A medical student with undiagnosed HbE-beta thalassemia and cholelithiasis

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SUMMARY

HbE/β- thalassaemia is the most common form of β-thalassaemia. The clinical presentation of HbE thalassaemia is heterogeneous, symptomatic individuals may vary significantly, while the onset can occur later in adulthood. This report illustrates a medical student with a long history of anaemia who finally got his diagnosis right after he was noticed to have jaundice and pallor by a physician. He also developed cholelithiasis as a complication due to his poor health-seeking behaviour, even though he is studying medicine. Therefore, early diagnosis of thalassaemia, including the genotype and proper management, is vital as this condition might be noticed and progress with the proper investigation and intervention.

INTRODUCTION

Thalassaemia, which includes α- and β- thalassaemia, is one of the Malaysia's most common genetic diseases. Almost 5% of the Malaysian population were reported to be carriers of this disease, and up to 40% were HbE carriers.[1] The clinical phenotype of HbE-thalassaemia is heterogeneous, with haemoglobin levels ranging from approximately 3 to 14 g/dL. HbE-beta0 thalassaemia can range from a β-thalassaemia intermedia phenotype to a transfusion-dependent, severe β-thalassaemia. Individuals with a less severe phenotype are also referred to as having non-transfusion-dependent β-thalassaemia (NTDT), where they typically do not require regular transfusions. These individuals are often homozygous or compound heterozygous for a β- + thalassaemia variant or heterozygous for a β- 0 thalassaemia variant.

The typical age of presentation is 2 to 4 years old or later in adolescence.[2] As insignificant thalassaemia, HbE-thalassaemia patients may also face complications such as anaemia, hepatomegaly, splenomegaly and pulmonary hypertension due to haemolysis and ineffective erythropoiesis.[3] Cholelithiasis has been described as one of the common complications of thalassaemia. Gallstone prevalence (detected by ultrasonography) in patients with β-thalassemia ranged from 17 to 57%.[8]

CASE PRESENTATION

A 22-year-old year, single male student at a local university was doing his primary care clinic attachment in Kuantan, Pahang. A resident physician accidentally noted that he looked pale and jaundiced. He admitted to experiencing intermittent symptoms of easily lethargy and palpitation for the past 3 years, which usually come on exertion. However, he has no symptoms of fever, chills, myalgia, arthralgia, diarrhoea, bleeding tendencies, headache, calf pain or shortness of breath. He also denies symptoms of no abdominal pain, dark-coloured urine, pale-coloured stool, bloating, nausea, vomiting, belching, early satiety, regurgitation or retrosternal burning. He also has no history of recent travel to the jungle or water activities, and he does not live in a dengue-endemic area.

He also noticed yellowish discolouration of the sclera and palpable abdominal mass, possibly hepatosplenomegaly, since he was in his second year of medical school. However, he had never sought further professional help. In 2022, he had a history of admission to a tertiary teaching hospital in Kuantan, Pahang, for fever and anaemia. He presented with a fever for 2 weeks, which was associated with daytime somnolence, fatigue and headache. During that time, his Hb was 3.3 g/dL, and he was transfused with two units of packed cells and later discharged with Hb of 7 g/dL. He was told that he might have thalassaemia intermedia, but the confirmed diagnosis was never known since his Hb analysis is still pending during that time. The medical department did defaulter tracing, but he was uncontactable. He attributed his busy academic schedule and negligible symptoms to his ignorance of medical care.

Upon further history taking, the fourth-year medical student affirmed that his mother told him that he had been diagnosed with 'thalassaemia trait' when he was 10 years old. He was unsure what test was performed as the report was eventually lost in a flood. According to him, his brother and mother were also found to have similar diagnoses during the check-up at that time. However, they do not portray symptoms like him. There was no history of anaemia in the family, and both his parents are non-consanguineous.

On examination, he was pale-looking and jaundiced. He was afebrile, and his other vital signs were normal. His BMI was 18 kg/m^2, with a height of 171 cm. There was no frontal bossing, conjunctival suffusion, fetor hepaticus, palmar erythema, finger clubbing or calf tenderness. The cardiorespiratory examination was unremarkable. Per abdomen revealed soft, non-tender abdomen with palpable hepatosplenomegaly. There was no ascites. Cutaneous stigmata of chronic liver disease or skin rashes were absent.

A basic laboratory workout in the clinic results showed mild hypochromic microcytic anaemia and mild hyperbilirubinemia with normal liver enzymes.

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Table I: Result for full blood count and liver function test

Parameters	Unit	Result	Reference
FBC			
RBC	10^{12}/L	4.57	4.5 to 5.50
HB	g/L	83	130 to 170
MCH	pg	18.1	27 to 32
MCV	fL	61	77 to 97
RDW	%	32	12 to 14
Liver function test			
Total bilirubin	mmol/L	98	5 to 21
Direct bilirubin	mmol/L	10.8	<3.4
Indirect bilirubin	mmol/L	87.2	3.4 to 12.0
AST	U/l	33	<50
ALT	U/l	11	<50
ALP	U/l	83	30 to 120
Random Blood Sugar	mmol/L	8.8	

Further investigation was sent to find out the cause of his current condition.

Table II: Result for iron study

Parameters	Unit	Result	Reference
Iron study			
Se iron	mmol/L	30.7	12.5 to 32.2
Se ferritin	Ug/L	198.8	23.9 to 336.2

Table III: Result for full blood picture and Hb analysis

Full blood picture	The haemoglobin level is moderately low. The absolute reticulocyte count is raised. The red cells are hypochromic microcytic. Marked anisopoikilocytosis. Presence of tear drop cells, target cells, cigar shaped cells. Nucleated RBC seen.
Hb Analysis	The HbA2 level is raised (HPLC) The HbF level is raised (both HPLC and CE). Abnormal peak HbE is observed (51.1%) No HbA Haemoglobin analysis: HbE-β thalassaemia
DNA analysis	The predicted genotype/phenotype is β0βE No pathogenic variants of HBA1 and HBA2 genes detected, significantly reduced the probability of alpha thalassaemia trait.

The iron study was normal, while Hb analysis showed HbE-β-thalassaemia (HbE/B-thalassaemia). DNA analysis and the result showed HbE- thalassaemia.

Because of the hepatosplenomegaly, hepatobiliary system ultrasonography was performed. The liver was enlarged with a craniocaudal length of 18.3 cm. The liver parenchymal echogenicity was normal, with no focal liver lesion. The gall bladder was well distended, with several small calculi seen within. The largest calculus was 0.7 cm in diameter. Otherwise, the gallbladder wall was not thickened and had no pericholecystic collection. Common duct and intrahepatic bile ducts were not dilated. The spleen was significantly enlarged, measuring 18.8 cm craniocaudally, with no focal lesion seen. Pancreas showed a normal appearance. The student was later referred to the surgical team. However, due to his asymptomatic status, he was not offered any surgical intervention.

DISCUSSION

HbE results from a β-globin mutation that reduces β-globin production. Individuals who are heterozygous for HbE are asymptomatic carriers. Individuals with homozygous HbE have mild microcytic anaemia. At the same time, HbE, in combination with β-thalassaemia, can range from mild to moderate to severe anaemia, depending on the other beta globin variant. More than half of patients with HbE plus β0 thalassaemia are transfusion-dependent.

In Southeast Asia, HbE/β-thalassaemia is the most common form of β-thalassaemia. According to the Thalassaemia Registry Malaysia, in 2019, the distribution of HbE-thalassaemia was 35.19%.[1] The HbE/β- thalassaemia forms the largest group of thalassaemia patients in Malaysia with 2878 (35.19%) patients, followed by β-thalassaemia major with 2671 (32.66%) patients, HbH disease with 1593 (19.48%) patients, β-thalassaemia intermedia with 738 (9.02%) patients. In contrast, the remaining 298 (3.64%) patients have other forms of thalassaemia.[1]

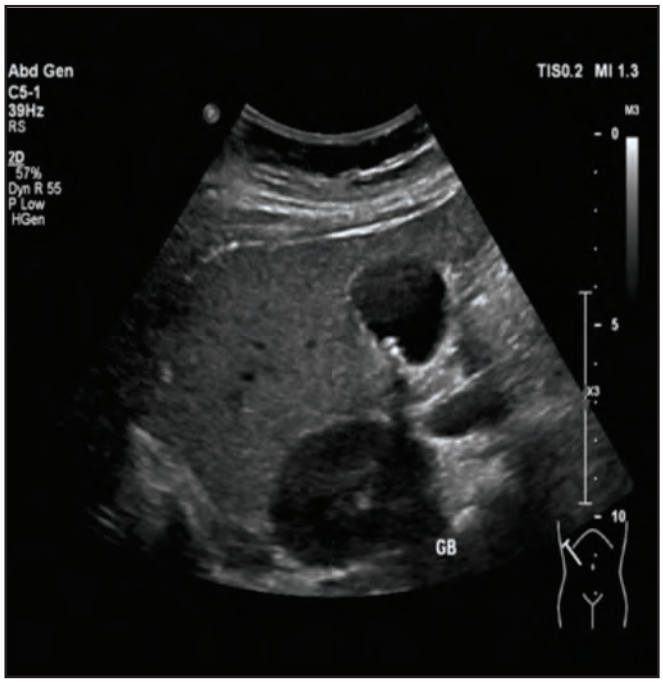

Fig. 1: Ultrasound hepatobiliary showed several small calculi within the gallbladder

Symptomatic individuals are typically homozygous or compound heterozygous for a clinically significant variant. Symptoms generally start in childhood, but in some cases, the initial presentation may occur later in adolescence or adulthood.[7] Heterozygous HbE individuals are not usually anaemic but may have minimal degrees of microcytosis and hypochromia. Homozygous (Hb E disease, Hb EE) meanwhile have minimal anaemia, prominent microcytosis, hypochromia and target cells along with jaundice. Sometimes, incidental findings of heterozygous individuals could happen when a complete blood count, haemoglobin analysis, or genetic testing is done for reasons other than clinical symptoms, such as in evaluation for another condition and reproductive testing.[5] HbE β-thalassaemia usually will be milder when the concomitant alpha thalassaemia trait exists, hence the importance of further diagnostic testing using DNA analysis.

Thalassaemia patients may face multiple complications with their disease, such as cholelithiasis due to chronic haemolysis and ineffective erythropoiesis.[5,6] Gallstone prevalence (by ultrasound) in β-thalassaemia patients was 17 to 57% in different countries, with lower incidences occurring among non-transfusion-dependent thalassaemia. Meanwhile, 23 to 57% of cases of cholelithiasis among β-thalassemia Intermedia were reported in Malaysia.[9] Significant predictors of gallstone prevalence include age and the presence of the Gilbert allele.[2] Most individuals with incidental findings of gallstones on abdominal imaging are asymptomatic. Most of them will remain asymptomatic, while those who develop symptoms typically report biliary colic. The occurrence of cholecystitis or cholangitis among thalassaemic is rare. It is also important to note that the development of pigmented gallstones among Non-Transfusion Dependent Thalassaemia (NTDT) significantly raises the risk of complex cholecystitis and iron buildup in the liver parenchyma, which can cause liver damage that may progress to fibrosis and eventually cirrhosis.[7]

Another issue that needs to be discussed is how medical students seek health care. Self-prescription is the most typical behaviour among medical students.[4] They frequently self-diagnose and self-treat themselves because they see symptoms and sickness differently. Refusal to consult doctors and self-treatment are evident when they start their careers as junior doctors.[4] This group of students is more likely to seek informal counsel from friends and family members, particularly regarding mental health care.

A variety of factors influence students' behaviour in seeking health care. Their primary source of influence over their health-seeking behaviours is their study of medicine. Ironically, their knowledge of the available health services, level of medical knowledge, or stage of study could either encourage the student to seek prompt care or overlook their health problem.[4]

CONCLUSION

HbE-β-thalassaemia can range from asymptomatic carrier status to severe clinical complications. Therefore, early diagnosis and determination of the specific type of thalassaemia are essential, as with proper tests, thalassaemia's clinical syndrome can be noticed and not misdiagnosed.[6] Primary care doctors may face challenges in diagnosing thalassaemia as the clinical symptoms are non-specific. In public primary care settings, the diagnostic test for thalassaemia must go through a strict procedure, i.e., be approved by a family medicine specialist. Hence, many suspected cases are left without testing. Hence, a good and focused history taking, and a targeted physical examination are required to justify the indication for the test.

Adequate training on this topic should also be conducted to increase primary care doctors' awareness and knowledge. For most of the population in Malaysia, the FBC screening program at secondary school and the pre-marital screening are preventive programs aimed at identifying those at risk of thalassemia. Cascade screening among family members of thalassaemic is a standard practice. For this case, even though some of his family had done the test in the past, accurate information and documentation are critical as this will prevent unnecessary repeat testing in the future.

Thalassaemia patients may develop jaundice due to ineffective erythropoiesis. However, jaundice in adults is generally caused by a wide range of diseases, including biliary system infections, pancreatitis, and cancers. Therefore, primary care doctors must include thalassaemia in the list of differentials for jaundice.

As safety netting, it is imperative to inform thalassaemic individuals regarding the signs and symptoms of anaemia and complications such as cholelithiasis, as early detection may lead to the initiation of medical care and prevent potential severe complications. Patient-centred and comprehensive health education should be given during the initial consultation to avoid late-seeking behaviour.

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CONFLICT OF INTEREST

None to declare.

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