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Case Report

Paediatrics Section

Hereditary Spastic Paraplegia Mimicking Cerebral Palsy-Heterozygous Mutation in ALDH18A1

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ABSTRACT

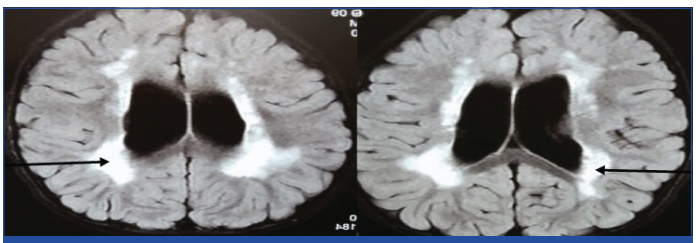
Spastic paraplegias are characterised by progressive rigidity and weakness of the lower limbs. Spastic paraplegia is a standard differential diagnosis for spastic diplegic cerebral palsy. Hereditary Spastic Paraplegias (HSP) are genetically and clinically heterogeneous group of neurodegenerative disorders causing paraplegias. Eighty forms of HSP have been noted and 64 genes have been identified. The Aldehyde Dehydrogenase 18 family member A1 (ALDH18A1) gene is located at 10q24.1 and it encodes delta-1-Pyrroline-5-Carboxylate Synthetase (P5CS), a mitochondrial bifunctional enzyme which is used for catalysing various amino acids. Mutations in this gene causes P5CS deficiency, which is responsible for neurodegenerative diseases. One should suspect neurometabolic conditions when no definite history of birth asphyxia is present in a case of cerebral palsy. Hereby, the authors report a case of a one-year-old male child with heterozygous mutation in ALDH18A1 gene resulting in spastic diplegia.

Keywords: Aldehyde dehydrogenase 18 family member A1, Central palsy, Neurodegenerative disorders

CASE REPORT

A one-year-old male child, born from the first uneventful pregnancy to healthy, non consanguineous married parents at the 37th gestational week by normal vaginal delivery. Birth history was uneventful. Baby cried immediately at birth with Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score of 8 (1 minute), 9 (5 minutes) and 9 (10 minutes). The baby's birth weight was 3000 gm, head circumference 33 cm and length 49 cm with no dysmorphic features. Neck holding was attained at three months and turn over at six months. Parents of the child noticed that he was unable to sit or stand and had stiffness in right leg. The child had very short attention span and limited interest in his surroundings. There was no history of convulsions or involuntary movements. Speech and intellectual disability were present. There was no history of similar complaints in the family or any history of unknown cause of death in family.

On examination, the child had hypertonia with brisk reflexes of right limb with extensor plantar reflex. He did not have any contractures or cutaneous involvement or bowel or bladder incontinence. Cerebral palsy was ruled out by birth history. Brain Magnetic Resonance Imaging (MRI) at the age of one year revealed hyperintense signals in bilateral periventricular white matter which represents sequelae of a metabolic insult rather than vascular insult [Table/Fig-1]. Fasting ammonia level was 20.6 µmol/L. Plasma proline, alanine, leucine, phenylalanine, serine and threonine was low. Valine was 139 µmol/L. The results of other blood tests were normal. Analysis by Whole Exome Sequencing (WES) was performed with BioneXome Gold at Bione ventures (Bangalore, Karnataka). A heterozygous variant at position Chr10:97373741 (c.1783G>A) in exon 14 of the ALDH18A1 gene were detected at a depth of 214X. This variation causes change of amino acid aspartate to asparagine 595 (p. Asp595Asn; ENTS00000371224.7) in the ALDH18A1 protein sequence.



[Table/Fig-1]: Showing hyperintense signals in bilateral periventricular white matter with ex-vacuo prominence of adjacent lateral ventricles in MRI brain.

The patient was started on muscle relaxant (baclofen at 1 mg/kg/day), limb physiotherapy and vitamin supplements. Patient was followed-up after every two months and at two and a half years of age he started walking with circumduction gait. No laboratory test were repeated as no changes were expected in biochemical parameters or MRI brain.

DISCUSSION

The HSPs present with progressive inability to walk as a result of length-dependent axonal degeneration of the pyramidal tract [1]. The HSPs can be classified based on the presence of spastic paraplegia (pure forms) or presence of other additional symptoms (complicated forms) [2].

The ALDH18A1 is located at 10q24.1 and causes mutations associated with neurodegeneration along with various non-neurological features [3-5]. It is classified as autosomal dominant and recessive HSP based on genotypic and phenotypic features.

Inborn Errors of Metabolism (IEM) present with pyramidal tract involvement and the neurons having extremely long axons are vulnerable to deranged metabolic profiles resulting in neurodegenerative diseases. The ALDH18A1 gene encodes for an enzyme delta-1-P5CS and its deficiency was first described in 1998 and molecularly characterised in 2000 [6].

The P5CS is an Adenosine Triphosphate (ATP) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) dependent enzyme, converting glutamate into L-Glutamate-5-Semi-Aldehyde (GSA) in two steps, catalysed sequentially by the L-glutamate 5-kinase domain and L-glutamyl-5-phosphate reductase domain [7]. The GSA is then converted into proline by pyrroline-5-carboxylate reductase or directed toward the urea cycle forming ornithine, arginine and citrulline [7].

Two conditions, ALDH18A1 related HSP and ALDH18A1 related Cutis Laxa, exist amongst the various clinical presentations of ALDH18A1 mutations [7]. The ALDH18A1 related disorders are classified into four groups: autosomal dominant and recessive HSP (SPG9A;601162 and SPG9B;616586, respectively), as well as autosomal dominant and recessive Cutis Laxa (ADCL3;616603 and ARCL3A;219150, respectively). Neurodegeneration is distinctly

present in all the groups [8]. The ALDH18A1 related HSP can be dominant or recessive forms characterised by spasticity of the lower limbs, developmental delay, persistent vomiting, hypotonia, early cataracts and connective tissues abnormalities [5,7,9].

The phenotypic characteristics are intrauterine growth retardation, short stature, dysmorphic features, microcephaly, global developmental delay, and cognitive impairment with progressive spastic paraplegia occuring due to biallelic ALDH18A1 mutations [3,4,5,10,11,12]. Increased blood ammonia and low plasma proline, ornithine, citrulline and arginine were described but the ammonia was normal in the index case and amino acid proline, alanine, leucine, phenylalanine, threonine were low [7]. The variation in this case has been located in aldehyde dehydrogenase domain of the ALDH18A1 protein. Since, this variation has not been reported in literature or any other affected individuals, therefore, based on the above evidence and considering American College of Medical Genetics (ACMG) classification, this ALDH18A1 gene variation has currently been classified as a variant of uncertain significance [13].

CONCLUSION(S)

This case is rare form of autosomal recessive HSP due to mutations in ALDH18A1 gene. The variation in the present case has been located in aldehyde dehydrogenase domain of the ALDH18A1 protein. Holistic approach should be used and one should be careful while interpreting MRI changes. Spastic cerebral palsy with normal MRI findings should raise suspicions of paraplegia and steps should be taken to rule it out.

REFERENCES

[1] Fink JK. Advances in the hereditary spastic paraplegias. Experimental Neurology. 2003;184:106-10.

[2] Fink JK. Hereditary spastic paraplegia. Current Neurology and Neuroscience Reports. 2006;6(1):65-76.

[3] Marco- Marín C, Escamilla- Honrubia JM, Llácer JL, Seri M, Panza E, Rubio V. Δ1-Pyrroline- 5-carboxylate synthetase deficiency: An emergent multifaceted urea cycle-related disorder. Journal of Inherited Metabolic Disease. 2020;43(4):657-70.

[4] Steenhof M, Kibæk M, Larsen MJ, Christensen M, Lund AM, Brusgaard K, et al. Compound heterozygous mutations in two different domains of ALDH18A1 do not affect the amino acid levels in a patient with hereditary spastic paraplegia. Neurogenetics. 2018;19(3):145-49.

[5] Coutelier M, Goizet C, Durr A, Habarou F, Morais S, Dionne-Laporte A, et al. Alteration of ornithine metabolism leads to dominant and recessive hereditary spastic paraplegia. Brain. 2015;138:2191-205. https://doi.org/10.1093/brain/awv143.

[6] Kamoun P, Aral B, Saudubray JM. A new inherited metabolic disease: Delta1pyrroline 5-carboxylate synthetase deficiency. Bull Acad Natl Med. 1998;182:131-37.

[7] Panza E, Martinelli D, Magini P, Dionisi Vici C, Seri M. Hereditary spastic paraplegia is a common phenotypic finding in ARG1 deficiency, P5CS deficiency and HHH syndrome: Three inborn errors of metabolism caused by alteration of an interconnected pathway of glutamate and urea cycle metabolism. Frontiers in Neurology. 2019;10:131.

[8] Kalmár T, Maróti Z, Zimmermann A, Sztriha L. Tremor as an early sign of hereditary spastic paraplegia due to mutations in ALDH18A1. Brain Dev. 2021;43(1):144-51.

[9] Coutelier M, Mochel F, Saudubray JM, Ottolenghi C, Stevanin G. Reply: ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. Brain. 2016;139(1):e4.

[10] Koh K, Ishiura H, Beppu M, Shimazaki H, Ichinose Y, Mitsui J, et al. Novel mutations in the ALDH18A1 gene in complicated hereditary spastic paraplegia with cerebellar ataxia and cognitive impairment. Journal of Human Genetics. 2018;63(9):1009-13.

[11] Denora PS, Schlesinger D, Casali C, Kok F, Tessa A, Boukhris A, et al. Screening of ARHSP-TCC patients expands the spectrum of SPG11 mutations and includes a large scale gene deletion. Human Mutation. 2009;30(3):E500-19.

[12] Chen YJ, Zhang ZQ, Wang MW. Novel compound missense and intronic splicing mutation in *ALDH18A1* causes autosomal recessive spastic paraplegia. Frontiers in Neurology. 2021;12:627531. Doi: 10.3389/fneur.2021.627531.

[13] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 2015;17(5):405-23.

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