CAPOS Syndrome: A Rare ATP1A3-Related Disorder

Sir,

CAPOS syndrome (OMIM #601338) is a rare neurological disorder of autosomal dominant inheritance. It was first described in 1996 by Nicolaides *et al*.,[1] and named after its dominant symptoms (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss). Before this report, 33 cases with CAPOS syndrome have been reported in the English literature.

Case Details

The index case was a 5-year-old girl from the Indian state of Bihar, born to nonconsanguineous parents with a normal perinatal period. She was well until 40 months of age when she had an episode of acute onset lethargy, and confusion following an upper respiratory tract infection and recovered spontaneously over a period of 5 days. During the recovery phase, she had rapid involuntary movements of the eyes, tremulous movements and instability of the hands and fingers, and an unsteady gait. The unsteadiness of gait gradually reduced and she learned to walk without falling. Over the next 3 months, she had two episodes of febrile illness and a transient increase in unsteadiness during these episodes. At the age of 48 months, she had febrile encephalopathy with seizures and was bed bound for 10 days. She returned to the baseline and was started on oral valproic acid. At 54 months of age, she had slowly progressive hearing loss.

She presented to us at 60 months of age, and at presentation, she could walk without support, converse in two word sentences, dress and undress, and feed herself. There was no history of visual impairment and similar illness in other family members.

On examination (at 60 months), she had normal anthropometry, left convergent squint, horizontal nystagmus, bilateral pale optic discs, hypotonia, areflexia, and perioral and appendicular dyskinesia (intermittent spontaneous jerky movements of fingers, toes, limbs, and lips suggestive of chorea). On cerebellar examination, she had gait incoordination (gait ataxia), truncal hypotonia, intentional tremors, positive finger nose test, dysdiadokokinesia, and incoordinated slurred speech (scanning speech). She did not have pes cavus. In view of recurrent encephalopathy with cerebellar dysfunction, a possibility of CAPOS syndrome or a respiratory chain disorder were considered.

Her magnetic resonance imaging of the brain and nerve conduction study were unremarkable. Pure tone audiometry showed profound bilateral sensorineural hearing impairment and brainstem evoked response audiometry was suggestive of bilateral profound hearing impairment. Flash visual evoked potential study showed bilateral mildly increased P-100 latencies. Metabolic profile (thyroid profile, lactate, ammonia, biotinidase levels, tandem mass spectrometry, and urinary organic acid profile) and cerebrospinal fluid autoimmune profile was normal. A targeted sequencing of ATP1A3 gene revealed a pathogenic heterozygous missense variant in exon 18 (c.2491G>A, p.E831K) [Figure 1], confirming the diagnosis of CAPOS syndrome.

Discussion

ATP1A3 gene encodes α3 subunit of Na+/K+ATPase, which maintains electrochemical gradients across the plasma membranes. Mutations in the encoding gene of this catalytic subunit are responsible for three different autosomal dominant neurological disorders: CAPOS syndrome, alternating hemiplegia of childhood, and rapid-onset dystonia-parkinsonism.[2,3] Demos *et al*.[4] reported the largest series of 10 patients from three different families. The onset of symptoms typically starts from infancy or early childhood with mean age of onset at 2.5 year (range: 6 months to 37 years).[5] Most of the episodes induced by fever and characterized by

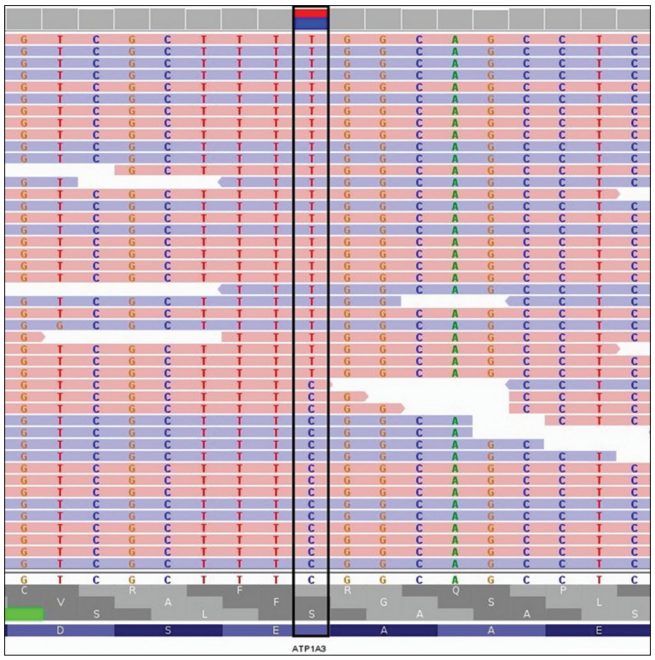

Figure 1: Raw next generation sequence alignment on human genome version GRCh37 (hg19) at ATP1A3 gene location depicting G>A variation at position (HGVS nomenclature of genomic position). Depth of coverage at this position was observed to be 66X

encephalopathy, cerebellar ataxia, hypotonia, paresis, and abnormal eye movements. One may have fever-triggered recurrent episodes. The common examination findings after an acute episode include sensorineural hearing loss (97%), areflexia (97%), cerebellar ataxia (94%), optic atrophy (91%), nystagmus (44%), pes cavus (34%), and dysarthria (37%). Other infrequent abnormalities are dystonia, myoclonus, cardiac conduction block, bradykinesia, and intellectual disability. Generalized tonic-clonic seizures seen in the index child have not been reported. Sensorineural hearing loss and optic atrophy may appear at the onset of symptoms or later. Normal electrophysiological studies in the presence of areflexia is an added clue to the diagnosis and can be explained by the ATP1A3 dysfunction in muscle stretch receptors. The combination of ataxia, sensorineural hearing loss, and optic atrophy is not sine qua non with CAPOS and is also seen in mitochondrial disorders, congenital disorders of glycosylation, peroxisomal disorders, riboflavin transporter defect, and biotinidase deficiency.[6] There is no definitive treatment for this condition and acetazolamide has been used with limited success.[7] Acetazolamide, being a carbonic anhydrase inhibitor, creates a state of cerebral and metabolic acidosis, reduces ion leakage, and normalizes neuronal excitability. The index child is currently 7-years-old, on neurorehabilitative measures, and oral acetazolamide therapy. However, her baseline symptoms persist.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Nicolaides P, Appleton RE, Fryer A. Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS): A new syndrome. J Med Genet 1996;33:419-21.
2. Carecchio M, Zorzi G, Ragona F, Zibordi F, Nardocci N. ATP1A3-related disorders: An update. Eur J Paediatr Neurol 2018;22:257-63.
3. Stagnaro M, Pisciotta L, Gherzi M, Di Rocco M, Gurrieri F, Parrini E, *et al*. ATP1A3 spectrum disorders: A video-documented history of 7 genetically confirmed early onset cases. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc 2018;22:264-71.
4. Demos MK, van Karnebeek CD, Ross CJ, Adam S, Shen Y, Zhan SH, *et al*. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. Orphanet J Rare Dis 2014;9:15.
5. Hayashida T, Saito Y, Ishii A, Hirose S, Hiraiwa R, Maegaki Y, *et al*. Further characterization of CAPOS/CAOS syndrome with the Glu818Lys mutation in the ATP1A3 gene: A case report. Brain Dev 2018;40:576-81.
6. Paquay S, Wiame E, Deggouj N, Boschi A, De Siati RD, Sznajer Y, *et al*. Childhood hearing loss is a key feature of CAPOS syndrome: A case report. Int J Pediatr Otorhinolaryngol 2018;104:191-4.
7. Maas RPPWM, Schieving JH, Schouten M, Kamsteeg E-J, van de Warrenburg BPC. The genetic homogeneity of CAPOS syndrome: Four new patients with the c. 2452G>A (p.Glu818Lys) mutation in the ATP1A3 Gene. Pediatr Neurol 2016;59:71-5.e1.

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