

Infant with Multiple Joint Dislocation and PIEZO2 Related Variant

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Abstract

The clinical presentation of congenital multiple joint dislocation in neonatal and pediatric age group is rare and may be difficult for pediatrician to reach final definitive diagnosis especially in case of syndromic and multiple joint dislocation that is not explained by birth problem or breech delivery. here, I present rare case of 2 month old boy with congenital joint dislocation (hip and shoulder) and ultra-rare autosomal recessives related PIEZO2 disease.

Keywords: Joint dislocation, Pediatric, PIEZO2

Abbreviation: NGS: Next Generation Sequencing; ACMG: American College of Medical Genetics

Introduction

Multiple joint dislocation in pediatric can be challenging presentation for any physician due to rare cases and narrow differential diagnosis like Larsen syndrome, Ehlers Danlos syndrome and Marfan syndrome.

This unique presentation can be accompanied by other facial dysmorphism or only as isolated finding.

In international nosology and classification of skeletal dysplasia there is one category that includes all causes of joint dislocation and possible gene panel and next generation sequencing.

Case Presentation

A 2 month old boy was referred to our hospital (tertiary Centre in Saudi Arabia) for further workup, he was product of full term uncomplicated pregnancy and birth weight of 3 kg. He has congenital hip dislocation and subtle facial dimorphism.

Initially child has been evaluated by orthopaedic and skeletal survey requested to rule out skeletal dysplasia or fracture and casting for hip done for him.

The primary team which is general paediatric team consult clinical genetics due to result of skeletal survey and subtle dimorphic features for further workup. Skeletal survey showed:

Multiple skeletal abnormalities in form of bilateral hip dislocation, bilateral shoulder dislocation, mild genu varus and congenital talipesequinevarus (Figures 1 and 2).

His abdominal and renal Ultrasound suggests right kidney hydronephrosis and ECHOCARDIOGRAM result showed small atrial septal defect and no cardiomyopathy.

Gene sequencing panel customized for connective tissue and Larsen syndrome was requested to reach genetic diagnosis for this infant. Although family history is not strongly suggestive for genetic diseases.

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NGS showed likely pathogenic variant (according to ACMG guidelines) in PIEZO2 gene present as homozygous variant. (Table 1)



Figure 1. Skeletal survey: shoulder joints dislocation.



Figure 2. Skeletal survey: hip dislocation and hyperextensibility of joints.

Table 1: Summary for our variant and previously reported variant.

Gene	DNA change	Zygosity	Protein change
PIEZO2	c.5621delT c.3019_3029del c.1550_1552delGCTinsCGAA c.10G>T c.4723C→T c.5053C→T	Homozygous HomozygousHomozygousHomozygousCompound Heterozygous	p.Leu1874Argfs*5 p.Pro1007Leufs*3 p.Ser517Thrfs*48 p.Glu4' p.R1575' p.R1685'

Discussion

The pathogenic variant in PIEZO2 gene may cause Distal arthrogryposis with impaired proprioception and touch is an autosomal recessive rare neurologic disorder characterized by loss of certain mechanosensation modalities resulting in ataxia, difficulty walking, dysmetria, muscle weakness and atrophy, and progressive skeletal contracture. Patients have onset of symptoms in early childhood [1].

DelleVedove et al. [2] reported few patients from four unrelated consanguineous families. The families were of Turkish, Indian, Libyan, and Pakistani origins, and the patients ranged in age from 5 to 27 years. In the neonatal period, patients had hypotonia with poor feeding and they often had respiratory insufficiency that resolved spontaneously. The patients had delayed motor development with walking around age 5 years, although several patients never achieved independent ambulation. They had distal muscle weakness and atrophy primarily of the lower limbs, and about half also had distal muscle weakness and atrophy of the upper limbs. Additional features included dysarthria and areflexia. Skeletal features included scoliosis, 'duck-bill' deformity of the thumb, congenital pes equinovarus, pes planus, sandal gap deformity, arachnodactyly, and camptodactyly, consistent with contracture. Some patients had myopathic facies with long nose, broad nasal bridge, thin upper lip, and high-arched palate. Two of 4 patients studied had evidence of an axonal-demyelinating peripheral sensory neuropathy, and another reported decreased vibration sense. Three patients from 2 unrelated families had mild cognitive impairment [2].

In mice, PIEZO2 has been shown to be essential for a variety of mechanosensory responses, including aspects of light touch and proprioception. Almost nothing is known about the role of PIEZO2 in humans, but it has been established that PIEZO2 is critically important for mechanotransduction in vitro, and genetic variants in PIEZO2, which are presumed to have gain-of-function effects on the protein, have been linked to arthrogryposis [3].

Our patient present with multiple joint dislocation in hip and shoulder as a cardinal feature and his homozygous variant create premature stop codon in exon 1 out of 52 (c.10G>T, p.Glu4'). His variant classified as likely pathogenic variant according to ACMG guidelines. This variant segregated well in family and this can support more our genetic diagnosis. Family fully counselled for

future pregnancy to prevent recurrence by antenatal amniocentesis or possible pre-implantation genetic diagnosis.

Conclusion

I present rare case of multiple joint dislocations and PIEZO2 related variant which is very rare genetic disease and to our knowledge this is the first reported case from Saudi Arabia.

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Ethical Approval

No approval was required.

Patient Consent

Informed consent was obtained from the patient's legal guardian for publication of this case report.

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