[Downloaded free from http://www.neurologyindia.com on Friday, July 26, 2019, IP: 47.15.218.131]

Primary generalized dystonia due to *TOR1A* ΔGAG mutation in an Indian family with intrafamilial clinical heterogeneity

Sir,

Primary dystonia is a movement disorder characterized by sustained involuntary muscle contraction leading to abnormal postures and twisting movements. The prevalence of dystonia varies worldwide. In India, the prevalence rate is about 49.06 per 100,000 individuals with a higher prevalence of late-onset primary dystonia.[1] There is strong evidence that genetic factors play a significant role in causing dystonia. So far, six genes (*TOR1A*, *CIZ1*, *THAP1*, *GNAL*, *ANO3*, and *TUBB4*) have been implicated for primary torsion dystonia (PTD); however, mutations in *TOR1A* and *THAP1* have been found to be responsible for manifestations in a large number of patients with PTD irrespective of their ethnic background. A trinucleotide deletion (ΔGAG) in *TOR1A* gene has been reported to be the most common cause of PTD (*DYT1*) in various populations.[2-5] This mutation was found to be more common in Ashkenazi Jew patients though it was found in most of the world dystonia cohorts. *DYT1* dystonia is an autosomal dominant primary dystonia with a reduced penetrance (30%–40%). Phenotypic characteristics of patients include early disease onset (<26 years) and the disease begins with the involvement of limbs which gradually progresses to other body parts except the craniocervical and oromandibular regions, leading to generalized dystonia. In this study, we report a family of four members from West Bengal, India, affected with *DYT1* dystonia due to ΔGAG mutation in *TOR1A* gene with atypical phenotype and intrafamilial phenotypic variability.

The patients were diagnosed in the Movement Disorders Clinic at Bangur Institute of Neurosciences, Kolkata, India, and have

[Downloaded free from http://www.neurologyindia.com on Friday, July 26, 2019, IP: 47.15.218.131]

negative history for developmental complications, malignancy, or any brain injury. Electroencephalogram, nerve conduction velocity (NCV) test with H-reflex, neuroimaging (computed tomography, magnetic resonance imaging, etc.) studies for any brain lesions, and measurement of biochemical parameters (e.g., serum ceruloplasmin, uric acid) were found to be normal. None of them had a Kayser–Fleischer (KF) ring, as verified by routine slit-lamp eye examination.

Case I

A 26-year old male patient [Figure 1a, proband, II: 1] was diagnosed as primary generalized dystonia with disease onset at 10 years. The proband was suffering from writing problem and holding objects in both the upper limbs. He felt an abnormal sensation with cramps in the right upper limb during writing and subsequently developed problem in holding objects. Gradually, the disease progressed to the lower limbs with abnormal posture during walking with a pattern of twisting gait. Later on, postural and action tremors developed in both the upper limbs along with a flexed posture in the right upper limb. The patient also developed truncal dystonia, an atypical feature for generalized dystonia with asymmetric distribution more towards the right side of the body (laterocorpus). The neck and shoulder position tilted slightly to the left side. At that time, the patient was treated with levodopa–carbidopa (55 mg TDS), clonazepam (0.5 mg BDS), tetrabenazine (25 mg BDS), and trihexyphenidyl (4 mg BDS).

Case II

The brother of proband [Figure 1a, II: 2], a 21-year old male, was also affected with primary generalized dystonia. He started having problem with dragging and lifting of toes during walking at 10 years of age. Gradually, the disease progressed to the upper body parts leading to generalized dystonia. He developed writer's cramp with overflow of muscle contraction and action tremor during writing with the right upper limb. Whole-body tremor, both postural and action, was also present. Asymmetric twisting posture with stiffness developed on the right side of the body. Twisting in the right toe was found during walking, though the tandem walking was normal. The tone and activation in both the upper limbs were normal. The patient was treated with the medicines including levodopa–carbidopa (110 mg TDS), clonazepam (0.5 mg BDS), trihexyphenidyl (2 mg TDS), and propranolol (40 mg OD). The personalized medications prescribed for both the patients were dependent on variable biological responses.

This study was approved by "Bioethical Committee for Animal and Human Research Studies, University of Calcutta" following the guidelines of Indian Council for Medical Research. For genetic study, blood samples were collected from the patients and their parents [Figure 1]. All exons, promoter and 3'UTR of *TOR1A* and *THAP1* genes were screened by polymerase chain reaction and sequencing, as described elsewhere.[6,7] A heterozygous trinucleotide deletion mutation (c.904-906/907-909ΔGAG; p.302/303ΔE) in *TOR1A* gene was detected in both the patients and their asymptomatic mother [Figure 1, I: 2], but not in their father [Figure 1, I: 1]. To understand the lack of penetrance in mother, we also analyzed the presence

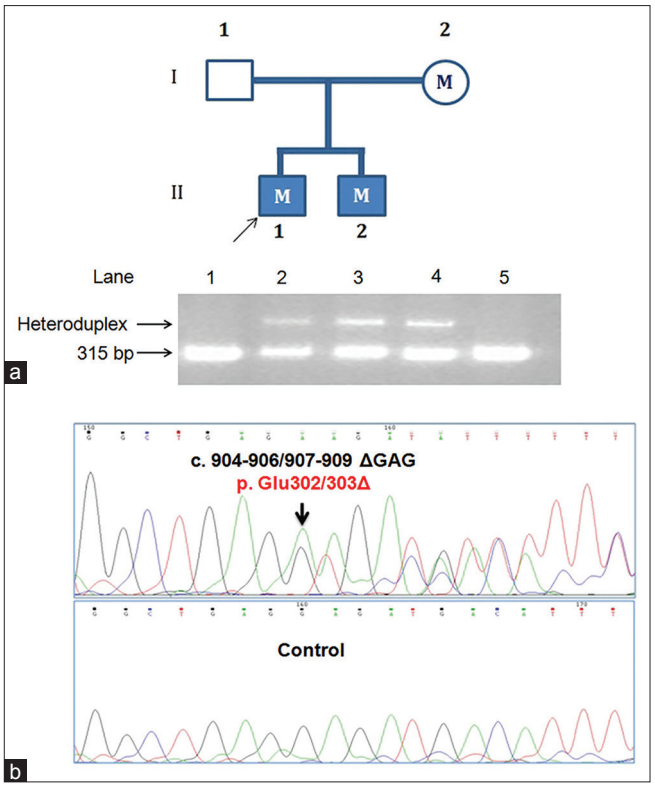

Figure 1: Identification of *TOR1A* ΔGAG mutation in an Indian family. (a) Upper panel: the pedigree with four family members. Shaded squares: affected individuals, shaded square with arrow: proband, M: presence of TOR1A ΔGAG variant. Lower panel: 7% PAGE of TOR1A exon 5 PCR products for all the family members (lanes 1, 2, 3, and 4 for I-1, II-1, II-2, and I-2, respectively) and one unrelated control (lane 5). The top gel band shows the heteroduplex formed due to the deletion. (b) The sequencing chromatogram of TOR1A exon 5 showing deletion (top panel) in affected individuals compared with the control (bottom panel)

and orientation of c. 646C allele of rs1801968 (c.646G>C, p.D216E), as the presence of this allele in trans-orientation to the ΔGAG can greatly suppress the disease expression.[8] However, none of the family members harbored the c. 646C allele in exon 4 of *TOR1A* gene. The clinical features of the individuals harboring ΔGAG mutations are presented in Table 1. Interestingly, while there are similarities in clinical features, several significantly different phenotypes were also observed among them.

Among the clinical features of primary dystonia, two phenotypes are relatively common: (1) early onset of symptoms and (2) onset of dystonia in a limb. However, the intrafamilial phenotypic variability of dystonia patients having ΔGAG deletion is relatively rare.[3,9] The occurrence of ΔGAG mutation in Indian primary dystonia patients is rare.[6] In this study, we are reporting two generalized dystonia patients having *TOR1A* ΔGAG mutation from a single family with atypical intrafamilial phenotypic variability. The anatomical sites for disease onset were different for the two patients; while the proband had upper limb onset, his brother had lower limb onset. The direction of disease progression to the generalized form was exactly opposite for both the patients. In addition, as the disease progressed, the proband developed truncal dystonia, whereas the sibling developed a tremor dominant generalized dystonia. So far, there are a few reports where

[Downloaded free from http://www.neurologyindia.com on Friday, July 26, 2019, IP: 47.15.218.131]

Table 1: Clinical characteristics of individuals harboring *TOR1A* ΔGAG mutation

Subjects	II: 1	II: 2	I: 2
Diagnosis	Generalized dystonia	Generalized dystonia	Asymptomatic
Sex/age (years)	Male/26	Male/21	Female/33
Age at onset	10 years	10 years	No symptoms
Nucleotide variation	c. 904-906/907-909ΔGAG	c. 904-906/907-909ΔGAG	c. 904-906/907-909ΔGAG
Gene region	Exon 5	Exon 5	Exon 5
Protein change	p.302/303ΔE	p.302/303ΔE	p.302/303ΔE
Protein structure	Sensor 2 domain	Sensor 2 domain	Sensor 2 domain
SIFT prediction	Damaging	Damaging	Damaging
Polyphen 2	Damaging	Damaging	Damaging
MutationTaster	Disease causing	Disease causing	Disease causing
rs1801968 (c.646 G>C)	c. 646 G	c. 646 G	c. 646 G
Clinical symptoms			
Site of onset	Both upper limbs	Both lower limbs	None
Disease progression	Upper limbs to lower body parts	Lower limb to upper body parts	No symptoms
Postural imbalance	Absent	Absent	Absent
Facial dystonia	Absent	Absent	Absent
Head movement	Normal	Normal	Normal
Neck dystonia	Present	Present	Absent
Upper limb dystonia	Present	Present	Absent
Lower limb dystonia	Present	Present	Absent
Truncal dystonia	Present	Absent	Absent
Tongue dystonia	Present	Present	Absent
Ocular movement	Broken saccadic movement	Normal	Normal
Dysphonia	Absent	Absent	Absent
Tremor	Action tremor in both upper limbs	Both postural and action tremor in whole body	Absent
Gait problem	Twisting gait in both lower limbs	Twisting gait only in right lower limb	Absent
Speech problem	Slurring of speech	Severe dysarthria	Absent
Associated pain	Absent	Absent	Absent
Memory problem	Absent	Absent	Absent
Psychiatric problem	Absent	Absent	Absent

generalized dystonia patients harboring *TOR1A* ΔGAG have truncal involvement.[3-5,10] Interestingly, the age of onset for both the patients was the same, that is, 10 years. This may be due to the age-related spatial expression of certain modifier genes in the cerebellum or could be triggered by environmental factors. Genetic analysis reveals that the mutant allele was inherited from their asymptomatic mother. Thus, in this family, the disease penetrance and phenotypic variation could be governed by some other genetic and/or environmental factors. This finding was previously presented in a conference as the first report of *TOR1A* ΔGAG mutation among Indian primary dystonia patients and published as a meeting proceeding.[11]

Acknowledgement

The authors are thankful to the participating patients and their family members for their cooperation toward this study.

Financial support and sponsorship

This study was supported by a grant from the Department of Science and Technology [(DST-PURSE) and (DST-CSI to JR)], Govt. of India. SG was supported by DST, INSPIRE fellowship.

Conflicts of interest

There are no conflicts of interest.

References

1. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Chaudhuri A, *et al*. Community survey of primary dystonia in the city of Kolkata, India. Mov Disord 2007;22:2031-6.
2. Grundmann K, Laubis-Herrmann U, Bauer I, Dressler D, Vollmer-Haase J, Bauer P, *et al*. Frequency and phenotypic variability of the GAG deletion of the DYT1 gene in an unselected group of patients with dystonia. Arch Neurol 2003;60:1266-70.
3. Szczaluba K, Jurek M, Milewski M, Friedman A, Kadziolka B, Szolna A, *et al*. Clinical characteristics of carriers of a GAG deletion in the DYT1 gene amongst Polish patients with primary dystonia. Eur J Neurol 2007;14:659-62.
4. O'Riordan S, Cockburn D, Barton D, Lynch T, Hutchinson M. Primary torsion dystonia due to the Tor1A GAG deletion in an Irish family. Ir J Med Sci 2002;171:31-2.
5. Akbari MT, Zand Z, Shahidi GA, Hamid M. Clinical features, DYT1 mutation screening and genotype-phenotype correlation in patients with dystonia from Iran. Med Princ Pract 2012;21:462-6.
6. Naiya T, Biswas A, Neogi R, Datta S, Misra A, Das S, *et al*. Clinical

[Downloaded free from http://www.neurologyindia.com on Friday, July 26, 2019, IP: 47.15.218.131]

characterization and evaluation of DYT1 gene in Indian primary dystonia patients. Acta Neurol Scand 2006;114:210-5.
7. Giri S, Naiya T, Equbal Z, Sankhla CS, Das SK, Ray K, *et al*. Genetic screening of THAP1 in primary dystonia patients of India. Neurosci Lett 2017;637:31-7.
8. Risch NJ, Bressman SB, Senthil G, Ozelius LJ. Intragenic Cis and Trans modification of genetic susceptibility in DYT1 torsion dystonia. Am J Hum Genet 2007;80:1188-93.
9. Opal P, Tintner R, Jankovic J, Leung J, Breakefield XO, Friedman J, *et al*. Intrafamilial phenotypic variability of the DYT1 dystonia: From asymptomatic TOR1A gene carrier status to dystonic storm. Mov Disord 2002;17:339-45.
10. Ikeuchi T, Shimohata T, Nakano R, Koide R, Takano H, Tsuji S. A case of primary torsion dystonia in Japan with the 3-bp (GAG) deletion in the DYT1 gene with a unique clinical presentation. Neurogenetics 1999;2:189-90.
11. Giri S, Biswas A, Das SK, Ray K, Ray J. Molecular basis of DYT1 and DYT6 primary dystonia in Indian patients. Mol Cytogenet 2014;7(Suppl 1):P121.

Subhajit Giri, Arindam Biswas, Shyamal Kumar Das[1], Kunal Ray[2], Jharna Ray

S. N. Pradhan Centre for Neurosciences, University of Calcutta, [1]Bangur Institute of Neurosciences, Kolkata, West Bengal, [2]Academy of Scientific and Innovative Research (AcSIR), New Delhi, India

Address for correspondence:
Dr. Jharna Ray,
S. N. Pradhan Centre for Neurosciences, University of Calcutta, Kolkata, West Bengal, India.
E-mail: jharnaray@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Website: www.neurologyindia.com

DOI: 10.4103/0028-3886.263172

Quick Response Code:

How to cite this article: Giri S, Biswas A, Das SK, Ray K, Ray J. Primary generalized dystonia due to *TOR1A* ΔGAG mutation in an Indian family with intrafamilial clinical heterogeneity. Neurol India 2019;67:872-5.

© 2019 Neurology India, Neurological Society of India | Published by Wolters Kluwer - Medknow