


# Severe Pediatric Dystonia Responding to Deep Brain Stimulation in 22q11.2 Microduplication Syndrome: Rare Clinical Presentation

Hanin Jaber AlGethami, MD,<sup>1,2</sup> Sara Breitbart, MN,<sup>3</sup> Nebras M. Warsi, MD, PhD,<sup>3,4</sup> Alfonso Fasano, MD, PhD,<sup>5,6,7,8,1</sup> George M. Ibrahim, MD, PhD,<sup>3,4,9</sup> and Carolina Gorodetsky, MD, MSc<sup>1,2,\*</sup> 

The 22q11.2 region is known to be susceptible to chromosomal rearrangements, such as microdeletion and microduplications. Microduplication syndrome manifests with a spectrum of presentations, ranging from normal to severely affected phenotypes.<sup>1,2</sup> Dystonia has not been previously reported in association with this syndrome. In this letter, we describe a case of an 8-year-old girl who presented with severe generalized dystonia that significantly impaired her quality of life. Genetic investigations identified 22q11.2 microduplication as the underlying etiology. Treatment with medications was ineffective, and thus the patient underwent deep brain stimulation (DBS) targeting the globus pallidus pars interna (GPi), resulting in favorable outcomes. This letter expands the microduplication syndrome phenotype and highlights DBS's potential role in future cases.

This letter pertains to an 8-year-old female who was born via C-section at 36 weeks of gestation and was discharged on the third day after delivery. The patient had been in good health until she reached the age of 1 month when she developed dystonic movements in her neck. The symptoms worsened by the age of 6 months and began to involve her arms and hands, causing gross and fine motor developmental delays. She was not able to sit or stand unsupported, and never achieved autonomous gait.

Her dystonia progressed over the next few years and she became wheelchair-bound, by the age of 5 years old, without any functional use of her hands. Her speech was affected, but no swallowing concerns. No family history was reported. Her neurological exam showed right-sided neck torticollis and generalized dystonia, affecting the left side of her body more than the

right. The movement sub-score of the Burke-Fahn-Marsden Dystonia Rating Scale<sup>3</sup> was 72/120 (Appendix S2). The patient did not exhibit any dysmorphic features or systemic manifestations (Video 1).

Her basic blood work and metabolic screening came back normal. An MRI of her brain showed no abnormalities, but genetic testing using microarray technology revealed a microduplication at 22q11.2 (2.8 Mb in one copy of chromosome 22q at band 22q11.21.). A genetic dystonia panel (GeneDx) was negative (Appendix S1), and levodopa treatment did not significantly improve her dystonia.

At 7 years of age, the patient underwent bilateral (GPi DBS, Fig. 1). Following surgery, she looked well, the mobile component of the dystonia improved significantly in the upper and lower extremities allowing for a bit more balanced and coordinated movements, (Video 2). The DBS settings were adjusted with ventral contacts being the most effective for her symptoms (Appendix S3).

During the patient's subsequent clinical encounters, and within the first 3–4 months, an amelioration of 30% was observed in the movement sub-score of the BFMDRS scale, which now scored 50 out of 120 (Appendix S2). The patient exhibited enhanced speech clarity, augmented ambulatory capability like walking a few steps with support, and an ability to perform jumping movements. Moreover, the patient demonstrated increased manual dexterity and fine motor skills, as evidenced by her ability to operate buttons with her right hand, and to perform drawing with her toes. The evaluation of the patient's quality of life utilizing the Pediatric Quality of Life Inventory<sup>4</sup>

<sup>1</sup>Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada; <sup>2</sup>Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada; <sup>3</sup>Division of Neurosurgery, The Hospital for Sick Children, Toronto, Ontario, Canada; <sup>4</sup>Department of Surgery, University of Toronto, Toronto, Ontario, Canada; <sup>5</sup>Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada; <sup>6</sup>Division of Neurology, University of Toronto, Toronto, Ontario, Canada; <sup>7</sup>Krembil Brain Institute, Toronto, Ontario, Canada; <sup>8</sup>CentRe for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada; <sup>9</sup>Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

\*Correspondence to: Carolina Gorodetsky, Division of Neurology, Assistant Professor, Faculty of Medicine, Division of Neurology, The Hospital for Sick Children, University of Toronto, 555 University Avenue Toronto, ONM5G 1X8, Canada. E-mail: [carolina.gorodetsky@sickkids.ca](mailto:carolina.gorodetsky@sickkids.ca)

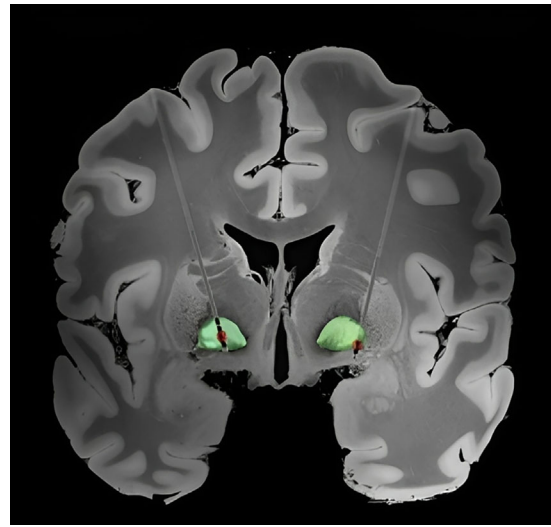
**Keywords:** 22q11 duplication, pediatric dystonia, deep brain stimulation.

Received 6 July 2023; revised 22 October 2023; accepted 29 November 2023.

Published online 9 January 2024 in Wiley Online Library ([wileyonlinelibrary.com](http://wileyonlinelibrary.com)). DOI: 10.1002/mdc3.13955



**Video 1.** Pre-DBS activation. DBS, deep brain stimulation. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13955>



**Figure 1.** Anatomical lead localization and volume of tissue activated (VTA). The Lead-DBS anatomical localization of implanted leads in the globus pallidus internus (GPI) for the patient. 3D reconstruction of the DBS leads was illustrated on a 100-micron resolution, 7.0 Tesla FLASH brain in MNI152 space30. The green highlighted structure is the GPI based on the DISTAL atlas within Lead-DBS. VTA (red) is shown based on the stimulation settings 1 year after the DBS surgery.<sup>5</sup>

showed an improvement from a baseline score of 47 to 80 one-year post-DBS (Video 2).

Microduplication of the 22q11.2 region refers to the presence of an additional copy at position q11.2 on chromosome 22. This condition typically presents with a broad range of symptoms, ranging from mild to severe phenotypes, such as intellectual disabilities, delayed psychomotor development, and hypotonia. Additionally, various anomalies have been associated with this condition, including hypertelorism, hearing impairment, velopharyngeal insufficiency, and seizures.<sup>1</sup> Recently, some literature has suggested a higher prevalence of autism spectrum and psychiatric disorders among the affected patients.<sup>6,7</sup> However, to the best of our knowledge, there have been no prior reports of dystonia associated with microduplication of 22q11.2, highlighting the importance of microarray analysis in children with suspected genetic dystonia.

There appear to be some similarities between microdeletion and microduplication syndromes. Microdeletion of 22q11.2 is a well-established condition, characterized by a variety of dysmorphic features and involvement of multiple organ systems, including cardiovascular, endocrine, immune, psychiatric, and neurological systems.<sup>2</sup> Parkinson's disease and dystonia have been reported as potential associations with the condition,<sup>8</sup> whereas 22q11.2 duplication syndrome is more associated with hypotonia. Although our patient exhibited a relatively large duplication, her clinical presentation was limited to generalized dystonia.



**Video 2.** Post DBS. DBS, deep brain stimulation. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13955>

Interestingly, the genes situated in the 22q11.2 region that could potentially play a role in the development of abnormal movements, include *DGCR8*, *microRNA-185*, *SEPT5*, and *COMT*.<sup>9</sup>

DBS has become increasingly popular in the pediatric population over the past decade, particularly in cases of genetic dystonias such as *DYT-TOR1A* and *DYT-KMT2B*, which have shown favorable clinical outcomes in studies. There are few reports suggesting the potential utility of DBS in ultra-rare conditions similar to the case here.<sup>10</sup> Further studies are necessary to investigate the effectiveness and safety of DBS in these rare conditions and to determine the most appropriate patient selection criteria and long-term outcomes.

## Acknowledgments

We wish to thank the health care providers who assisted in caring for this individual as well as the patient and his family.

## Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

H.A.: 3A

S.B.: 3B.

N. W.: 3B.

A.F.: 3B.

G.I.:3B.

C.G.: 1A, 1B, 1C.

## Disclosures

**Ethical Approval:** We confirm that the approval of an institutional review board was not required for this work, and an

informed consent was obtained. Also, we confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

**Funding Sources and Conflicts of Interest:** We declare that there are no conflicts of interest relevant to this work.

**Financial Disclosures for the Previous 12 Months:** We declare that there are no additional disclosures to report. ■

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## Supporting Information

Supporting information may be found in the online version of this article.

**Appendix S1.** Supporting Information.