the surgical treatment with DBS should not be delayed in refractory dystonia patients, specially in the DYT1-type, as it has great prognosis and leads to a great difference in their quality of life.
Case Report

Motta CCA, Lopes BM, Fujita DR, Aguiar PHSP, Lara Junior NA, Aguiar PHP - DBS Treatment in an 18-Year-Old with Refractory Dystonia Due to DYT1 Mutation: a case report

REFERENCES


CORRESPONDING AUTHOR

Camilla Caetano Alves da Motta
Medical student
Faculty of Medical Sciences of Santa Casa de São Paulo
São Paulo, São Paulo, Brazil
E-mail: camillamotta1@gmail.com

Funding: nothing to disclose.
Conflicts of interest: nothing to disclose.