European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.es/

Article

A Rare Link between Bone and Blood: Unveiling Ghosal Hematodiaphyseal Dysplasia.

Article History:
Received: 12/10/25
Accepted: 26/11/25
Published: 28/12/25

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How to cite this article:
Dr Neelam Vijayshankar Singh , . Dr Abhilasha S,, Dr Arjun Garg , Dr Hershavardhini K . A Rare Link between Bone and Blood: Unveiling Ghosal Hematodiaphyseal Dysplasia..*" European Journal of Clinical Pharmacy, vol. x, no. x, 2026 pp.1464-1468.*

Abstract: *Background: Ghosal hematodiaphyseal dysplasia (GHDD) is a rare autosomal recessive disorder caused by TBXAS1 gene mutations, characterized by increased bone density and steroid-responsive cytopenias.*

Case Presentation: A 3-year-old boy presented with refractory anemia and thrombocytopenia since 18 months of age, causing recurrent epistaxis and fatigue requiring multiple transfusions. Bone marrow findings were normal, excluding immune and inherited thrombocytopenias. Radiographs performed for suspected rickets revealed metaphyseal and diaphyseal dysplasia of the ulna. The combination of skeletal changes and cytopenias suggested GHDD. Whole-exome sequencing confirmed a homozygous TBXAS1 mutation. Corticosteroid therapy led to rapid improvement, with platelet count rising to 120,000/μL within 20 days and sustained hematologic stability above 150,000/μL for two years on low-dose maintenance therapy.

Conclusion: This case emphasizes the importance of recognizing rare inherited bone dysplasias in children with refractory cytopenias, enabling timely molecular diagnosis and targeted corticosteroid treatment to achieve optimal outcomes.

Keywords: Hematodiaphyseal dysplasia, Thrombocytopenia, Anemia, Steroid-responsive thrombocytopenia

GHDD presents as a rare inherited condition transmitted in an autosomal recessive manner, characterized by enhanced bone mineralization, particularly affecting the long bone diaphysis, accompanied by steroid-responsive cytopenias, including thrombocytopenia and anemia.1-3 It was first documented in 1988 and is also referred to as Ghosal syndrome.4 The severe thrombocytopenia, normocytic anemia, and bone abnormalities result from loss-of-function mutations in thromboxane A synthase 1 (TBXAS1). 1.5 Thromboxane synthase plays a critical role in modulating inflammatory responses, hemostatic mechanisms, and osteoclastic function; its dysfunction consequently disrupts skeletal remodelling processes and compromises marrow hematopoietic capacity1,3,6. Mutations affecting TBXAS1 underlie this condition, with molecular confirmation established in less than 40 patients worldwide, primarily among populations of Middle Eastern, North African, and South Asian ancestry.7,8 The disorder presents with defective hematopoiesis ranging from mild myelophthisic anemia to severe pancytopenia requiring red blood cell transfusions.7,8Both homozygous and compound heterozygous variants in TBXAS1 have been identified, demonstrating variable clinical expressivity even within affected families. 9 In this communication, we report a case of an Indian child presenting with persistent bleeding due to chronic thrombocytopenia and incidental radiological findings of diaphyseal dysplasia, suggestive of GHDD, confirmed through genetic analysis and successfully managed with corticosteroid therapy

CASE PRESENTATION

A 3-year-old male child, third born out of a non-consanguineous marriage, was referred to our pediatric hematology clinic for evaluation of persistent epistaxis, skin and mucosal bleeds, thrombocytopenia and anemia since 18 months of age. The child initially presented with complaints

of intermittent fever, epistaxis and easy fatiguability at 1.5 years of age, which had been managed conservatively. A complete hemogram revealed hemoglobin of 8.9 gm/dL, a red blood cell count of 3.17 x 10^6/µL, platelet count of 22 x 10^3/µL and WBC count of 4600/cumm with a differential count consisting of 20% neutrophils and 76% lymphocytes. Peripheral smear showed microcytic hypochromic anemia. Apart from anemia and thrombocytopenia, the other remarkable finding was relative neutropenia with an absolute neutrophil count of 920. The child had been transfused with six units of random donor platelets and two units of red blood cell transfusion as part of management for epistaxis and oral mucosal bleed in the past 18 months. He was also on oral hematinics for the management of iron deficiency, which was due to chronic blood loss due to thrombocytopenia

Initially, a diagnosis of Immune thrombocytopenia (ITP) was considered and the child was subjected to bone marrow aspiration and biopsy. It revealed micronormoblastic erythroid hyperplasia with normal myeloid and megakaryocyte series; hence, ITP was ruled out. A provisional diagnosis of inherited bone marrow failure syndrome with iron deficiency anemia and rickets was made. However, over the course of the year, the child received multiple blood and platelet transfusions in view of persistent thrombocytopenia and anemia. There was no significant family history of bleeding disorder or blood transfusion. Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

On examination, the child had normal vital parameters. His anthropometric measurements showed, weight of 14kgs (0 to +1z), height of 89cms (-3z to -2z), and head circumference of 51cms (0 to +1z). The child had attained normal developmental milestones for his age. General physical examination findings included pallor and multiple petechiae, purpura and ecchymosis all over the body. The child also had some clinical features of rickets, which included frontal bossing, bowing of lower limbs and mild hypotonia. Per abdomen examination showed hepatomegaly of 2cm, and no splenomegaly. Other systems examination was unremarkable.

The child was admitted for further evaluation. A complete blood count (CBC) was ordered which revealed hemoglobin 9.3 gm/dL, red blood cell count 3.19×10^{6}/µL, platelet count 86×10^{3}/µL, and WBC count 4900/cumm. This CBC also showed relative neutropenia with an absolute neutrophil count of 882. Iron studies revealed ferritin of 2.99ng/ml, serum iron of 16mcg/dl, and transferrin receptor saturation of 3% suggestive of iron deficiency anemia. Due to thrombocytopenia and risk of bleeding, the child was given Injection Romiplostim-thrombopoetin analogue, 125 micrograms subcutaneously and oral iron, calcium and vitamin D supplementation.

The previous bone marrow slides and biopsy blocks were reviewed at our centre, which revealed similar findings. The child was subjected to an X-ray as part of the workup for rickets and also to rule out a rare possibility of osteopetrosis leading to pancytopenia. However, interestingly, skeletal radiography revealed bilateral metaphyseal dysplasia of the humerus characterized by cortical thickening and generalized increased cortical density (**Fig. 1**). Due to the coexistence of pancytopenia and diaphyseal dysplasia, which was an incidental finding, the possibility of GHDD was considered and a genetic workup was planned.

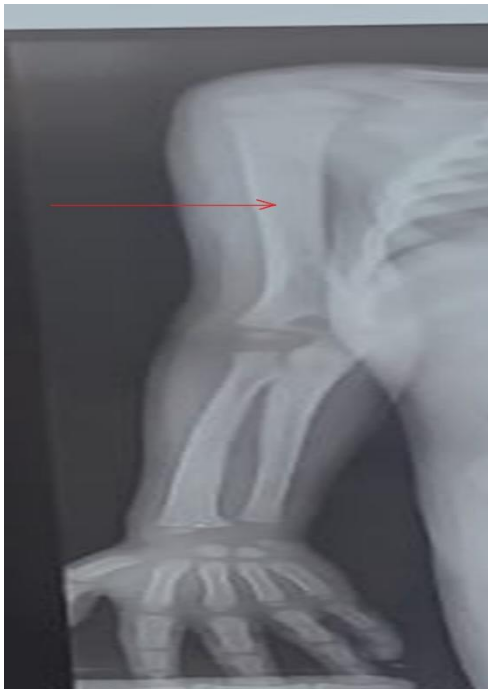

Fig. 1- Metaphyseal dysplasia of the humerus with cortical thickening

Genetic workup included whole exome sequencing with confirmatory Sanger sequencing. TBXAS1 gene mutation analysis by Sanger sequencing of all 13 exons and exon-intron boundaries revealed a homozygous mutation c.1238G>A (p.Arg413Glu) in exon 16 (NM_001130966.2), confirming GHDD.

The child was initiated on oral prednisolone at a dose of 2mg per kg per day with a subsequent rise in platelets to 120000/cumm after 20 days of therapy. Prednisolone was tapered progressively to 1mg per kg, then 0.5mg per kg after 40 days as platelet count improved to 226,000/cumm. Hemoglobin increased to 11.2 g/dL after 2 months. Skeletal manifestations improved after 3 months (**Fig. 2**). The child is on follow-up since 2.5 years on low-dose steroids between 0.3-0.5 mg per kg per day, maintaining platelet counts above 150,000/cumm. Two steroid cessation attempts resulted in thrombocytopenia relapse below 50,000/cumm, necessitating continued therapy. There was no further episode of bleeding and anemia and even the skeletal manifestations improved. The child is thriving well.

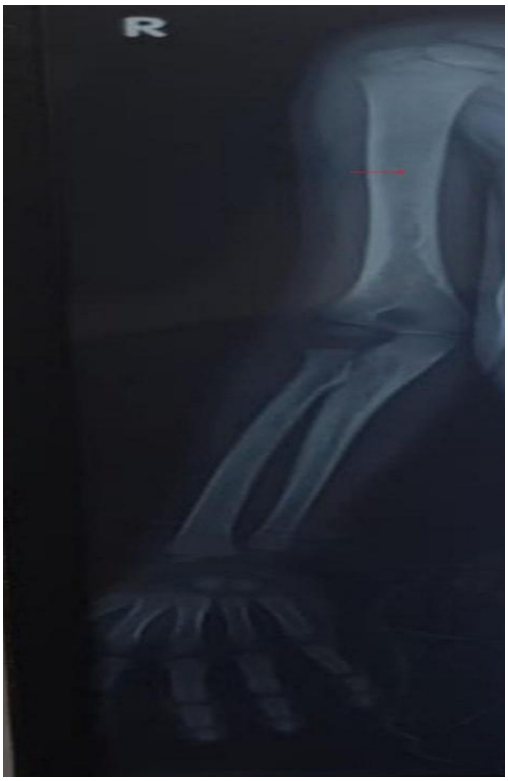

Fig. 2- Improvement in cortical thickening and dysplasia after 3 months of treatment

DISCUSSION

GHDD's rarity frequently delays clinical recognition, as even with characteristic signs and symptoms, diagnosis is often delayed due to the requirement for genetic analysis, particularly in resource-limited settings.[1] The condition presents with overlapping hematological features as seen in various disorders, causing diagnostic delays.[6] Our case presented with anemia and thrombocytopenia, unresponsive to conventional treatment, followed by diaphyseal dysplasias involving long bones. There was a gap of approximately 1.5 years for bony changes to become obvious, as the initial skeletal survey was normal, resulting in a delay in the diagnosis and treatment of our patient. Late diagnosis in adulthood can lead to significant morbidity and suboptimal response to treatment.[10]

GHDD arises from biallelic pathogenic variants in the TBXAS1 gene, which encodes thromboxane synthase—a key enzyme in the arachidonic acid pathway.[2,11] Thromboxane A2 (TXA2), the molecule produced by this enzyme, controls bone remodeling by regulating RANKL and osteoprotegerin in bone cells, and it also promotes the formation of osteoclasts. [1,12] Through these mechanisms, TXA2 serves as a critical regulator of bone mineral density.[1] When TXA2 synthesis is impaired, prostaglandin H2 accumulates and is shunted toward alternative metabolic pathways, leading to increased production of proinflammatory prostaglandins and leukotrienes.[12,13] These accumulated metabolites are believed to cause direct bone marrow injury, ultimately contributing to the characteristic cortical bone remodelling seen in GHDD.[13]

GHDD treatment currently involves corticosteroids, though optimal dosing and duration lack consensus.[5] Long-term low-dose oral steroids improve platelet count and hemoglobin levels, reducing transfusion requirements.[3] Our patient responded well to steroid therapy, while maintaining stable hematological parameters without bony dysplasia progression. Novel compound heterozygous variants in TBXAS1 have demonstrated successful normalization of blood counts with chronic oral steroid therapy.[6,9]

Emerging evidence indicates that cyclooxygenase (COX)-1 and -2 inhibitors (NSAIDs) provide therapeutic benefit in TBXAS1-deficient patients by diminishing prostaglandin synthesis, thereby restoring hematologic homeostasis.[5,8] NSAIDs surprisingly reduced both COX and lipoxygenase (LOX) products, resolving cytopenia.[5] Subsequent French multicenter studies corroborated these findings, with patients achieving sustained remission on low-dose aspirin (75-150mg/day).[8] Ravikumar et al. reported marked hematological improvement in a middle-aged adult treated with daily aspirin 150mg, documenting hemoglobin elevation from 6.1 to 11 gm/dL over three months.[12] More data is needed for NSAIDS to be considered for first-line treatment for GHDD. However, in our patient, NSAIDS were not administered. These findings represent a paradigm shift toward mechanism-based therapy with potentially fewer adverse effects than chronic corticosteroids.[2,5,8]

The identified mutation (p.Arg413Glu) is recurrent in South Asian populations, suggesting a founder effect.[14]
Molecular characterization demonstrating biallelic TBXAS1 variants confirms the genetic basis linking chronic cytopenias with elevated skeletal density, while corticosteroid intervention has successfully eliminated transfusion dependency in affected individuals.[6,9] Unlike many marrow failure syndromes, GHDD has a good long-term prognosis with treatment.[3,8] Genetic counselling is essential as GHDD follows autosomal recessive inheritance with a 25% recurrence risk.[1,9]

This case demonstrates that refractory anemia, thrombocytopenia, and bone manifestations should prompt investigation for uncommon inherited bone dysplasias. Skeletal radiography is critical in unexplained cytopenia. Early recognition enables appropriate cost-effective therapy with corticosteroids or emerging NSAID-based treatment, preventing transfusion dependence and permanent skeletal sequelae, thus improving long-term outcomes.

Abbreviations

GHDD-Ghosal hematodiaphyseal dysplasia
TBXAS1-thromboxane A synthase-1
TXA2-Thromboxane A2
ITP- immune thrombocytopenia
CBC- Complete blood count
RBC- Red blood cells
WBC-White blood cells
NSAIDS- Nonsteroidal Anti-Inflammatory Drugs
RANKL-Receptor Activator of Nuclear Factor-κB Ligand
COX-Cyclooxygenase
LOX-Lipoxygenase.

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