Persistent painless eyelid hematoma as an atypical ocular manifestation in Hemoglobin E (HbE) trait hemoglobinopathy: A Case Report

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Background: Hemoglobinopathies encompass all genetic diseases of haemoglobin and fall into two main groups which are thalassemia syndromes and structural hemoglobin variants or abnormal hemoglobins. These diseases can affect any organ in the body. Ocular manifestations in thalassemia cases reported include decreased visual acuity, colour vision anomalies, cataract, visual field defects and optic neuropathy.
Objective: To report an atypical ocular manifestation of Hemoglobin E (HbE) trait haemoglobinopathy who presented with persistent painless lower lid bruising.
Method: Case report
Results: A seven-year-old boy with no known medical illness presented with painless right eye lower lid bruising for the past one year. The patient denied any history of trauma. There were no other ocular or systemic symptoms and the child was otherwise well. Visual acuity was 6/6 in both eyes. There was black discolouration of the right eye lower lid which extended to the temporal upper lid. No swelling or proptosis was noted. The bruising did not increase with Valsalva maneuver. Further examination of the right eye was normal. Examination of the left eye was unremarkable. Systemic examination revealed a round black discolouration of the skin measuring 1.5cm in diameter over the left mid-thoracic region. Retrospective history from the patient's mother noted the trunk discolouration appeared shortly after the right eyelid bruising which persisted until now. The patient was diagnosed as HbE trait hemoglobinopathy carrier via peripheral blood film and hemoglobin electrophoresis testing. In conclusion, persistent painless eyelid discolouration should raise suspicion of bleeding disorders.
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Introduction

Hemoglobin is a protein heterotetramer composed of two chains of α-globin and two chains of β-globin along with four molecules of heme and iron. HbA (α2β2) is the major

component of hemoglobin in normal adults and in children over 7 months old, usually comprising about 97% of the total hemoglobin. The remainder is Hb A2 ($\alpha 2\delta 2$), which usually constitutes about 2−3% in normal individuals.[1]

The hemoglobinopathies encompass all genetic diseases of hemoglobin. They fall into two main groups which are thalassemia syndromes and structural hemoglobin variants (abnormal hemoglobins).[2] Both groups of hemoglobinopathies are caused by mutations and/or deletions in the α- or β-globin genes. When gene defects cause hemoglobin synthesis disorders, this gives rise to thalassemia whereby hemoglobin structure in these cases is normal. When they cause changes in hemoglobin structure, this gives rise to abnormal haemoglobin such as HbS, HbE and HbC.[2-5] There are also many mixed forms that combine features of both groups, such as β0/β+-thalassemias, HbSC disease and HbE α-thalassemias.

Alpha and beta thalassemia are the main types of thalassemia. The highly variable clinical manifestations of the hemoglobinopathies range from mild hypochromic anemia to moderate hematological disease to severe, lifelong, transfusion-dependent anemia with multiorgan involvement. With approximately 7% of the worldwide population being carriers, hemoglobinopathies are the most common monogenic diseases and one of the world's major health problems.[2] They were originally found mainly in the Mediterranean area and large parts of Asia and Africa.[1, 2] International migration has spread them from those areas all over the world.

Ocular findings in beta-thalassemia may correlate to the disease itself, iron overload or the chelating agents used.[6, 7] Various studies have documented ocular manifestations of beta-thalassemia such as ocular surface disease, decreased visual acuity, colour vision anomalies, night blindness due to cataract, visual field defects and optic neuropathy.[2, 6, 7] To the best of our knowledge, no studies have reported about the ocular manifestation in cases of abnormal haemoglobin or haemoglobin variant. We discuss a case of atypical presentation of haemoglobin E trait patient who presented with persistent painless eyelid hematoma.

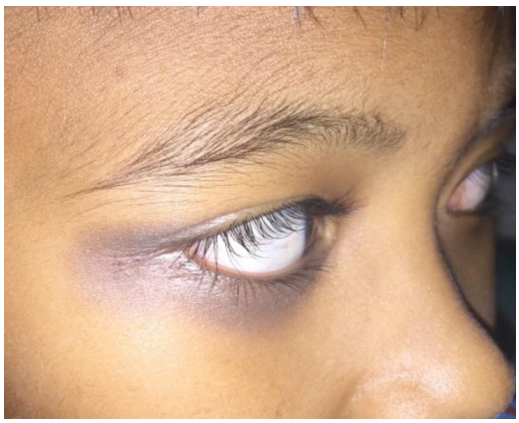
Case Report

A seven-year-old boy with no known medical illness presented with painless right eye lower lid bruising for the past one year. The patient denied any history of trauma preceded the symptom. The bruise was not increasing in size and not causing any proptosis. He had no bleeding tendencies and there was no known family history of malignancy or bleeding disorder. Retrospective history from the patient's mother revealed that a small coin-shaped discolouration at patient's trunk appeared shortly after the right eyelid bruising and has persisted until now. There were no other ocular or systemic symptoms and the child was otherwise well. None of his family members had similar symptoms like him.

At presentation, his visual acuity was 6/6 in both eyes and his intraocular pressure was normal. There was no relative afferent pupillary defect (RAPD). On examination, there was black discolouration of the right eye lower lid which extended to the temporal upper lid (Figure 1 and 2). No swelling or proptosis was noted. The

bruising did not increase with the Valsalva maneuver. Further examination of the right eye was normal. Examination of the left eye was unremarkable. Systemic examination revealed a round black discolouration of the skin measuring 1.5cm in diameter over the left mid-thoracic region (Figure 3). There was no similar skin discolouration at other parts of his head and body. As the lower lid bruising did not cause any proptosis, not increasing in size and has persisted for about one year, there was no radio imaging such as CT scan or MRI done for him.

Subsequently the patient was referred to the paediatric team for further assessment and to rule out any bleeding disorder. His full blood count and coagulation profile result were within normal range.



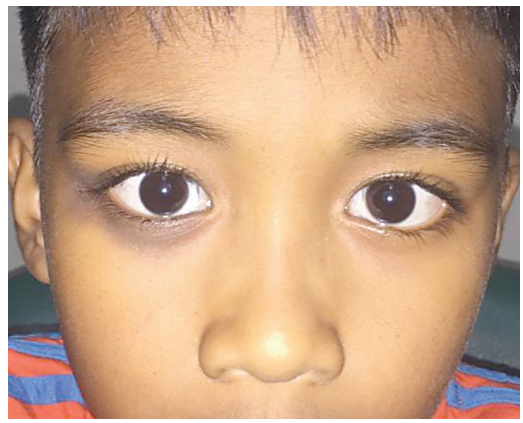


Figure 1 and 2: Right lower lid bruising which extended to the temporal upper eyelid

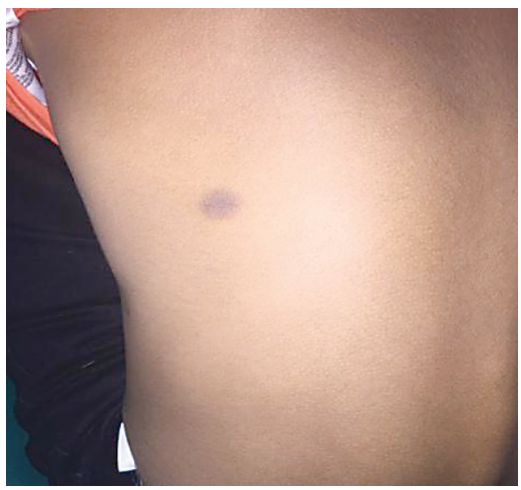


Figure 3: A coin-size bruise noted over the patient's trunk

His peripheral blood film result showed hypochromic microcytic features and his haemoglobin electrophoresis test revealed Hemoglobin E trait (Heterozygous HbE). The patient was eventually diagnosed as having Hemoglobin E trait and family members were screened for haemoglobinopathy.

Discussion

Hemoglobin E (HbE) is an abnormal hemoglobin with a single point mutation in the β chain. At position 26 there is a change in the amino acid, from glutamic acid to lysine.8,9 HbE is the second commonest abnormal hemoglobin after sickle cell hemoglobin (HbS). It is common in South East Asia, where its prevalence can reach 30-40% in some parts of Thailand, Cambodia and in Laos.[8] Hb E is also found in Sri Lanka, North Eastern India, Bangladesh, Pakistan, Nepal, Vietnam, Malaysia.

The βE mutation affects β-gene expression creating an alternate splicing site in the mRNA at codons[25-27] of the β-globin gene. Through this mechanism, there is a mild deficiency in normal β mRNA and production of small amounts of anomalous β mRNA. The reduced synthesis of the β chain may cause β-thalassemia. Also, this hemoglobin variant has a weak union between α- and β-globin, causing instability when there is a high amount of oxidant.

Hemoglobin E disease results when the offspring inherits the gene for HbE from both parents. At birth, babies homozygous for the hemoglobin E allele do not present symptoms because they still have HbF (fetal hemoglobin).[8, 9] In the first months of life, fetal hemoglobin disappears and the amount of hemoglobin E increases, so the subjects start to have a mild β-thalassemia. Subjects homozygous for the hemoglobin E allele (two abnormal alleles) have a mild hemolytic anemia and mild enlargement of the spleen.

Heterozygous AE occurs when the gene for hemoglobin E is inherited from one parent and the gene for hemoglobin A from the other. This is called hemoglobin E trait, and it is not a disease. People who have hemoglobin E trait (heterozygous) are asymptomatic and their state does not usually result in health problems. They may have a low mean corpuscular volume (MCV) and very abnormal red blood cells (target cells), but clinical relevance is mainly due to the potential for transmitting E or β-thalassemia.[8]

In our case report, the patient was initially presented with persistent painless lower lid bruising for the past one year with no history of trauma preceded the symptoms or no other bleeding tendencies. His full blood count and coagulation profile result were within normal range, while his peripheral blood film result showed hypochromic microcytic features. The haemoglobin electrophoresis test revealed Hemoglobin E trait (Heterozygous HbE).

The presence of painless hematoma is a coincidence finding in this case and the pathophysiology of hematoma is unknown. The hematoma was soft on palpation, non tender and no indurated or hard mass palpable beneath it. The patient has no other remarkable ocular findings such as conjunctival chemosis, corkscrew vessels, limitation in extraocular movement and optic nerve compression. However radio imaging was not performed in this case to see the extension of hematoma. Patient was given six monthly appointments to monitor the progression of his signs and symptoms and during his subsequent appointment, the lower lid bruising and coin-shaped discolouration at his trunk were static and similar in size.

Conclusion

There is no study reported about eyelid involvement in the ocular manifestation of haemoglobin E trait, specifically eyelid bruising. Persistent painless eyelid discolouration should raise suspicion of bleeding disorders. Screening also should be done among other family members for early detection and prompt intervention.

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