Double Trouble: A Case of DYT-TOR1A Diagnosed in the Postoperative Period

Dear Editor,

Dystonia is a neurological condition characterized by sustained or intermittent muscle contractions resulting in abnormal involuntary movements or postures. The 2013 consensus update on the classification of phenomenology and clinical features classifies dystonia as isolated, in which dystonia is the only clinical feature without other neurological or systemic manifestations and combined forms in which other neurological and/or systemic manifestations coexist.[1] While isolated dystonia may result from genetic mutations, the etiology still remains unknown in some patients. Based on the parts of the body affected, dystonia can be subclassified as focal in which one region of the body is affected, segmental (in which adjacent regions are involved), and generalized (in which several different regions are affected). The discovery of the genetic origin underlying isolated or combined dystonia has provided a better understanding of the pathophysiology.[2] The *TOR1A* gene, the most common cause of isolated genetic dystonia in childhood, is associated with early-onset generalized dystonia.[3] In most patients with DYT-TOR1A, an in-frame GAG deletion in *TOR1A* leads to a glutamic acid residue in the protein torsinA.[4] TorsinA, a ubiquitously expressed enzyme, plays a role as a chaperone in the endoplasmic reticulum.[5] TorsinA acts as an *in vitro* molecular chaperone, increasing heat shock proteins in stress situations.[6] In this paper, we present a DYT-TOR1A case with a history of spinal surgery due to dystonia, in whom clinical findings progressed gradually and generalized in the postoperative period. Thus, we want to contribute to elucidate the pathomechanism of this particular condition.

A previously healthy 9-year-old female patient was presented to the neurosurgery department with left leg contraction that began 1 year ago. Spinal MRI revealed intradural extramedullary lesion with a mass effect at the levels of the cervical 7 and thoracal 2 (C7-T2) vertebrae [Figure 1] and was operated (extramedullary cyst drainage). She was discharged uneventfully, and a pathological study revealed an arachnoid cyst. During the postoperative follow-up as the complaints increased, the child was referred to pediatric neurology with contraction in her left arm and left leg and a new complaint, speech disorder. Personal and family medical histories were unremarkable. Neurodevelopment was compatible with her age. Neurological examination revealed bilateral brisk patellar deep tendon reflexes, failure to speak due to contraction of the tongue, and activity-induced convoluted dystonic movements in the left leg and left arm. Dystonic movements disappeared during rest and sleep. Brain and spinal MRIs and extensive biochemical and metabolic evaluations were unremarkable. To exclude dopamine-responsive dystonia, levodopa was started at a dose of 1 mg/kg/day and gradually increased within 2 months to reach the optimal dose but discontinued due to lack of benefit. Therefore, a single gene analysis was planned for *TOR1A.* The DYT-TOR1A gene analysis was performed because it is the most common cause of early-onset isolated genetic dystonia and the clinical findings of our patient are similar. Oral baclofen and intramuscular botulinum toxin was used for symptomatic relief. Aside from failing to respond to these treatments, the dystonia progressed to the right upper extremity muscle groups. In genetic analysis, a de novo heterozygous pathogenic variant *(*c907_909del p.Glu303del E303 del) was found in the fifth exon of the *TOR1A* gene. Her parents are unaffected and do not indicate for this variant. In addition, this variant in the TOR1A gene was interpreted as pathogenic according to the American College of Medical Genetics (ACMG) criteria. Trihexyphenidyl was started at a dose of 4 mg/kg/day and was gradually increased to 30 mg/day. During follow-up, the Burke-Fahn-Marsden Dystonia Rating score decreased from 19 to 12.[7]

Dystonia is a heterogeneous entity with diverse etiologies and clinical presentations. Aside from being commonly referred to as basal ganglia disease, abnormal motor circuits including the cerebral cortex, thalamus, and cerebellum, together with altered neural connectivity and synaptic plasticity, have been reported to be a possible explanation for the pathogenesis of dystonia.[8-10] In addition, an association of the dystonia with structural changes in the brainstem, spinal cord, and peripheral nerves has also been reported.[11] Although surgery history of the spinal lesion in our patient initially suggested the possibility of spinal causes, acquired focal dystonia of childhood mostly originates from the cerebral cortex, cerebellum, and basal ganglia. Dystonia due to rare spinal cord lesions is seen especially in the upper extremity or cervical muscles.[12,13] However, our patient's lesion was located between C7 and T2

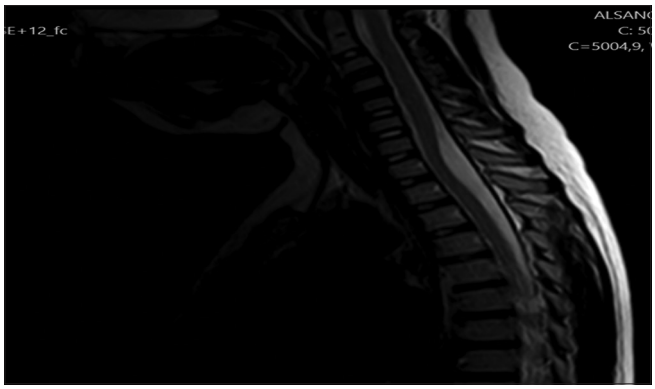

Figure 1: Intradural extramedullary lesion at the levels of C7–T2 vertebrae

vertebrae. In addition, the progressive spread of the disease to the tongue suggested neurodegenerative conditions leading to dystonia. Therefore, we ruled out dopamine-responsive dystonia due to her levodopa unresponsiveness at the first stage. We then performed a single gene analysis for *TOR1A*, since DYT-TOR1A is the most common cause of isolated genetic dystonia in childhood.[3]

In a study evaluating the relationship of trauma with DYT-TOR1A, which was under the title of idiopathic torsion dystonia according to the old classification, a genetic cause was found in 85% of the patients, leading to the speculation of genetic predisposing factors in the development of post-traumatic dystonia.[14] The effect of environmental factors, especially in the development of monogenic dystonias, has been investigated for years. It has been reported that environmental factors may include perinatal stress, pain, drug, and trauma.[15-17] Investigating environmental factors may help determine when clinical signs of TOR1A, whose penetrans is relatively low, will appear. TorsinA, the product of the *TOR1A* gene, is an endoplasmic reticulum (ER) protein.[18,19] In a very recent study on the pathogenesis of DYT-TOR1A, the levels and localization of TorsinA and TorsinB proteins, which normally regulate cell stress, were impaired in the presence of *TOR1A* mutations. The stress-specific proteomic disturbances were also identified in the DYT-TOR1A genotype.[20] In the case of ER stress, an increase in torsinA level has been shown in another study.[21] The evidence of clinical findings in stress situations in DYT-TOR1A with defective (decreased or impaired) torsinA production can be explained by this mechanism. Therefore, we considered that DYT-TOR1A may occur or progress after a stress situation such as surgery. Although this subject has been an ongoing focus of attention for many studies in the following years, the pathomechanism still remains a mystery.[18] In a study published in 2021, it was emphasized that environmental factors may be effective in the development of isolated monogenic dystonia. Rauschenberger *et al*. suggested that environmental factors disturb a sensorimotor system, where maladaptive plasticity or an otherwise structural and neurochemical endophenotype is barely compensated (second hit hypothesis). For this reason, while TOR1A was the preexisting fertile background for the development of dystonia, surgical stress precipitated it by decompensating maladaptive plasticity in the sensorimotor system.[22] Based on this information, we emphasize the intrusive aspect of our case. Elucidating the gene function and pathogenesis of DYT-TOR1A will help explain the possible association with stress. Arachnoid cysts are a common incidental finding on intracranial imaging in pediatric patients. In a study of more than 10000 pediatric patients, the prevalence of arachnoid cysts was found to be 2.6%.[23] Torsion dystonia may not have been caused by an arachnoid cyst. We thought that the arachnoid cyst with a high prevalence was coincidental in our patient.

Further studies are needed on the effect of cellular stress on the pathogenesis of DYT-TOR1A, a common isolated early-onset genetic dystonia of childhood. The peculiarity of our case is that it draws attention to the consideration of a genetically related movement disorder in the presence of a neurological lesion, such as a space occupying lesion in the operated cervical spine. In the presence of a movement disorder, we think that surgical interventions can be prevented by first defining the phenomenology well and, if considered, using genetic analysis methods.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, *et al*. Phenomenology and classification of dystonia: A consensus update. Mov Disord 2013;28:863-73.
2. Balint B, Mencacci NE, Valente EM, Pisani A, Rothwell J, Jankovic J, *et al*. Dystonia. Nat Rev Dis Primers 2018;4:25.
3. Gonzalez-Alegre P. Advances in molecular and cell biology of dystonia: Focus on torsinA. Neurobiol Dis 2019;127:233-41.
4. Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, *et al*. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;17:40-8.
5. Weisheit CE, Pappas SS, Dauer WT. Inherited dystonias: Clinical features and molecular pathways. Handb Clin Neurol 2018;147:241-54.

6. Burdette AJ, Churchill PF, Caldwell GA, Caldwell KA. The early-onset torsion dystonia-associated protein, torsinA, displays molecular chaperone activity *in vitro*. Cell Stress Chaperones 2010;15:605-17.
7. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35:73-7.
8. Calabresi P, Pisani A, Rothwell J, Ghiglieri V, Obeso JA, Picconi B. Hyperkinetic disorders and loss of synaptic downscaling. Nat Neurosci 2016;19:868-75.
9. Schirinzi T, Sciamanna G, Mercuri NB, Pisani A. Dystonia as a network disorder: A concept in evolution. Curr Opin Neurol 2018;31:498-503.
10. Shakkottai VG, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, *et al*. Current opinions and areas of consensus on the role of the cerebellum in dystonia. Cerebellum 2017;16:577-94.
11. Frucht S, Fahn S, Ford B. Focal task-specific dystonia induced by peripheral trauma. Mov Disord 2000;15:348-50.
12. Beauvais G, Rodriguez-Losada N, Ying L, Zakirova Z, Watson JL, Readhead B, *et al*. Exploring the ınteraction between eIF2α dysregulation, acute endoplasmic reticulum stress and DYT1 dystonia in the mammalian brain. Neuroscience 2018;371:455-68.
13. Liuzzi D, Gigante AF, Leo A, Defazio G. The anatomical basis of upper limb dystonia: Lesson from secondary cases. Neurol Sci 2016;37:1393-8.
14. Fletcher NA, Harding AE, Marsden CD. The relationship between trauma and idiopathic torsion dystonia. J Neurol Neurosurg Psychiatry 1991;54:713-7.
15. Gioltzoglou T, Milonas I, Lees AJ. Case of DYT1 dystonia triggered by bite from a moray. Mov Disord 2006;21:1536-7.
16. Martino D, Gajos A, Gallo V, Cif L, Coubes P, Tinazzi M, *et al*. Extragenetic factors and clinical penetrance of DYT1 dystonia: An exploratory study. J Neurol 2013;260:1081-6.
17. Edwards MJ, Huang YZ, Wood NW, Rothwell JC, Bhatia KP. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. Brain 2003;126:2074-80.
18. Tanabe LM, Kim CE, Alagem N, Dauer WT. Primary dystonia: Molecules and mechanisms. Nat Rev Neurol 2009;5:598-609.
19. Bragg DC, Armata IA, Nery FC, Breakefield XO, Sharma N. Molecular pathways in dystonia. Neurobiol Dis 2011;42:136-47.
20. Shroff K, Caffall ZF, Calakos N. DYT-TOR1A subcellular proteomics reveals selective vulnerability of the nuclear proteome to cell stress. Neurobiol Dis 2021;158:105464.
21. LeDoux MS, Brady KA. Secondary cervical dystonia associated with structural lesions of the central nervous system. Mov Disord 2003;18:60-9.
22. Rauschenberger L, Knorr S, Pisani A, Hallett M, Volkmann J, Ip CW. Second hit hypothesis in dystonia: Dysfunctional cross talk between neuroplasticity and environment? Neurobiol Dis 2021;159:105511.
23. Al-Holou WN, Yew AY, Boomsaad ZE, Garton HJ, Muraszko KM, Maher CO. Prevalence and natural history of arachnoid cysts in children. J Neurosurg Pediatr 2010;5:578-85.

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