Dyggve-Melchior-Clausen Syndrome: A Case Report

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Abstract

We report a case of short stature with delayed mile stones. The child was evaluated and the diagnosis of Dyggve-Melchoir-Clausen Syndrome was considered . Confirmation of the diagnosis was done by next generation sequencing-based molecular genetic testing, as the mother had an ongoing pregnancy and prenatal diagnosis requires confirmation in the index case. This case report highlights the utility of next generation sequencing in definitive diagnosis of the proband and for offering prenatal diagnosis in the next pregnancy.

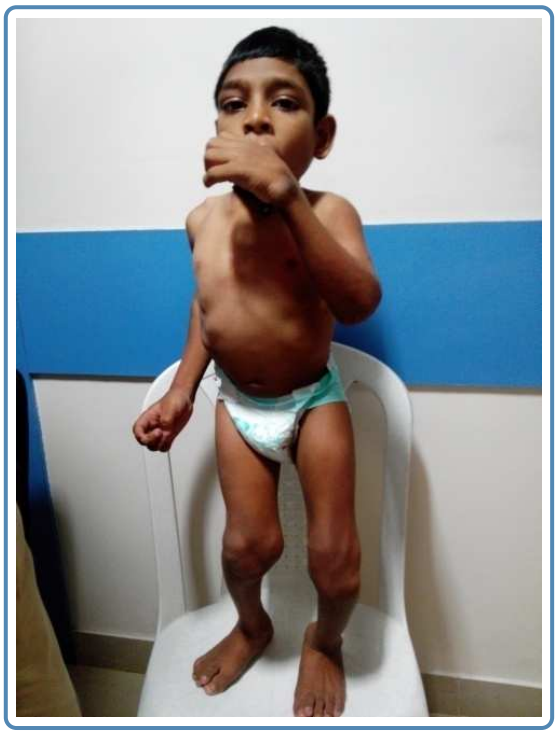


Figure 1 Child with Dyggve-Melchior-Clausen syndrome.

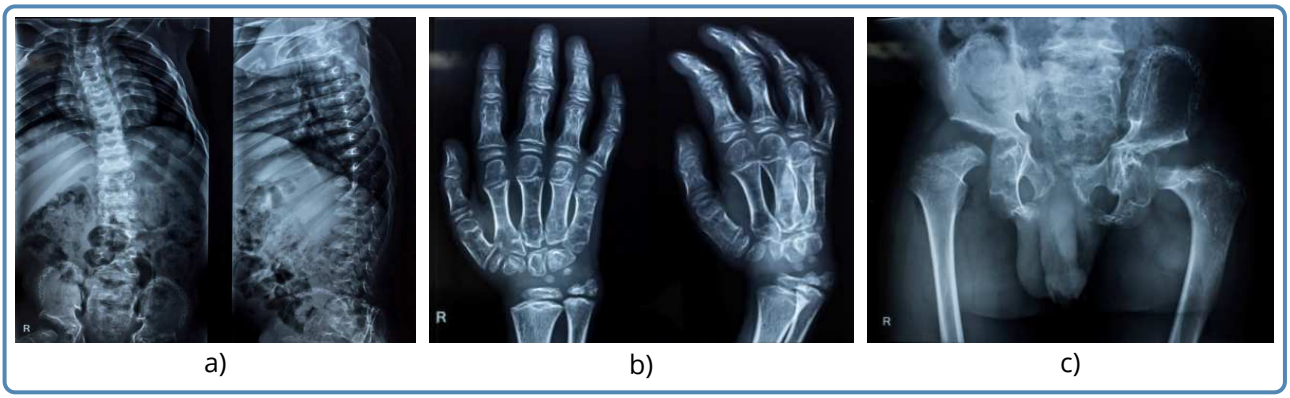
Background

Dyggve-Melchior-Clausen syndrome (DMC) is a rare type of autosomal recessive skeletal dysplasia. It is characterized by microcephaly, coarse facies and progressive spondyloepimetaphyseal dysplasia leading to disproportionate short stature. Dyggve-Melchior-Clausen disease (DMC) (OMIM # 223800) is caused by homozygous or compound heterozygous mutation in the *DYM* gene. The diagnosis of Dyggve-Melchior-Clausen syndrome is based on clinical and radiological findings. Prenatal diagnosis can be offered for the parents who had a previous child with Dyggve-Melchior-Clausen syndrome which has been confirmed by molecular diagnosis. We report a case wherein prenatal diagnosis of Dyggve-Melchior-Clausen syndrome was done after confirming the molecular diagnosis in the previous sibling. This case report highlights the utility of next generation sequencing in definitive diagnosis of the proband and for offering prenatal diagnosis in the next pregnancy.

Case report

A consanguineous couple was referred to the genetic clinic during their second pregnancy as they had a 10-year-old child with history of delayed milestones. The child was born at full term by Caesarean section with a birth weight of 3 kgs. His development was normal till six months of age. From then on, he started having coarse facial features and failed to attain new motor and mental milestones.

On examination, at ten years of age, he had coarse facies, a big mouth, prominent mandible (prognathism), short neck, short trunk, protruding sternum, scoliosis with flaring of lower ribs, small hands and feet with clawing of fingers, and enlarged elbow and knee joints causing knock knees.



a) b) c)

Figure 2 2a) Xrays (anteroposterior and lateral views) of the thoracolumbar spine. 2b) Xray of the right hand (anteroposterior and lateral). 2c) Xray of the pelvis and bilateral hip joints.

(Figure 1). There was no cataract or corneal clouding and no hepatosplenomegaly. His head circumference was 50cms (< −3SD), height was 92 cm (< −3SD), weight 12 kg (< −3SD), and his upper to lower segment ratio was 0.80. 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 an infant of age 1 year or less. He was screened for mucopolysaccharidosis with urine glycosaminoglycan assay which was normal. X rays of the spine revealed a double hump appearance, central beaking and scoliosis with convexity towards the right (Figure 2a). X-ray of the hand showed short tubular and proximal pointing metacarpals with mild radioulnar subluxation at wrist joint (Figure 2b). The pelvic Xray was suggestive of a lacy pattern in the iliac crest (Figure 2c). Based on the clinical and radiological findings, a provisional diagnosis of Dyggve-Melchior-Clausen syndrome was considered. Confirmation of the clinical features by molecular diagnosis was offered as the couple had ongoing pregnancy and prenatal diagnosis in the present pregnancy would be possible only after identifying the pathogenic mutations in the index child.

Clinical exome sequencing of the index child showed homozygous pathogenic variant p.Arg204Ter, caused by a substitution in exon 7 of the *DYM* gene, which confirmed the diagnosis of Dyggve-Melchior-Clausen syndrome in the proband. By then, the mother had ongoing 16 weeks of pregnancy and amniocentesis was done. Fetal genomic DNA was isolated from the amniotic fluid. PCR amplification and Sanger sequencing of the fetal DNA was done for exon 7 of the *DYM* gene. The sequence electropherogram was analysed and the presence of c.610C>T (p.Arg204Ter) variant in exon 7 was evaluated by comparing the sample sequence with the reference sequence. The variant c.610C>T (p.Arg204Ter) was not observed in the *DYM* gene in the fetus, which suggested that the fetus was not affected (Figure 3). The couple continued the pregnancy and delivered a healthy baby boy at full term.

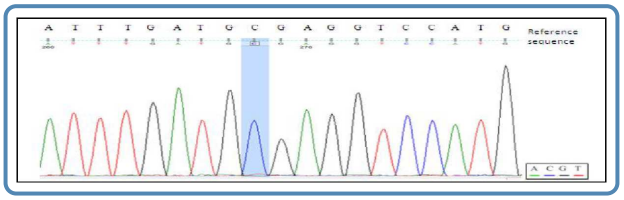


Figure 3 Sanger sequencing of fetal DNA showing absence of the *DYM* gene mutation found in the proband.

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 lace-like appearance of iliac crests are pathognomonic

Table 1 Features differentiating Dyggve-Melchior-Clausen syndrome from similar phenotypic conditions.

Differential Diagnosis			
Clinical features	**Dyggve-Melchoir-Clausen syndrome**	**Smith-McCort dysplasia**	**Morquio Syndrome**
Coarse features	Present	Present	Present
X ray findings (pathognomonic)	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
Intelligence	Severe mental retardation	Normal intelligence	Normal intelligence
Associated gene	*DYM* gene	*DYM* gene	*GALNS* (Morquio A) or *GLB1* (Morquio B)

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 Smith-McCort 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 pregnancy.

References

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