Case Report

An Extremely Rare Association of Dyggve–Melchior–Clausen Syndrome with Mania: Coincidence or Comorbidity

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ABSTRACT

Dyggve–Melchior–Clausen syndrome is a progressive spondylo-epi-metaphyseal dysplasia associated with mental retardation, characterized by a triad of skeletal deformities (short trunk dwarfism, scoliosis, microcephaly, and limb deformities), facial dysmorphism, and intellectual disability. It an extremely rare condition. Till now, there was no evidence of association of Dyggve–Melchior–Clausen Syndrome with mood disorder. This case report highlights the extremely rare association of Dyggve–Melchior–Clausen syndrome with bipolar affective disorder. The patient had responded well to the combination of mood stabilizer and antipsychotics (sodium valproate and risperidone). To the best of author's knowledge, this is the first case report depicting such association. Both Dyggve–Melchior–Clausen syndrome and bipolar affective disorder are associated with 18q chromosome. This background information raises the possibility of co-morbid association of two disorders rather than a chance association due to genetic linkage.

Key words: *Bipolar affective disorder, Dyggve–Melchior–Clausen syndrome, genetic linkage, sodium valproate*

INTRODUCTION

Dyggve–Melchior–Clausen (DMC) syndrome is a very rare, autosomal recessive disorder.[1] It is clinically characterized by skeletal deformities (short trunk dwarfism, scoliosis, microcephaly and limb deformities), facial dysmorphism and intellectual disability.[1,2] Radiological findings are characterized by short hand, short long bones with metaphyseal dysplasia, epiphyseal dysplasia, acetabular dysplasia, small and lacelike iliac crest, bulky jaw, platyspondyly with double humped end plates, scoliosis, widened sacroiliac joint, widened symphysis pubis out of which double-humped vertebrae and lacelike iliac crest are characteristic of Dyggve–Melchior–Clausen (DMC) syndrome.[1-3] Linkage analysis has revealed that the gene responsible for Dyggve–Melchior–Clausen (DMC) syndrome is located in the chromosome 18q21.1 (dymeclin gene) which encodes a membrane protein that is associated with Golgi apparatus.[4,5] Research findings are also suggestive of involvement of other genes like-4q31.1 locus, with DMC syndrome.[6] Different subtypes of DMC syndrome have been identified, out of which Smith–MacCort syndrome variant presents with features of DMC syndrome without intellectual disability and are extremely rare.[4]

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CASE REPORT

A 15-year-old boy was brought for psychiatric consultation being referred from a tertiary care hospital,

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with the history of delayed developmental milestones, inability to carry out activities of daily living on his own, inability to read, write, or calculate since birth, along with increased talkativeness, irritability, grandiosity, excessive sociability for last 2 months (prior to consultation). The child was earlier diagnosed to be suffering from 'Dyggve–Melchior–Clausen syndrome' on the basis of clinical features and findings of radiological and urinary investigation.

As per his parents account, his gross and fine motor language as well as social milestones had been delayed. A perusal of his perinatal documents revealed that there had been history of birth asphyxia. The patient had been unable to keep up with his peers at school and had been taken out of school after only a few months, on the insistence of his teachers, that he needed 'special schooling'. He would generally stay calm, and would do all activities of daily living with continuous assistance of his parents. For the 2 months prior to psychiatric consultation, he had been showing a dramatic change in his behavior in the form of talking excessively, shouting for no apparent reason, grandiosity, behaving in a domineering way, talking to strangers without any inhibition and repeatedly attempting to leave the house. His sleep was also reduced to 3 to 4 h from the premorbid level of 8 to 9 h in a day. He had started demanding for new things like jacket, expensive toys, and sweets quite often. When his demands were not met, he used to become very aggressive and even beat his mother very often. There was no past history of any similar episode or evidence of hyperactivity or inattentiveness or features of oppositional defiant or conduct disturbance. There was no family history of any psychiatric disorder or intellectual disability.

On physical examination, the patient's anthropometric findings were grossly abnormal, with a head circumference of 46 cm (Microcephaly), a height of 105 cm (height age: 9 years) and arm span of 106 cm. He weighed only 24 kg. Physical examination also revealed other skeletal abnormalities, such as Genu Varum, flat spatulate hands, pectus carinatum, knocked knees, pes planus, and a bilateral overlapping of the toes (second over third, and fifth over fourth) as shown in Figures 1 and 2.

On mental status examination, the patient had authoritative attitude, over familiarity, increased psychomotor activity, increased flow of speech, authoritative attitude, elated affect, grandiose ideas, inflated self-esteem with impairment of judgment, and insight. His routine blood investigations were within normal limits. A urinary evaluation was done for mucopolysaccharides, which came out to be negative.

Radiological examinations revealed stout stubby bones of the hand, tapering proximal ends of metacarpals (bullet-shaped metacarpals), a coarsening of trabecular pattern of the long bones, J-shaped sella tursica, flared bilateral iliac blades (ribbon-like iliac blades) along with abnormal configuration of bilateral femoral head epiphysis as shown in Figure 3.

Intelligence assessment (after improvement of manic symptoms) revealed moderate mental retardation with IQ 38 on Seguin Form Board test (SFBT) and Colored Progressive Matrices (CPM).

Based on the history and mental status examination, a diagnosis of Dyggve–Melchior–Clausen Syndrome, with moderate mental retardation with manic episode (as per ICD-10 diagnostic criteria) was made. The patient was initially started with antipsychotic risperidone 4 mg/day and was later increased to 6 mg/day. There was little improvement with risperidone alone, which he had taken for approximately for 6 weeks. Subsequently

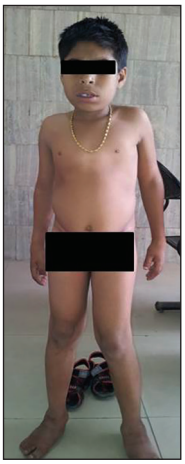

Figure 1: The figure highlights the short neck, genu varum, pectus carinatum deformity of chest, knocked knees and overall short stature (105 cm) in a 15 years old boy

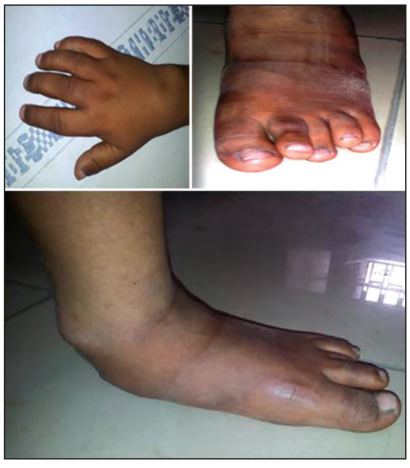

Figure 2: The figure highlights – flat spatulate hands, pes planus deformity of foot and overlapping of toes

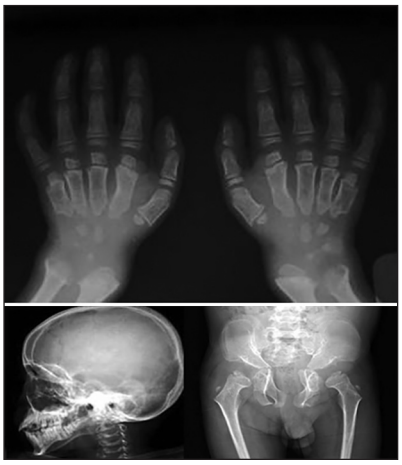

Figure 3: The figure highlights – stout stubby bones with tapering proximal ends of metacarpals and coarsening of trabecular pattern, J-shaped sellaturcica and flared bilateral iliac blades with abnormal configuration of bilateral femoral head epiphysis on X-ray

mood stabilizer, sodium valproate had been added at a dosage of 600 mg/day in divided doses and later increased to 1000 mg/day, to which he had responded well. The patient was maintained well on these medications in follow up.

DISCUSSION

Dyggve–Melchior–Clausen syndrome is a progressive spondylo-epi-metaphyseal dysplasia associated with mental retardation, characterized by a triad of skeletal deformities, facial dysmorphism, and intellectual disability.[1,2] Because of the close resemblance of its manifestations with Morquio's disease (Mucopolysaccharidosis Type IV), it is also called Pseudo-Morquio's Disease. Initially, it was thought to be a mucopolysaccharidosis, but subsequently it was disproved.[7]

It is inherited in an autosomal-recessive fashion.[1,2] Recent researches suggest that dominant mutation of transient receptor potential vanilloid 4 (TRPV4) may be responsible for 'Spondylo-epiphyseal dysplasia' Maroteaux type (Pseudo-Morquio syndrome type-2).[8,9]

There have been only about 60 published case reports of Dyggve–Melchior–Clausen syndrome, and our case is unique owing to the concomitant presence of a mood disorder, which so far has never been reported in conjunction with this syndrome. To the best of author's knowledge, this is the third published case report from India. It is an extremely rare disorder. Intellectual disability is a common neuropsychiatric developmental disability reported in patients of Dyggve–Melchior–Clausen syndrome.[1,2] In an association study on Japanese population, it was found that the gene (Dymeclin gene) responsible for DMC syndrome is also associated with schizophrenia.[10] There is no evidence of association of mood disorder in patients of Dyggve–Melchior–Clausen syndrome. To the best of author's knowledge, this is the first case report of the world to report such rare association.

Behavioral problems are frequently seen in the background of intellectual disability. It is possible to miss the mood disorder in children with intellectual disability. So, the clinician should be cautious enough to understand the psychopathology of behavioral problems in the background of intellectual disability. In this case, the patient had responded poorly to the antipsychotics, but had shown good response on addition of mood stabilizer.

Linkage studies have revealed that bipolar affective disorder has association with multiple chromosomes out of which association with chromosome 18q is a strong and consistent association.[11-13] Chromosome 18q 21.1 is linked with Dyggve–Melchior–Clausen syndrome.[4] The association of Dyggve–Melchior–Clausen syndrome and mood disorder can be merely by chance or a co-morbid one. But as the chromosomal involvement in both the disorders overlap, there is likely a possibility of genetic linkage that might be responsible for mood disorder (manic features) in the background of Dyggve–Melchior–Clausen syndrome. Further study is needed in this domain to gain insight into to any possible linkage between Dyggve–Melchior–Clausen syndrome and bipolar affective disorder.

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