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RESEARCH ARTICLE

TOR1A GENETIC MUTATION PRESENTING AS INFANTILE ONSET CHOREA: A NEW PHENOTYPE OF TORSIN FAMILY GENETIC MUTATION

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ABSTRACT

The mutations in TOR1A or DYT1 genes are commonly known to be associated with primary dystonia in childhood and rarely with benign essential blepharospasm and head tremors.1 However, the association of TOR1A gene mutation with chorea has never been described in the literature. Here we describe a 5-year old boy with an infantile onset generalized chorea, with normal cognition, whose genetic analysis revealed a known pathogenic mutation in the TOR1A gene (c.646G>T). Thus, we report a novel association of TOR1A gene (c.646G>T) mutation with infantile onset chorea and expand the phenotypic manifestations of the same.

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INTRODUCTION

The mutations in TOR1A or DYT1 genes are commonly known to be associated with primary dystonia in childhood, rarely with benign essential blepharospasm and head tremors (Yilmaz et al., 2013). However, the association of TOR1A gene mutation with chorea has never been described in the literature. Here we describe a 5-year old boy with an infantile onset generalized chorea, with normal cognition, whose genetic analysis revealed a known pathogenic mutation in the TOR1A gene (c.646G>T). Thus, we report a novel association of TOR1A gene (c.646G>T) mutation with infantile onset chorea and expand the phenotypic manifestations of the same.

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Case report

A 5- year old boy had presented to us with choreiform movements, involving the limbs, and the face, which was noted since one year of age. The movements were non-purposeful, non-stereotypic, non-rhythmic and they disappeared during sleep. He was first born to a non-consanguineous couple with no perinatal complications. There was delay in both motor and language milestones. There was no family history of any movement disorders. On examination, his anthropometry and head circumference was normal. Neurogically he had near continuous, semi-purposeful, non-stereotypic, non-rhythmic movements involving the limbs, neck and the face. There was no dystonia, myoclonus, tremor or tics.

His deep tendon reflexes were diminished with flexor plantar response. He was able to walk independently with a choreiform gait. Based on his phenotype a clinical possibility of an infantile onset choreiform movement disorders like benign hereditary chorea, ADCY5 related choreiform disorder or genetic choreas were considered. His biochemical and hematological investigations including serum calcium and phosphorus were normal. Slit Lamp examination did not show any KF ring. MRI scan of the brain including the gradient echo sequence was normal. Next Generation Sequencing was performed at an average sequencing depth of 100X employing Agilent Sure Select Focused Exome panel to evaluate disease associated genetic targets. While no known pathogenic variants of genes associated with pediatric/ infantile onset chorea were identified, genetic analysis revealed a heterozygous mutation in a known pathogenic variant in chromosome 9 of TOR1A gene (c.646G>T). This pathogenic variant of the TOR1A gene (c.646G>T) is responsible for change in the amino acid torsinA protein at 216 position from Aspartate to Histidine (p.Asp216His). Both the parents were asymptomatic and they had heterozygous mutations in the same gene. Presently at 6 years of age the child is gaining milestones, his choreiform movements are reduced on clonazepam, trihexyphenidyl and levodopa.

DISCUSSION

TOR1A dystonia is the most common primary dystonia seen in childhood and is caused by the deletion of a GAG triplet in exon 5 of the DYT1 gene.1Both generalized and segmental dystonias can be associated with DYT1 mutation (Lee et al., 2012). The neurological disorders reported to be associated with mutations of torsinA gene are early onset primary Dystonia, benign essential blepharospasm (Tuffery-Giraud et al., 2001) and fluctuating unilateral myoclonic dystonia (Gatto, 2003). Isolated tremor of the head without relevant cervical dystonia has been also been described in a patient with the three-bp GAG deletion in the DYT1 gene (Lee et al., 2009). The pathogenic variant of TOR1A gene (c.646G>T) identified in the index child, has been previously described in the literature to be associated with dystonia even among the patients lacking the deletion of the GAG triplet (Caputo et al., 2013). Mutations in TOR1A gene are inherited as Autosomal dominant disorders, with a penetrance rate of only 30% (Ozelius et al., 1999). Though both the parents of the index child were heterozygous carriers of the same mutation in the proband, they did not manifest the disease possibly due to the incomplete penetrance of TOR1A gene. Thus we describe a 5-year old boy with infantile-onset generalized choreiform movement disorder, which could probably be secondary to the pathogenic mutation in TOR1A gene (c.646G>T).

Conclusion

Infantile onset chorea could probably also be a sole manifestation of TOR1A or DYT1 mutation. Children with chorea with no other cause identified should undergo a screening for TOR1A mutation.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURES

None of the authors has any conflict of interest to disclose.

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