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Case Report

A novel ECEL1 Gene Mutation in a Child with Distal Arthrogryposis Type 5D

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Abstract

Aim: *A six-month-old female child born to a second-degree consanguineous couple presented with symptoms of failure to thrive, bronchopneumonia, and peripheral limb contractures. A clinical exome sequencing revealed a novel homozygous mutation in the ECEL1 gene, which remains an important cause of Distal arthrogryposis. The child was treated with oxygen support and antibiotics, and had dysmorphic facies, including bulbous nose, small head, small mouth, short neck, low set ears, increased intercanthal distance, high arched eyebrows, adducted thumbs, deformed toes, hypertonia, and simian crease. The child was started on physiotherapy and dietary advice, and currently in follow-up for growth and neurodevelopment. ECEL1 is a specific gene that codes for neuronal endopeptidase, which affects the interface between nerves and muscles, leading to poor contractility.*

Among the distal arthrogryposis group, DA5D remains the only type showing an autosomal recessive pattern. Patients with DA5D have normal cognition but may have delayed attainment of motor milestones due to contractures and reduced muscle mass. Most patients survive till adulthood, but those with restrictive lung disease tend to develop hypoxemia, hypercarbia, and pulmonary hypertension leading to death. No permanent treatment for this condition has been authorized in the literature, and supportive treatment remains the only course of management recognized.

Keywords: *Oxygen, Dieterich, Child, Nose, Failure*

Introduction

We report a case of Distal Arthrogryposis, a rare genetic disease with only a few case reports found worldwide. The child was born to a second-degree consanguineous couple and presented with symptoms of failure to thrive, bronchopneumonia and peripheral limb contractures and was evaluated by doing a clinical exome sequencing which showed a novel homozygous mutation in the ECEL1 gene, whose mutation remains an important cause of Distal arthrogryposis. The treatment of the disease remains predominantly supportive with no definitive cure till date. There is a need for further research on the disease to make way for early diagnosis and definitive treatment in order to reduce the morbidity and mortality in patients with this disease.

Arthrogryposis is characterized by congenital contractures involving multiple body parts with an incidence of 1/3000 to 1/5000. When the joints involved primarily are distal, the term distal arthrogryposis (DA) is used (1). Our index case, Distal arthrogryposis type 5D (DA5D), is autosomal recessive in condition. Numerous classifications have been proposed to classify this interesting clinical heterogeneity so that the additional subgroups can be defined clearly for a better understanding of their etiology and natural course (2).

Clinical Report

A six months old female child born to a second-degree consanguineous couple (fig1) presented with a history of delayed attainment of milestones and failure to thrive admitted for bronchopneumonia, for which the child was treated with oxygen support and iv antibiotics. On examination, the child had failure to thrive with low centiles of weight(- 6.4z), length(-7.49z) and head circumference(-4z) on the WHO chart. The child was found to have dysmorphic facies- bulbous nose, small head, small mouth, short neck, low set ears, increased intercanthal distance, high arched eyebrows, adducted thumbs, deformed toes, hypertonia, and simian crease and delayed attainment of milestones. The ophthalmic examination however did not show any abnormalities till date. A possibility of a clinical syndrome was considered i/v/o dysmorphism and consanguinity in parents, and a clinical exome sequencing was sent. The clinical exome sequencing showed a novel homozygous mutation in the ECEL1 gene, which was autosomal recessive in the inheritance with variation c.38del with protein sequence p.Glu13GlyfsTer8. The child was started on physiotherapy. Dietary

advice and supplements were started to improve the failure to thrive, and currently in follow up for growth and neurodevelopment.

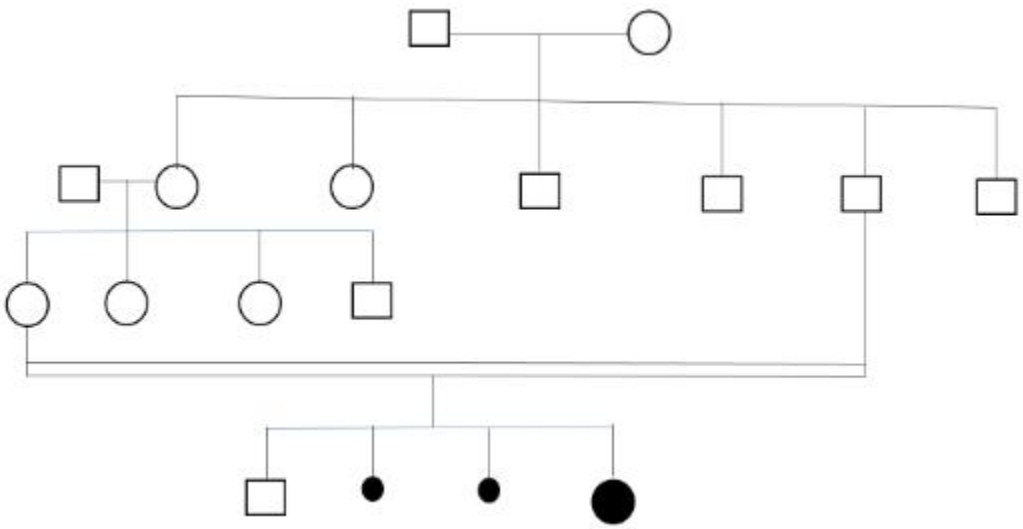

Figure 1: Depicts 3 generation pedigree chart.

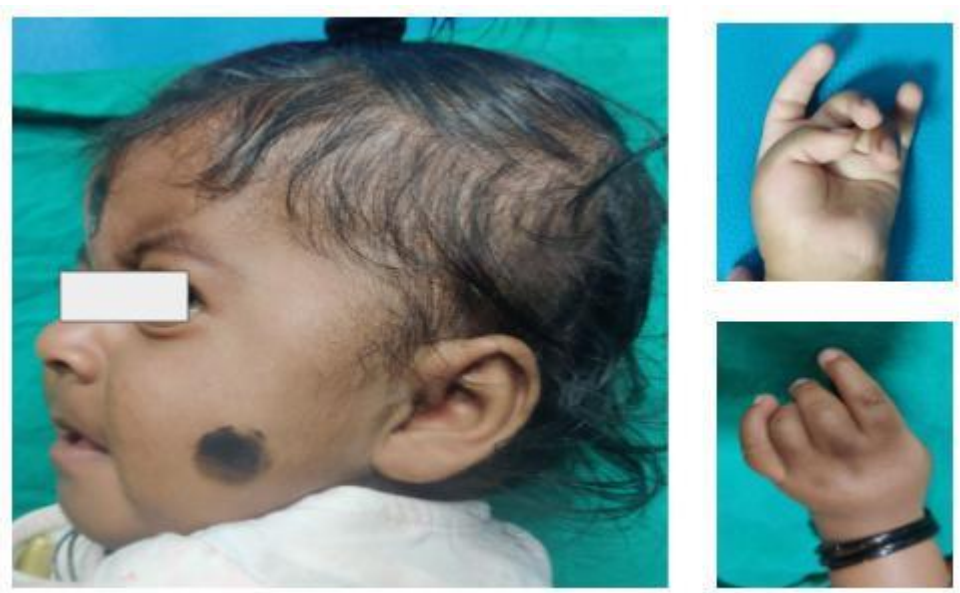

Figure 2A- depicts the masked facies of the child showing low set ears and high arched eyebrows; 2B shows both dorsal and ventral view of hand with contractures at proximal interphalangeal joints of thumb, middle and ring fingers.

Discussion

ECEL1 is a specific gene that codes for neuronal endopeptidase. The deficiency of neuronal endopeptidase grossly affects the interface between nerves and muscles, leading to poor contractility (3). Among the distal arthrogryposis group, DA5D remains the only type that shows an autosomal recessive pattern. The homozygous and compound heterozygous variants in the ECEL1 gene which codes for the member of the neprilysin family of zinc metalloendopeptidases, the expression of which is found to be high in brain and peripheral nerves in the early stages of intrauterine development, which in turn explains the abnormal neurodevelopment in DA5D (3)(6). The currently published case series and case reports describe the presence of standard features of the bulbous nose, camptodactyly, interdigital webbing in hands and feet, adducted thumb, fissured tongue, ophthalmoplegia, ptosis, strabismus were seen; however, in our index case bulbous nose, adducted thumb, no ocular manifestations, and the presence of simian crease happen to be a unique finding. The ocular manifestations have variable presentations, presence of ptosis, and strabismus with no structural ocular malformations was noted by Dieterich et al. (9). Apart from Distal arthrogryposis, Simian crease can be found in various other genetic syndromes such as Down, Fetal alcohol, Carpenters, Fetal Hydantoin, Pitt-Hopkins and Zellwgers(10). Patients with DA5D have normal cognition but might have delayed attainment of motor milestones due to contractures and reduced muscle mass. (5). The reduction in muscle mass was one of the notable features in the cases noted by Dieterich et al., McMillan et al., and Shaheen R et al. (7)(9)(5). Most of the patients survive till adulthood, but those with restrictive lung disease tend to develop hypoxemia, hypercarbia, and pulmonary hypertension leading to death(7). To date, no permanent treatment for this condition has been authorized in the literature; supportive treatment remains the only course of management recognized(8).

Conclusion

Among the distal arthrogryposis group, DA5D remains the only type with an autosomal recessive pattern. Patients with DA5D have normal cognition but may have delayed motor milestones due to contractures and reduced muscle mass. Most patients survive till adulthood, but those with restrictive lung disease tend to develop hypoxemia, hypercarbia, and pulmonary hypertension, leading to death. No permanent treatment for this condition has been authorized in the literature, and supportive treatment remains the only course of management recognized.

Conflicts of Interest: There are no conflicts of interest.

Reference

1. Hall JG. Arthrogryposis. I am Fam Physician. 1989 Jan;39(1):113-9.

2. Hall JG. Arthrogryposis multiplex congenital: etiology, genetics, classification, diagnostic approach, and general aspects. J Pediatr Orthop B. 1997 Jul;6(3):159-66.

3. Nagata K, Kiryu-Seo S, Maeda M, Yoshida K, Morita T, Kiyama H. Damage-induced neuronal endopeptidase is critical for presynaptic formation of neuromuscular junctions. J Neurosci. 2010 May 19;30(20):6954-62. .

4. Lowry RB, Sibbald B, Bedard T, Hall JG. Prevalence of multiple congenital contractures including arthrogryposis multiplex congenital in Alberta, Canada, and a strategy for classification and coding. Birth Defects Res A Clin Mol Teratol. 2010 Dec;88(12):1057-61.

5. Patil SJ, Rai GK, Bhat V, Ramesh VA, Nagarajaram HA, Matalia J, Phadke SR. Distal arthrogryposis type 5D with a novel ECEL1 gene mutation. Am J Med Genet A. 2014 Nov;164A(11):2857-62

6. Alesi V, Sessini F, Genovese S, Calvieri G, Sallicandro E, Ciocca L, Mingoia M, Novelli A, Moi P. A New Intronic Variant in ECEL1 in Two Patients with Distal Arthrogryposis Type 5D. Int J Mol Sci. 2021 Feb 20;22(4):2106.

7. McMillin MJ, Below JE, Shively KM, Beck AE, Gildersleeve HI, Pinner J, Gogola GR, Hecht JT, Grange DK, Harris DJ, Earl DL, Jagadeesh S, Mehta SG, Robertson SP, Swanson JM, Faustman EM, Mefford HC, Shendure J, Nickerson DA, Bamshad MJ; University of Washington Center for Mendelian Genomics. Mutations in ECEL1 cause distal arthrogryposis type 5D. Am J Hum Genet. 2013 Jan 10;92(1):150-6.

8. Shaheen R, Al-Owain M, Khan AO, Zaki MS, Hossni HA, Al-Tassan R, Eyaid W, Alkuraya FS. Identification of three novel ECEL1 mutations in three families with distal arthrogryposis type 5D. Clin Genet. 2014 Jun;85(6):568-72.

9. Dieterich K, Quijano-Roy S, Monnier N, Zhou J, Fauré J, Smirnow DA, Carlier R, Laroche C, Marcorelles P, Mercier S, Mégarbané A, Odent S, Romero N, Sternberg D, Marty I, Estournet B, Jouk PS,

Melki J, Lunardi J. The neuronal endopeptidase ECEL1 is associated with a distinct form of recessive distal arthrogryposis. Hum Mol Genet. 2013 Apr 15;22(8):1483-92.

10. Kenneth J, Merilyn J, Miguel del C. Smith's Recognizable Patterns of Human Malformation 8th Edition. Philadelphia: Elsevier;2021