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An Indian Case of Distal Arthrogryposis Type - 5D

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ABSTRACT

INTRODUCTION

Arthrogryposis is also termed as arthrogryposis multiplex congenita used to describe variety of conditions effecting multiple joints contractures (or stiffness). The joint motion is impaired resulting in inability to partially or fully extend or bend. The symptoms vary from person to person, in majority of patients, both the upper limbs and lower limbs are involved. Muscle contractures of joints will occur at multiple joints like shoulder, elbow, wrist, hand, hip, knee and ankle joint. The exact etiology is not known. It is observed that inadequate amniotic fluid and decreased room in utero. Sometimes the patients may also present with underlying neurological or connective tissue disorders. There is no prenatal test available for diagnosis of arthrogryposis. After detailed history and medical examination and complete assessment the diagnosis of arthrogryposis is made in a patient with more than two joint contractures at different sites of body. Once diagnosed genetic testing must be done for identification of primary cause of disease.

CASE

A 44 - year-old male patient presented with complaints of headache on and off episodes since 2 years each episode lasts for 3-4 days for every 10 days. He has history of bilateral eye mature cataract and operated in right eye for cataract, restricted ocular movements in left eye (depression, adduction, lateral rotation) right eye (adduction defect),history of difficulty in seeing objects, fissured tongue, fused ear

lobules to cheeks, wasting of muscles present in bilateral forearm, hands, (claw hand deformity) marked atrophy of muscles legs and foot (inverted champagne bottle appearance, hammer toes, Pes planus), the patient is unable to stand straight and extend legs since childhood and unable to flex legs completely since childhood fixed flexion deformity of knee, wasting of b/l infraspinatus muscle, latissimus dorsi muscle on right side without involving autonomic ,cerebellum, bowel and bladder control is normal ,the findings representing a suspected case of neuropathic disorder most probably Charcot Marie tooth disease and history of similar deformities in hands seen in younger brother and cousin sister(mother's sister's daughter).MRI brain revealed cystic prominence with CSF intensity in left retro cerebellar region abutting the retro cerebellar hemispheres, measuring 3.3×2.2 cm. Age related cerebral cortical atrophy noted in the form of prominent ventricular system, sulcal spaces and cistern spaces. Arachnoid cyst in left retro cerebellar region. RI whole spine revealed multi-level dessicatory changes noted involving the intervertebral discs, Multi-level C2-3 to C 6-7 mild diffuse bulges causing indentation over thecal sac more prominent in C5-C6 level, Hemangioma in T10 vertebral body.

Multilevel diffuse disc bulges in lumbar intervertebral disc spaces (L3-4 to L5 –S 1 levels) causing indentation over anterior thecal sac. Muscle biopsy of calf muscle (vastus medialis) revealed mild variation in size of skeletal muscle fibres. CBP is normal. Nerve conduction studies are as follows:

Nerve: Peroneal-Lt R-site: EDB

Stim site	Lat 1(ms)	Lat 2(ms)	Amp	Dist (mm)	CV (m/s)
Ankle	3.50	19.00	0.74mV		
Knee	9.75	23.88	1.09mV	320	51.20

Nerve: Peroneal-Rt R-site: EDB

Stim site	Lat 1(ms)	Lat 2(ms)	Amp	Dist (mm)	CV (m/s)
Ankle	3.25	11.00	2.62mV		
Knee	9.38	17.50	2.54mV	320	52.24

Left and right peroneal nerve amplitude reduced and left radial nerve conduction velocity is reduced.

Nerve: Radial-Lt R-site: Extensor Indicis

Stim site	Lat 1(ms)	Lat 2(ms)	Amp	Dist (mm)	CV (m/s)
Forearm	2.00	14.00	5.07mV		
Above elbow	6.50	17.00	5.23mV	190	42.22
Erb's	8.13	21.38	9.60mV		

Nerve: Tibial-Lt R-site: EHL

Stim site	Lat 1(ms)	Lat 2(ms)	Amp	Dist (mm)	CV (m/s)
Ankle	6.13	16.75	5.99mV		
Popliteal fossa	15.75	26.38	4.06mV	380	39.48

Nerve: Tibial-Rt R-site: EHL

Stim site	Lat 1(ms)	Lat 2(ms)	Amp	Dist (mm)	CV (m/s)
Ankle	6.38	15.63	5.82mV		
Popliteal fossa	14.75	25.75	4.71mV	380	45.37

B/L tibial latency prolonged. Genetic analysis is done and it revealed homozygous autosomal recessive digital arthrogryposis type-5D

DISCUSSION

Digital arthrogryposis type 5D is the only sub type that follows autosomal recessive pattern. Itis caused due to mutations of the ECEL1 gene (endothelin-converting enzyme-like1) a member of M13 family of endopeptidases is a transmembrane zinc metalloprotease mostly situated in endoplasmic reticulum. It plays an integral role in regulating the neuropeptides and peptide hormones activity. It is commonly seen in brain and peripheral nerves in the early stages of intrauterine development, implying abnormal neuronal development can be the pathogenic mechanism of DA type 5D. ECEL1 biallelic deficiency affects the neuromuscular junctions causing poor contractility.

In our case, the patient presented with clinical indications of bilateral eye mature cataract and operated in right eye for cataract, restricted ocular movements in left eye (depression, adduction, lateral rotation) and right eye (adduction defect) ,wasting of muscles present in bilateral fore arm, hands (claw hand deformity), legs and foot (inverted champagne bottle appearance , hammer toes, Pes planus), fixed flexion deformity of knee, wasting of bilateral infraspinatus muscle, latissimus dorsi muscle on right side.There is family history of similar deformities in hands seen in younger brother and cousin sister. The patient is suspected to be affected with Charcot Marie tooth disease and has been evaluated for pathogenic variations, and there are no pathogenic or likely pathogenic variations of the causative phenotype were detected.

Genetic analysis revealed the presence of homozygous variants ECEL1 (-c.1506G>p.Lys502Asn) in ECEL1.The detected variant is least common in human population and is classified under uncertain significance according to ACMG criteria 9.The *ECEL1* protein consists of 755 amino acidswith an N-terminal cytoplasmic domain (residues 1–59), a single transmembrane domain (residues 60–82) and a large luminal C-terminal domain (residues 83–775)

with a zinc-binding motif and an active site (residues 612–676).Thirty-eight gene variants have been described as pathogenic: 14 missense variants, 9 frameshifts, 7 splicing affecting, 6 nonsense, 1 in frame duplication and 1 in frame deletion. No intronic variants have been noted so far in DA5D patients. Thirty-five variants out the 38 affect the C-terminal domain, while the remaining 3 are missense variants located within the cytoplasmic N-terminus.

The structure of ECEL1 can be roughly divided into a cytoplasmic domain, a transmembrane domain, and an extracellular domain with a zinc binding motif (the 612^{th}-616^{th} AA) essential for enzymatic activity. The nonsense mutation in our patient (c.1506G>p.Lys502Asn) occurred in the cytoplasmic domain, producing a premature terminated protein. The missense mutation (c.1506G>p.Lys502Asn) occurred near the activation site, potentially affecting biological function.

CONCLUSION

Arthrogryposis distal type-5D is also known as digital Arthrogryposis type-5D is a condition most commonly involving both the upper and lower limbs. ECEL1 gene (endothelin-converting enzyme-like1) is an important gene associated with digital arthrogryposis type-5D. It most commonly involves neuromuscular and connective tissues.

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