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Case Series

Beyond nutritional: a case series of thalassemia trait

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ABSTRACT

Microcytic anemia in children is frequently attributed to iron deficiency, yet not all cases improve with adequate iron therapy. When anemia persists despite normal iron stores, other causes-particularly hemoglobinopathies-must be considered. This report describes three children who presented with ongoing microcytic hypochromic anemia that did not resolve with appropriate iron supplementation. All had documented treatment adherence and iron profiles within the expected range for sufficiency. Each child underwent a structured evaluation. Two were found to have elevated HbA2 levels on hemoglobin electrophoresis, establishing a diagnosis of beta-thalassemia trait. The third child had nondiagnostic electrophoresis findings but demonstrated heterozygous deletions in the HBA1 and HBA2 genes on molecular analysis, confirming alpha-thalassemia trait. None of the children exhibited organomegaly, significant clinical symptoms, or dysmorphic features, and their growth parameters were appropriate for age. The consistent finding across all cases was persistent microcytosis despite biochemical evidence of adequate iron. These cases emphasize the importance of considering thalassemia traits when confronted with pediatric anemia that does not respond as expected to iron therapy. Recognizing characteristic red-cell indices and pursuing targeted investigations can prevent repeated or unnecessary treatment and allow families to receive appropriate genetic counseling. Early and accurate identification of hemoglobinopathies contributes to better long-term management and ensures that healthcare resources are used appropriately.

Keywords: Thalassemia trait, Microcytic anemia, Iron-refractory anemia, Pediatric hemoglobinopathy, Genetic analysis

INTRODUCTION

Iron deficiency anemia remains the leading cause of anemia worldwide, especially among children; however, hemoglobinopathies, chronic infections, and long-standing medical conditions also contribute substantially to the global burden. Pediatric anemia is clinically significant, as it is associated with neurodevelopmental delays, low birth weight, increased susceptibility to infection, cardiac complications, and-in severe cases-increased mortality.[1] A structured diagnostic approach should include a detailed evaluation of dietary patterns, environmental exposures, and family history, supported by a focused physical examination that may reveal features suggestive of inherited or syndromic causes. Stepwise laboratory testing, complemented by genetic analysis where appropriate, has greatly improved the identification of inherited anemias.[1] When microcytosis persists despite adequate iron supplementation and normal iron stores, hemoglobinopathies and other non-nutritional causes must be considered.

Thalassemias constitute a heterogeneous group of inherited disorders caused by impaired synthesis of the alpha or beta globin chains that form hemoglobin. Reduced production of beta-globin results in beta thalassemia, whereas alpha thalassemia stems from inadequate or absent alpha-globin synthesis.[2,4] These globin chains form the structural backbone that supports the heme molecule, enabling oxygen binding and

delivery. The beta-globin genes are located on chromosome 11 and the alpha-globin genes on chromosome 16, with globin gene expression varying across developmental stages-for instance, gamma-globin predominates in fetal life before transitioning to adult hemoglobin patterns after birth.[2,3]

Disturbances in the balance of globin chain production can lead to ineffective erythropoiesis and varying degrees of hemolysis. Individuals with mild forms, such as alpha-thalassemia silent carriers or alpha/beta thalassemia traits, generally remain asymptomatic and do not require therapy.[4] More severe forms, however, result in significant morbidity: hemoglobin H disease produces chronic hemolytic anemia, while alpha thalassemia major (hemoglobin Bart's hydrops fetalis) is typically fatal in utero.[3]

Thalassemia distribution varies widely across the world, with the highest carrier frequencies observed in South Asia, Southeast Asia, the Mediterranean region, the Middle East, and parts of Africa-geographical patterns that reflect the historical selective advantage conferred against malaria.[15] India carries one of the largest global burdens of thalassemia carriers, whereas countries such as Australia encounter thalassemia largely through migration, resulting in increased detection during antenatal and pediatric screening.[17]

Genetic counseling is strongly recommended for affected individuals or carriers, particularly when planning a pregnancy. Prenatal diagnostic options-including chorionic villus sampling-may be considered in families at risk for severe forms such as hemoglobin Bart's, which also increases maternal risks including toxemia and postpartum hemorrhage.[5] Although individuals with thalassemia trait generally have normal life expectancy, those with transfusion-dependent beta thalassemia face complications related to chronic anemia and iron overload. Nonetheless, advances in transfusion safety, iron chelation therapy, and long-term monitoring have significantly improved survival and quality of life.[3] Population-based screening and early detection remain key strategies for reducing the incidence and severity of thalassemia.[2]

CASE SERIES

Case 1

A 6-year-old girl, developmentally normal child born to non-consanguineous marriage, was evaluated for respiratory tract infections. There was no significant natal or postnatal history of anemia. The mother reported a history of anemia during pregnancy that was refractory to iron treatment. On examination, the child was found to be anemic but showed no signs of hepatosplenomegaly or facial dysmorphisms. She had been started on iron supplements elsewhere. Despite adherence to iron supplementation and dietary modifications, the child's hemoglobin remained below 8 g/dL for over six months. Serum iron and ferritin levels were within normal limits. Consequently, hemoglobin electrophoresis was performed, which suggested a diagnosis of beta-thalassemia trait. The parents were counselled regarding the same and the child was continued on folic acid supplementation.

Table 1: Investigations for case 1.

Hb electrophoresis	Value
Hemoglobin A	82.9 (low)
Hemoglobin A2	5.5 (high)
Hemoglobin F	0.9
Hemoglobin S	0
Hemoglobin D	0
Hemoglobin C	0
Hemoglobin E+A2	0
Serum iron	146 mcg/dl
Ferritin	275 ng/ml

Case 2

A 12 year old developmentally normal girl with no facial dysmorphism or hepatosplenomegaly, child who is a known case of type 1 diabetes mellitus diagnosed at 7 years of age with family history of diabetes mellitus, upon routine investigation showed iron deficiency anemia, she was empirically started on iron folic acid supplements from elsewhere, despite normal serum iron and ferritin levels and continued iron supplementation, the child remained anemic, with a microcytic hypochromic blood picture. Hemoglobin electrophoresis was conducted, which ruled out beta-thalassemia trait. Further genetic evaluation for deletions, duplications, and variations in the HbA1 and HbA2 genes associated with alpha-thalassemia revealed a heterozygous deletion in both the HbA1 and HbA2 genes.

Table 4: Investigations for case 2.

Heterozygous deletion	**HBAP1, HBA2 (upstream, exon 1-3) HBA1 (upstream, exon 1-3) and HBQ1 (upstream and exon 1)**	**Alpha thalassemia A3.7/SEA deletion hetrozygous deletion of HbA1 and HbA2**
Heterozygous deletion	HBA2 (exon 3, intron 2, exon 2)	
Hemoglobin (24/02/2024)	9.5	g/dl

Case 3

A 5 year old developmentally normal girl child was admitted with complaints of AURI, on routine blood evaluation she was found to have anemia with a Hb value of 6.8 g/dl, with normal iron and ferritin levels, PBS showed severe microcytic hypochromic anemia, on

systemic examination there was no facial dysmorphism or hepatosplenomegaly, and hence Hb electrophoresis was sent and she was found to have features suggestive of beta thalassemia trait and was started on folic acid.

Table 3: Investigations for case 3.

Examinations	Results
Hemoglobin A	76.0 low (94.3-98.5)
Hemoglobin A2	1.2 low (1.5-3.7)
Hemoglobin F	0
Hemoglobin S	0
Hemoglobin D	0
Hemoglobin C	0
Hemoglobin E+A2	0
Hb	6.8 g/dl
PCV	23
MCV	54
MCH	16
MCHC	29.4
Retic	1.8
PBS	Severe microcytic hypochromic anemia. Target cells present with relative neutrophilia
Ferritin	259
LDH	489
Free T4	11.02
TSH	2.11
Stool occult blood	Negative

DISCUSSION

Iron deficiency anemia remains the most common cause of anemia in children globally; however, when anemia persists despite adequate iron supplementation and normal serum iron and ferritin levels, clinicians must consider alternative etiologies, including hemoglobinopathies. Thalassemia, both alpha and beta types, should be considered in the differential diagnosis, particularly in cases with a microcytic hypochromic blood picture.[2-4] The persistence of anemia despite iron therapy may point to underlying genetic disorders, such as thalassemia, which can present with subtle symptoms, especially in carriers of thalassemia traits.[1]

In children who remain anemic despite iron therapy, hemoglobin electrophoresis is an essential diagnostic tool to rule out or confirm thalassemia traits.[5,6] Beta-thalassemia trait can often be identified through this method, while more subtle forms, such as alpha-thalassemia, may require molecular genetic testing to detect deletions or mutations in the HbA1 and HbA2 genes.[7,8] This approach is crucial because thalassemia traits are typically asymptomatic and can be easily overlooked if only iron deficiency is considered as the primary cause of anemia.[9]

Failure to respond to iron supplementation warrants further evaluation, as misdiagnosis can lead to unnecessary iron therapy, which may not only be ineffective but could also carry potential risks such as iron overload.[10] The identification of thalassemia traits is also important for genetic counseling, as it helps inform reproductive planning and prevents the inheritance of more severe forms of thalassemia, such as thalassemia major, which can lead to significant morbidity and reduced life expectancy.[2,11] Advances in genetic testing have made it possible to identify carriers of thalassemia traits early, which helps prevent complications in affected pregnancies.[12,13]

Early and accurate diagnosis of hemoglobinopathies through a structured diagnostic approach, including hemoglobin electrophoresis and genetic testing, plays a critical role in managing pediatric anemia. This approach ensures that children receive appropriate treatment and counseling, thus reducing potential long-term complications associated with undiagnosed hemoglobinopathies.[14,15] Furthermore, timely diagnosis can significantly reduce the burden on healthcare systems by decreasing need for unnecessary iron supplementation and avoiding the complications of untreated thalassemia major.[16]

Guidelines from Canadian hemoglobinopathy association recommend that unexplained microcytosis in the absence of iron deficiency is an indication for high-performance liquid chromatography testing.[5] People with thalassemia should not receive iron unless they have documented iron deficiency. If serum ferritin is >300 mcg/L, then iron overload should be suspected.[4] Mild forms of thalassemia might not require treatment, but in severe cases requiring blood transfusion, iron overload can occur from transfused RBCs, especially affecting liver and heart.[3] Iron chelation is initiated if serum ferritin is >1000 ng/mL, liver iron concentration exceeds 3 mg iron/gm of dry weight/after transfusion of 20-25 units of PRBCs.[4,3] Bone marrow transplantation might cure thalassemia.[3]

Follow up

All three patients were monitored through scheduled outpatient follow-up visits as part of routine hematology surveillance. Each child remained clinically stable, with no new symptoms or complications reported during the observation period. Hemoglobin levels were reassessed periodically, and all patients continued on the recommended management plan. No progression of anemia, development of organomegaly, or emergence of transfusion requirements was noted.

For the children diagnosed with thalassemia traits, growth parameters, energy levels, and school functioning remained appropriate for age. The child with alpha-thalassemia trait underwent ongoing monitoring to ensure no secondary hematologic abnormalities developed. Families received anticipatory guidance regarding triggers that may exacerbate anemia (such as acute

infections or nutritional deficits), and no clinically significant events occurred during follow-up.

Parents were counselled on the chronic, non-progressive nature of thalassemia traits, the low likelihood of future complications, and the importance of genetic counselling for future pregnancies. Compliance with follow-up recommendations was satisfactory across all cases, and no additional interventions were required during the surveillance period.

CONCLUSION

This case series highlights the importance of considering hemoglobinopathies as a cause of persistent microcytic anemia in children who do not respond to adequate iron therapy. Despite the subtle or asymptomatic presentation typical of thalassemia traits, a structured diagnostic approach that includes hemoglobin electrophoresis and, when indicated, molecular genetic testing allows clinicians to accurately distinguish inherited hemoglobin disorders from nutritional deficiencies. In each of the presented cases, timely identification of alpha- or beta-thalassemia trait prevented prolonged and unnecessary iron supplementation, clarified the etiology of anemia, and supported appropriate long-term management.

The findings reinforce that thalassemia traits remain underrecognized in routine pediatric practice, particularly in regions where iron deficiency is often presumed to be the primary cause of microcytosis. By demonstrating how these conditions may appear in otherwise well children with normal growth, no organomegaly, and unremarkable systemic examinations, this series underscores the need for clinicians to maintain a broader differential diagnosis when iron indices are normal. The uncomplicated follow-up of all three children also illustrates that early diagnosis not only guides appropriate therapy but reduces the risk of avoidable investigations, treatment delays, and potential complications.

Beyond clinical management, this case series contributes to broader understanding by emphasizing the role of genetic evaluation in detecting alpha-thalassemia, which may be missed on electrophoresis alone. It also highlights the value of family education and counselling, given the reproductive implications of carrier states. Taken together, these cases demonstrate how early recognition of thalassemia traits enhances patient care, improves diagnostic precision, and supports more efficient use of healthcare resources-thereby advancing knowledge and awareness of hemoglobinopathies in the evaluation of pediatric anemia.

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