A pale Chinese boy with recurrent painful digital swelling

Introduction

Thalassaemia is the most common haemoglobinopathy in the Chinese population. However, recurrent painful digital swelling is not a typical manifestation of this well-known hereditary condition. We describe a case of co-inheritance of beta-thalassaemia and sickle cell trait in a Chinese family and a child who suffered from sickle cell/beta-thalassaemia with recurrent dactylitis. This report highlights awareness of this rare condition in the Chinese population, since acute manifestations can be life-threatening and mimic other emergency conditions. Prompt management can prevent further complications and avoid unnecessary interventions due to delay in diagnosis. A detailed family history and examination of the patient’s peripheral blood smear is crucial to reach a correct diagnosis.

Case report

A 9-year-old Chinese boy presented with pallor and recurrent painful swelling of right proximal phalanges, which he had endured from the age of 2 years. At the first episode he presented to the emergency department for right proximal thumb swelling. The swelling was suspected to be due to trauma and subsided over a few days. From the age of 4 years, he had recurrent episodes of painful digital swelling involving fingers and toes. Each episode lasted a few days, but his large joints were never affected. The painful swellings were initially attributed to allergic reactions or infection. A second opinion was also sought from a Chinese herbalist from whom he received traditional Chinese medication without improvement. Usually the pain was not severe, but in one episode he developed severe painful swelling in the fingers of the left hand after swimming, for which he attended the emergency department and was admitted to hospital. Physical examination showed that he was pale and there was a tinge of jaundice. Abdominal examination revealed a palpable liver 3 cm below right costal margin and a spleen 6 cm below left costal margin. He had painful swellings in the proximal, middle, and distal phalanges of the digits in the left hand with decreased range of movement, and was diagnosed to have dactylitis.

In view of the patient’s unusual clinical findings, a detailed family history was obtained and a peripheral blood smear was examined. The patient’s father was in Guangdong and had a history of thalassaemia trait. His mother was also “Chinese” and born in Hong Kong. His mother’s grandmother was a child of Chinese man and an aboriginal lady in Brunei. The detailed family pedigree is shown in Figure 1.

The complete blood picture showed the following: Hb 70 g/L (reference range [RR], 115-155 g/L), mean corpuscular volume 74.4 fL (RR, 78-95 fL), white cell count 11.3 x 10^9/L (RR, 4.5-13.5 x 10^9/L), and platelet count 215 x 10^9/L (RR, 40-400 x 10^9/L). The Hb pattern tested by high-performance liquid chromatography showed the presence of trace of Hb-A with increased levels of Hb-F (29.9%; reference level, <1.1%) and Hb-A2 (5.6%; RR, 2.5-3.6%) and a variant Hb electrophoretic mobility consistent with Hb-S. Beta-globin gene sequencing showed a heterozygous mutation of GAG to GTG at codon 6 of beta-globin gene which resulted in production of Hb S variant and heterozygous mutation (C to T) at nucleotide 654 in IVS II region which generated a new
donor splice site and led to formation of beta-globin RNA with an insertion of 73 nucleotides between exons 2 and 3. This resulted in interference of normal RNA splicing. He was therefore diagnosed to have sickle cell/beta-thalassaemia with recurrent dactylitis. Magnetic resonance imaging of the brain and abdomen showed extensive splenic infarcts but no evidence of cerebral infarcts (Fig 2). Pneumococcal, meningococcal, and *Haemophilus influenzae* B vaccines were given.

Genetic study confirmed that his father had thalassaemia trait and mother was demonstrated to have the sickle cell trait. His elder sister had the thalassaemia trait. On genetic screening of his maternal relatives, one uncle, one auntie and one of the latter’s daughters were also identified to have sickle cell trait (Fig 1).

Various treatment options (haematopoietic stem cell transplantation, regular top-up packed cell transfusions, and hydroxyurea therapy) were explained to the family. Treatment with hydroxyurea 500 mg on alternate days was started when the boy was 4 years old. He did not suffer further sickle cell crises. Now he is 9 years old and has no neurological deficit.

**Discussion**

Sickle cell disease was first described in 1910 in a Caribbean student who was hospitalised with back and muscle pain and the presence of crescent-shaped red blood cells. Ingram subsequently described the detailed pathophysiology of sickle cell disease which was attributed to a point mutation at 6th amino acid (substitution of glutamine by valine) in the Hb-A *β*-chain to produce Hb-S. This entity is the most common among people whose ancestors originated from former and current malarial zones (Africa, Asia, the Middle and Far East, Mediterranean islands, and South America). Because of migration and inter-race marriage, it is also encountered in persons not originating from malarial zones of the world, including northern Europe. It is also associated with a hypercoagulability state, making affected subjects prone to thromboembolic phenomena. Usually patients manifest decreased levels of natural anticoagulant proteins, as well as increased markers of thrombin generation and platelet activation. The abnormal phospholipid membrane asymmetry in the red blood cells of sickle cell anaemic patients

**FIG 1. Family pedigree**

Square denotes male and circle female
and the resulting phosphatidylserine exposure appear to play an important role in the aetiology of the hypercoagulability. Sickle cell disease is not a typical haemoglobinopathy of the Chinese, whereas thalassaemia is much more common in this part of the world. Our case illustrates the co-inheritance of these two conditions in a boy of Chinese ethnicity, due to genetic dissemination through economic migration and inter-race marriages.

Sickle cell beta-thalassaemia is similar to sickle cell disease and can cause serious health problems such as painful episodes, fatigue, thromboembolic events, and a high risk of septicaemia. The diversity of clinical presentations is due to its molecular variability, since it is the result of compound heterozygosity for sickle cell and beta-thalassaemia trait. Clinical manifestations of sickle cell crisis are easily recognised in foreign medical settings where the disease is common (especially among African Americans). However, such crises are almost ‘never’ encountered in the Chinese, so that many local colleagues are unfamiliar with the clinical presentations. For the early diagnosis of sickle cell crisis, the recognition of triggering factors (dehydration, fever, temperature change, hypoxia) can be potentially life-threatening if treatment cannot be initiated promptly. Moreover, some of the clinical features of a crisis are similar to other emergencies, such as an acute chest syndrome, abdominal crisis, or stroke. Patients can be saved from unnecessary investigations and interventions if clinicians can recognise this rare condition early. A detailed family history and complete blood picture provided important clues to make an early diagnosis of this ‘rare’ condition.

Regular top-up packed cell transfusions and haematopoietic stem cell transplantation are standard treatments for hereditary haemoglobinopathies, but are associated with significant long-term morbidity and mortality. Fine-tuning of the imbalanced globin chain synthesis by increasing levels of Hb-F and the induction of globin gene synthesis by pharmacological agents have been shown to ameliorate the severity of the disease. Hydroxyurea is an anti-neoplastic drug which inhibits DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein. It is an effective, low-toxicity agent for activating the gamma-globin gene, which has been shown to enhance Hb-F synthesis in experimental animals and in patients with sickle cell anaemia. Our patient was treated with hydroxyurea 500 mg on alternate days for 6 years, during which time no sickle cell crises have occurred.

**Conclusion**

In this era of frequent economic migration and inter-race marriages, sickle cell crisis can present in Chinese patients. The patient’s family history and complete blood picture should be thoroughly explored if there are unexplained clinical features. Early diagnosis and prompt initiation of treatment is important to prevent further complications.

**References**