Original Research Paper

Volume - 13 | Issue - 04 | April - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

DYGGVE-MELCHIOR-CLAUSEN SYNDROME-A CASE REPORT

Dr Maneesh G	Post Graduate, Department of Paediatrics , Vydehi Institute Of Medical Sciences and Research Centre, Bangalore, India.
Dr Neushree	Post Graduate, Department of Paediatrics, Vydehi Institute Of Medical Sciences And Research Centre, Bangalore, India.
Dr Vijay Sarathi	Professor , Department Of Endocrinology, Vydehi Institute Of Medical Science and Research Centre, Bangalore, India.

ABSTRACT We report a case of short stature and bony deformities. The child wasevaluated and differential diagnosis of Pseudoachondroplasia, Morquio and Dyggve- Melchior- Clausen syndrome were considered. Confirmation of thediagnosis was done by molecular genetic testing and required confirmation in the index case for planning further conception.This casereport highlights the utility of molecular genetic testing in definitive diagnosis ofthe proband.

KEYWORDS :

BACKGROUND:-

Dyggve- Melchior- Clausen (DMC) syndrome [MIM# 223800] is a rare disease included in the heterogenous group of spondylo-epi-metaphysal dysplasias disorders, all of them defined by the combination of vertebral, epiphyseal and metaphyseal abnormalities. DMC syndrome is characterized by short trunk dwarfism, microcephaly and mental retardation (Beighton, 1990). The prevalence of this syndrome is < 1/1,000,000, and there are about 100 cases reported worldwide (Orphanet, 2022). DMC syndrome is caused by homozygous null mutations in the DYM gene (Dimitrov et al., 2009; Dupuis et al., 2015). This gene (NCBI ID: 54,808) is located in chromosome 18 (18q21.1) (Cohn et al., 2003; el Ghouzzi et al., 2003) and is consists of 17 exons which encode dymeclin, a 669-amino acid protein whose function remains unknown. However it has been proposed that it may be an integral protein of the endoplasmic reticulum membrane that could play a role in the transport of intracellular compounds. Furthermore, it could also have a critical role in both the formation and function of the Golgi apparatus and in the tracking of associated vesicles.

Case Report:-

A 6 years old 1st born male child to non consaguinous couple was brought to OPD with complaints of delayed developmental milestones, inadequate gain of height and weight and bony deformities.The child was born at full term by normal vaginal delivery with a birth weight of 2.5kg. Antenatal, Perinatal, Natal and Postnatal was uneventful.His development was normal till 1 and 1/2 year of age. From then on, he failed to attain newer motor and mental milestones.

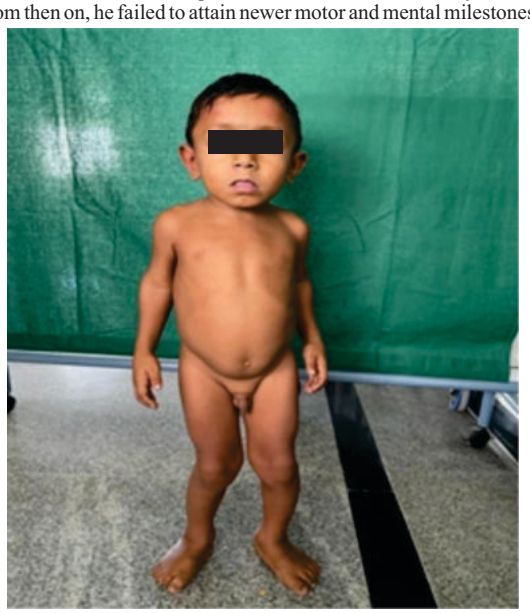
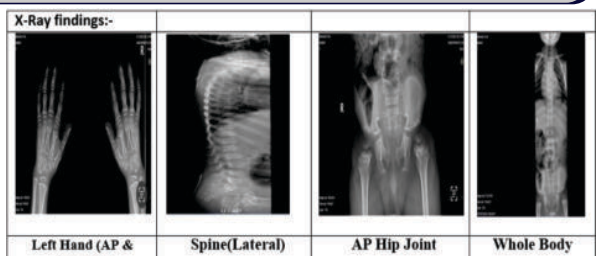


Figure 1-



Left Hand (AP & Lateral) Figure-2a | Spine(Lateral) Figure-2b | AP Hip Joint Figure-2c | Whole Body Figure-2d

On examination, at 6 years of age, he had coarse facies, a small mouth(microstomia), prominent mandible(prognathism), short neck, short trunk, protruding sternum, flaring of lower ribs,exaggerated lumbar lordosis, small hands and feet and enlarged wrist and knee joints causing knock knees with genu valgum ,pes planus (Figure 1).

There was no cataract or corneal clouding and no hepatosplenomegaly. His head circumference was 45 cms (< −3SD), height was 80 cm (< −3SD), weight 10.2 kg (< −3SD), and his upper to lower segment ratio was 1.2. He was walking independently but had a clumsy gait. There was no history of seizures, falls or abnormal behaviour. His developmental age was equivalent to a child of age 1 and ½ year or less. He was screened for mucopolysaccharidosis with urine glycosa minoglycan assay which was normal. X rays of the cervical spine revealed a double hump appearance, central beaking(figure-2d). Xray of the thoracolumbar spine showed anterior/ inferior beaking with oar shaped lower ribs (figure-2b). X-ray of the hand showed short tubular and proximal pointing metacarpals (figure-2a).

The pelvic Xray was suggestive of widened acetabular margins with lateral subluxation of femoral head (figure-2c).Based on the clinical and radiological findings, aprovisional diagnosis of Dyggve-Melchoir-Clausen Syndrome was considered. Confirmation of the clinicalfeatures by molecular diagnosis was offered as the couple were planningfurther conception. Clinical exome sequencing of the index child showed homozygous pathogenic variant **c.963del(p. Ser322 HisfsTer78)** caused by a substitution in **exon 10** of the DYM gene, which confirmed the diagnosis of Dyggve-Melchior- Clausen syndrome in the proband.

Variant Description-

A homozygous single base pair deletion in exon 10 of the ***DYM*** gene **(chr18:g.49282162del;Depth:57 x)** that results in a frameshift and premature truncation of the protein 78 amino acids downstream to codon 322 p.Ser322HisfsTer78; ENST00000675505.1 was detected. This variant has been reported as pathogenic by ClinVar Database. Thisvariant hasnot been reported in the 1000 genomes and gnomAD databases and has a minor allele frequency of 0.002% in internal database.

DISCUSSION

DMC is a rare, progressive genetic condition characterized by

abnormal skeletal development, microcephaly, and intellectual disability. It was initially described in 1962 by Dyggve and colleagues. The clinical and radiographic features were described completely in 1975 by Spranger and colleagues (Schorr et al., 1977) Only about 100 cases have been reported till date.

It is characterized by a short trunk and extremities and a barrel shaped chest, mental retardation and microcephaly (Beighton, 1990). The radiographic appearance of generalized platyspondyly with double-humped end plates and the lacelike appearance of iliac crests are pathognomonic and distinctive of DMC syndrome. The lace-like appearance of the iliac crests, which is a characteristic radiologic sign, is found to be caused by bone tissue deposited in a wavy pattern at the osteochondral junction. It is caused by biallelic mutations in the DYM gene on chromosome 18q21. Mutations in the same gene cause Smith-McCort dysplasia(OMIM # 223800). Management requires both a multidisciplinary approach and a long-term follow-up as the disease is progressive. DMC needs to be differentiated from SmithMcCort dysplasia and Morquio syndrome. The differentiating findings are detailed in Table 1. Though DMC and Smith- McCort dysplasia are allelic disorders, in view of intellectual disability and the typical clinical and radiographic findings, a clinical diagnosis of DCM was considered in our child. DYM is a relatively large gene with 17 exons, but with next generation sequencing-based testing, the exact mutations could be identified, which helped in confirmation of the diagnosis of the proband, in providing accurate genetic counselling to the family and in offering prenatal diagnosis for their next planned pregnancy.

Differential Diagnosis

Clinical Features	**Dyggve-Melchior-Clausen Syndrome**	**Smith-McCort Dysplasia**	**Morquio Syndrome**	**Pseudoachondroplasia**
Coarse Features	Present	Present	Present	Absent
Xray Findings (Pathognomic)	Double hump vertebral bodies and lacy pattern in pelvic crest	lacy pattern in pelvic crest	Central Beaking,Goblet shaped vertebrae,flared iliac wings,increased acetabular angles and constricted iliac bone	Anterior beaking of vertebra,platyspondyly, odontoid dysplasia
Intelligence	Mental Retardation	Normal	Normal	Normal
Associate dGenes	DYM Gene	DYM Gene	GALNS(Morquio A) or GLB1(Morquio B)	COMP Gene

REFERENCES:-

1. Beighton P. Dyggve–Melchior–Clausen syndrome. J Med Genet 1990; 27: 512- 515.
2. Schorr S, et al. The Dyggve–Melchior– Clausen syndrome. Am J Roentgenol 1977; 128:107-113.
3. ToledoSP, Saldanha PH, Lamego C, Mourao PA, Dietrich CP, Mattar E.Dyggve Melchior- Clausen syndrome: genetic studies and report of affected ribs.
4. Spranger J, et al. Heterogeneity of DyggveMelchior-Clausen dwarfism. Hum Genet 1976; 33: 279-287.