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CASE REPORT

Ghosal Hematodiaphyseal Dysplasia Syndrome (GHDD): First Case Report of Association with Atrial Septal Defect and Successful Surgical Repair

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Abstract:

Background: Ghosal hematodiaphyseal dysplasia (GHDD) is an rare autosomal recessive skeletal condition that is recognized by thickening of the diaphyseal bones and progressive bone marrow sway. Less than 40 cases have been reported globally, primarily from the Indian subcontinent. The condition is due to biallelic pathogenic variants in the TBXAS1 gene causing ineffective thromboxane A synthase. Mutations causing GHDD are known to strictly cause hematologic and skeletal abnormality, without an association to congenital heart disease. This is the first case that describes GHDD associated with an atrial septal defect (ASD).

Case Presentation: A 17-month-old girl was brought in with severe failure to thrive and deformity of her left upper limb. Upon examination left radius bone was not there and growth parameters were below the 3rd centile. Wide and fixed split S2 with ejection systolic murmur was found on cardiac auscultation. Radiography shows enlarged heart, big pulmonary arteries and small bones. A large ostium secundum ASD with left to right shunt and right heart dilatation was seen in echocardiography. Hematologic test showed isolated thrombocytopenia with preservation of other cell lines. A pathogenic TBXAS1 mutation responsible for GHDD was identified in a patient suspected to have Holt-Oram syndrome. The child had successful surgical ASD patch closure, during which a left atrial membrane was discovered and removed. The post-op recovery was uncomplicated and the patient continues to be monitored for developing hematological involvement.

Keywords: Ghosal Hematodiaphyseal syndrome, ASD, left radius bone

INTRODUCTION

Ghosal hematodiaphyseal dysplasia (GHDD) is an extremely rare autosomal recessive disorder characterized by a combination of diaphyseal dysplasia of long bones and progressive bone marrow dysfunction leading to cytopenias (1). The condition was first described in 1988 by Ghosal et al. Currently, it is one of the least commonly reported skeletal dysplasias worldwide. In the literature, fewer than 40 cases are documented. The condition has mainly been reported from the Indian subcontinent and Middle Eastern regions. It is due to genetic clustering and higher rates of consanguinity in some populations (2).

Mutations in the TBXAS1 gene on chromosome 7q33–34 are the underlying etiology of GHDD. This gene codes for thromboxane A synthase, which is required for producing thromboxane A2 from prostaglandin H2. The latter is a potent stimulator of vasoconstriction and platelet aggregation. Mutations that cause loss of function greatly reduce thromboxane A2 production and cause an increase in prostaglandin E2 (3). High levels of prostaglandin E2 could be causing bone marrow cells that make red blood cells to go into death. It can also be a reason for other blood-related problems like anaemia or a lower number of blood platelets. Hematologic manifestations typically respond well to corticosteroid therapy, making their early identification clinically significant (4).

The equal growth of long bones and spinal cord because of a genetic mutation is known as an achondroplasia disease. On imaging, these alterations present as thickened cortex, narrowed medullary cavities and widening deformity of the metaphyseal regions (1) In a clinical setting, children may show deformity of limbs, bone pain, delayed growth, and abnormal walk. In most cases reported, the hematologic manifestations develop slowly (usually between 2 to 5 years of age) and skeletal abnormalities can either predate or succeed cytopenias (5).

A limited number of cases have been published, which has made phenotypic spectrum of GHDD incompletely defined. So far, nothing has been reported associated with congenital heart disease. Children born with limb deformities and heart defects are usually mentioned in syndromes like Holt–Oram syndrome (6) and Thrombocytopenia-Absent Radius (TAR) syndrome or VACTERL association. In these situations, it is possible to delay the diagnosis and genetic counselling for GHDD. Consequently, it is imperative to broaden the acknowledged clinical spectrum of GHDD to enhance diagnostic accuracy (7).

This case report is the first recorded case of GHDD associated with atrial septal defect (ASD) confirmed by whole exome sequencing after being suspected of Holt–Oram syndrome. The uncommon combination of absent radius, isolated thrombocytopenia, severe growth failure and significant structural congenital heart defect. By surgically correcting the ASD, we see the importance of an early diagnosis and multidisciplinary management. According to Hill et al48, this case makes a case for considering GHDD in the differential diagnosis of infants with skeletal and hematologic problems in conjunction with congenital heart disease (8).

CASE REPORT

Patient Presentation: A 17-month-old female was taken to Pediatric Cardiology OPD for evaluation of suspected congenital heart disease (CHD). She was born to an unrelated first baby to an unrelated consanguineous couple at term. At the time of presentation, the child was severely failed to thrive. They were also growth delayed, and had a deformity of the left upper limb noticed since birth. A family history of skeletal anomalies, congenital heart disease, recurrent infections or early anaemia is absent.

Clinical Findings: On examination, the child appeared severely malnourished. The anthropometric measurements of the child were below third percentile as per age. His weight was 4.4 kg, length 62 cm and head circumference 42 cm. Examination of the upper limb showed severe deficiency of the upper skeletal support of the left forearm. There was shortening of the limb and no bony contour felt along the radial aspect. No other skeletal deformities were observed. When the heart was listened to, a sound was heard that was longer than normal. Also, a heart sound was heard from the lungs and not the heart.

Fig 1: Clinical Deformity with left forearm absent radius.

Diagnostic Assessment: A chest X-ray showed an enlarged heart and enlarged blood vessels in lungs. The left forearm X-ray showed that the radius is completely absent but the ulna is partially intact. There is soft tissue deformity in the region. The evaluation of the blood indicated the hemoglobin level to be 11 gm/dL. MCV it was 71.2 fL MCH was similar to 23. The TLC got booked for 9900/µL however there was thrombocytopenia 1.2 lakh/µL with no anemia or leukopenia evidence. Liver and renal function tests were within normal limits.

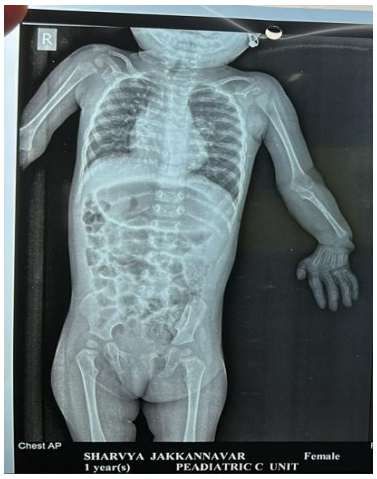

Fig 2: Radiographic presentation of deformity with left forearm absent radius.

An echocardiogram showed a big hole in the heart with blood shifting from left to right. The right atrium and right ventricle are bigger. Yet, both ventricles function normally. Doctors suspected the child had Holt–Oram syndrome due to both upper limb malformation and congenital heart defect.

Whole exome sequencing was applied to specify the diagnosis. A pathogenic homozygous mutation in TBXAS1 was detected, confirming Ghosal hematodiaphyseal dysplasia (GHDD), genetic analysis.

This means that Holt–Oram syndrome was not suspected.

Therapeutic Intervention: A multidisciplinary evaluation involving pediatric cardiology, hematology, and cardiothoracic surgery eventually planned for surgical repair of the ASD. Surgery was successful in patching the defect in the child. A membrane of the left atrium was identified and cut out during surgery. The surgical procedure was completed without complications. Because of thrombocytopenia, jeopardy of bleeding was observed and preventive measures taken, but transfusion was not needed.

Follow-Up and Outcomes: The child had an uneventful postoperative recovery, maintaining stable hemodynamic status and improving oral intake. She was discharged with instructions for close follow-up. At subsequent visits, she remained clinically stable with normal cardiac examination and improving weight trajectory. Hematologic parameters continue to be monitored for possible evolving cytopenias, as GHDD-related marrow dysfunction often manifests progressively with age. Orthopedic assessment was continued for long-term management of the limb deformity.

DISCUSSION

Ghosal Hematodiaphyseal Dysplasia (GHDD) is a very rare skeletal dysplasia that is inherited in an autosomal recessive manner and is associated with diaphyseal skeletal abnormalities and progressive bone marrow dysfunction. Less than 40 cases have been reported since its first description. With more children having genetic assessments for atypical skeletal and hematologic features, the phenotypic spectrum is widening (1). This is the first time a association between GHDD and a congenital heart disease an ostium secundum atrial septal defect (ASD) is documented in this case. This finding has not been reported in any previous GHDD literature. It adds new clinical dimension regarding our understanding of the disorder.

Biallelic pathogenic mutations in TBXAS1, encoding thromboxane A synthase, underpin the pathophysiology of GHDD.

The inactivity of this enzyme leads to a reduction in thromboxane A2 along with a simultaneous increase in prostaglandin 2 levels which might inhibit erythroid progenitors activity and cause the classic anaemia (3). Most classical cases describe pancytopenia – but the child in our case report had isolated thrombocytopenia with preserved hemoglobin and leukocyte levels. The child's young age may be responsible for this as most hematological manifestations evolve gradually and will not be prominent early on in life (9). It is critical to carry on monitoring continuously since early institution of the corticosteroids has shown restoration of the cytopenias. It also stops the advancement of the bone lesions (10).

Skeletal involvement in GHDD commonly consists of symmetrical cortical thickening, diaphyseal expansion and metaphyseal widening. The complete absence of the radius, as observed in our patient, is an unusual finding that initially led to a consideration of Holt–Oram syndrome or Thrombocytopenia-Absent Radius (TAR) syndrome (11). This makes the suspicion more likely, given that the individual has ASD. In such cases, clinical and radiological findings can be misleading. Thus, there is a need for the genetic analysis. The diagnosis revealed a TBXAS1 mutation via whole exome sequencing indicating its key role in discriminating overlapping congenital syndromes (12).

A significant structural heart defect is another important aspect of this case. Until now, congenital heart defects have been recorded in Holt–Oram syndrome, TAR syndrome, and other chromosomal abnormalities but not associated with GHDD (13). It is unclear whether the ASD in this child is a chance finding or an unrecognised phenotypic extension of GHDD. Because this condition is not one that you see often, it is possible that other cardiac features that are unique or subtle have been missed. The finding of a membrane in the left atrium at surgery raises the possibility of more extensive developmental disturbances, but further cases will be needed before a definitive genotype–phenotype correlation can be made (14).

The ASD surgery was successful despite the background of Thrombocytopenia. It teaches that most standard cardiothoracic surgeries can be safely done in GHDD children with adequate perioperative planning. Bleeding complications were not significant which implies that early skeletal dysplasias, which are without severe pancytopenia, may not be at risk of excessive procedures at all (15). Improvements in growth parameters and general health after surgery also suggest that timely correction of hemodynamically significant cardiac defects may influence overall development of children positively (16).

The case shows the importance of having a wide differential diagnosis in infants who present with a combination of skeletal and cardiac malformations and that genetic testing must be done to avoid diagnostic anchoring. These types of cases require close collaboration between cardiology, hematology, genetics, and orthopedic teams. With increasing awareness of GHDD, clinicians will begin to recognize greater associations or atypical presentations to further define the clinical picture.

The report gives more information on your condition. It also links congenital heart disease to this genetic condition for the first time. In order to find out whether heart problems are an insignificant coincidence or an

important extension of this already complex syndrome, we must continue investigating the genetic links of similar reports.

CONCLUSION

It is the first case of the association of Ghosal Hematodiaphyseal Dysplasia with congenital heart disease, namely ostium secundum atrial septal defect. A child with severe growth failure, isolated thrombocytopenia, and a characteristic upper limb skeletal anomaly was initially thought to have Holt–Oram syndrome. A diagnosis of GHDD; a TBXAS1 pathogenic mutation was identified through whole exome sequencing. The successful surgical closure of the atrial septal defect (ASD), along with the uneventful postoperative recovery, shows that corrective heart surgery can safely be performed on children with rare skeletal dysplasias and constitutional haematology. Timely identification, correct genetic assessment and coordinated multidisciplinary therapy are essential for optimising outcomes. This is especially pertinent as the hematologic abnormalities in GHDD worsens with age and timely steroid therapy is essential. The case provides further evidence that generalised hypopituitarism due to GH deficiency should be suspected in the presence of cardiac, skeletal, and hematologic findings.

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