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A rare case of Hb H disease caused by compound heterozygous for α thalassemia and Hb Quong Sze in Chinese Indonesian proband: A case report



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ABSTRACT

Background: Hemoglobin H (HbH) disease is alpha thalassemia characterized by inactivation of three of four α -globin genes due to deletions with or without non-deletional α -thalassemia. Hb Quong Sze (Hb QS) is a very rare non-deletional α -thalassemia in Indonesia caused by a C_{TG}⁴⁹³>C_{CG}⁷⁶⁰ nucleotide substitution at codon 125 of α_2 globin gene generating highly unstable hemoglobin. Compound heterozygosity for Hb QS and Southeast Asian double α -globin gene deletion (α -SEA) result in accumulation of b-globin tetramers, causing hemolytic anemia.

Case Report: A 49 years old Chinese Indonesian female was assessed for thalassemia screening. The phenotype of the proband was normal and only mild anemia was noticeable. She experienced blood transfusion five years ago due to a sudden fall of hemoglobin level after

malarial infection. Complete blood count found hemoglobin 8.3 g/dL, Mean Corpuscular Volume (MCV) 65.7 fl and Mean Corpuscular Hemoglobin (MCH) 17.1 pg. HbH disease suggested by abundant Hb H inclusion bodies in the red blood cells. Microcapillary hemoglobin electrophoresis result showed HbH 31.8 %, Hb Bart 0.4%, HbA 67.3% and HbA₂ 0.5%. Molecular studies were carried out using multiplex polymerase chain reaction (PCR) method, and the common α^0 -thalassemia (α -SEA) was detected in one allele. Direct sequencing analysis of the α_1 and α_2 globin genes revealed Hb QS in the other allele. **Conclusion:** Non-deletional Hb H disease due to compound heterozygous of Hb QS with Southeast Asian double α -globin gene deletion (α -SEA) has a very low incidence in Indonesia. An advanced molecular analysis should be performed to determine this rare mutation.

Keywords: Hb Quong Sze, HbH disease, α -thalassemia, α -globin gene, mutation

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INTRODUCTION

Thalassemia is one of the most common genetic disorders in the world. Thalassemia is caused by a decrease or absence of globin chain synthesis forming hemoglobin.^{1,2} Based on the type of globin chain whose synthesis is disrupted, thalassemia divided into thalassemia a, b, g, d, db and gdb.^{2,3} Alpha thalassemia is caused by deletion mutations or non-deletional mutations from α globin genes. Deletion mutation is the most common type of mutation found in alpha thalassemia. Deletion of alpha globin gene will result in a decrease or absence of synthesis of alpha globin chains. Deletion in alpha thalassemia can occur in one or both alpha globin genes (HbA₁ and HbA₂) located in the telomeric region of chromosome 16 (16p13.3). The deletion can affect one alpha globin gene, both alpha globin genes in tandem or the entire alpha globin cluster of genes.^{3,4,5}

Non-deletional defects that inactivate one of the two globin alpha genes are sporadic. Most mutations involve the α_2 gene which has a higher expression level than the α_1 gene with a ratio of 3:1.⁶ The type of non-deletional mutation generally causes a variant of the alpha globin chain without clinical

significance, but if the non-deletional mutation lies in an important amino acid residue, there will be a decrease in the production of alpha globin chains that are heavier than the type of deletion mutation cause very unstable hemoglobin and causes clinical symptoms of hemolytic anemia.^{2,4,5} Most unstable hemoglobin variants are identified when the variant interacts with other types of alpha thalassemia, with manifestations of Hemoglobin H (HbH) disease – a clinical condition that similar to beta thalassemia intermedia.⁷⁻⁹ The condition of a person experiencing two different variants of mutations in the globin alpha gene cluster or two different mutation variants in the globin beta gene cluster is referred to as compound heterozygosity.^{1,2,6}

In Southeast Asia and South China, the majority of HbH disease cases are caused by gene deletion and approximately 20 - 40% of cases are caused by compound heterozygosity of deletional mutation of alpha thalassemia with a non-deletional mutation which results in a more severe phenotype.⁶

Hb Quong Sze (Hb QS) is a non-deletional alpha thalassemia (hemoglobin variant) due to a missense

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 mutation in codon 125 of the α_2 globin chain (CTG *CCG or Leu * Pro) which leads to the formation of very unstable hemoglobin and cannot be detected using hemoglobin electrophoresis examination. Hb Quong Sze is commonly found in GuangXi province, China and very rarely found in Southeast Asia. The incidence of Hb Quong Sze is less than 1% of the ethnic Chinese population in Malaysia. The prevalence of Hb Quong Sze in Indonesia has not been reported. Interaction of Hb Quong Sze with Southeast Asia (SEA) double α globin gene deletion results in the non-deletional type of HbH disease.^{6,10,11,12}

In this case report, it describes HbH disease presenting as thalassemia intermedia phenotype caused by compound heterozygosity of deletion mutation (Southeast Asia double α globin gene deletion) and non-deletional mutation (Hb Quong Sze) of α globin gene.

Case Description

A 49-year-old Chinese ethnic woman presented to the private clinical laboratory for thalassemia screening. The patient had no clinical symptoms and undertook voluntary thalassemia screening due to low hemoglobin level result from a previously routine medical checkup. The patient had received blood transfusion five years ago while suffering from malaria. As from the physical examination, a pale conjunctiva palpebra was found, without splenomegaly. There was no family history of thalassemia. Low hemoglobin level (8,3 g/dL) and microcytosis (MCV < 80 fl dan MCH < 27 pg) were defined (Figure 1).

Peripheral blood morphology shows anisopoikilocytosis, polychromasia, and presence of microcytes, tear drop cells, pear shape cells, target cells, and macrocytes leading to suspicion of the hemolytic process (Figure 2).

Microscopic examination of the blood smear showed numerous HbH inclusion bodies (Figure 3). Hb analysis using microcapillary hemoglobin method found increased in HbH and Hb Bart level (31.8% and 0.4% respectively) (Figure 4).

DNA analysis using multiplex PCR method confirmed of heterozygous mutations (deletion) in 2 alpha globin/SEA (--SEA/ $\alpha\alpha$) α globin genes. Heterozygous deletion of 2 globin alpha genes are carriers of alpha thalassemia which usually do not present as severe anemia, and usually, HbH is not detected in Hb analysis. The genetic finding has a discrepancy with the clinical and Hb electrophoresis finding who were found to be anemic, and it has high HbH level (31.8%). Therefore, further DNA analysis was needed to determine other types of mutations (non-deletional mutations)

WBC	6.27	[10 ³ /uL]
RBC	4.84 *	[10 ⁶ /uL]
HGB	8.3	[g/dL]
HCT	31.3 *	[%]
MCV	64.7 *	[fL]
MCH	17.1 *	[pg]
MCHC	26.5 *	[g/dL]
PLT	339 *	[10 ³ /uL]
RDW-SD	56.9 *	[fL]
RDW-CV	26.1 *	[%]
PDW	----	[fL]
MPV	----	[fL]
P-LCR	----	[%]
PCT	----	[%]

Figure 1 Complete blood count (CBC) panel

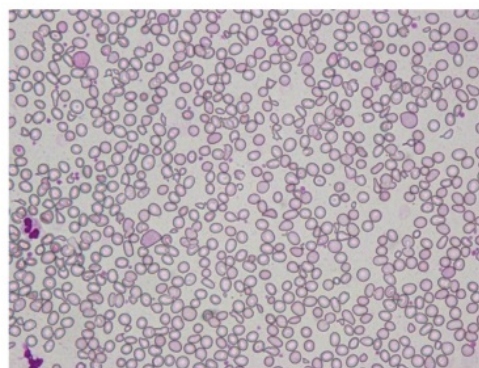


Figure 2 Photomicrograph of peripheral blood film shows anisopoikilocytosis, polychromasia, and presence of microcytes, tear drop cells, pear shape cells, target cells, and macrocytes. (Giemsa stain, 400x)

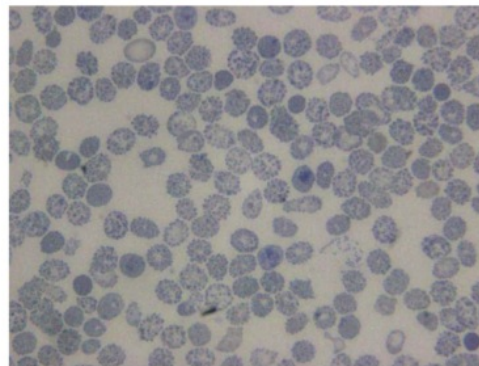


Figure 3 Photomicrograph of peripheral blood film shows numerous erythrocytes containing HbH inclusions (incubated Brilliant Cresyl Blue stain, 1000x)

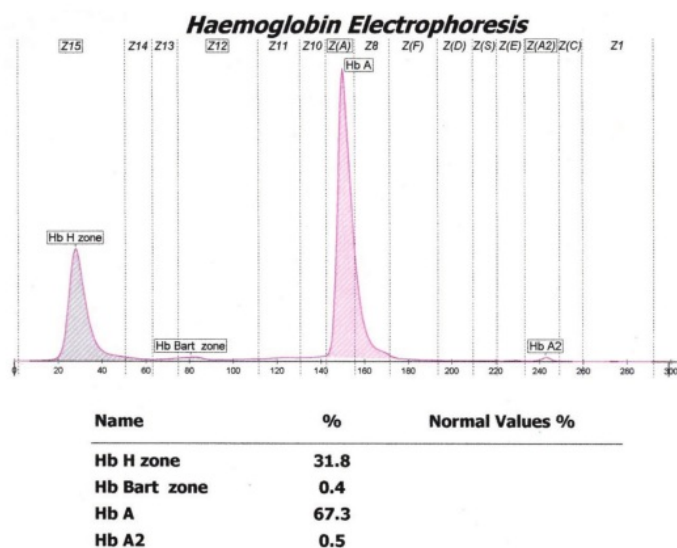


Figure 4 Hemoglobin electrophoresis report of the patient shows increased in HbH and Hb Bart level

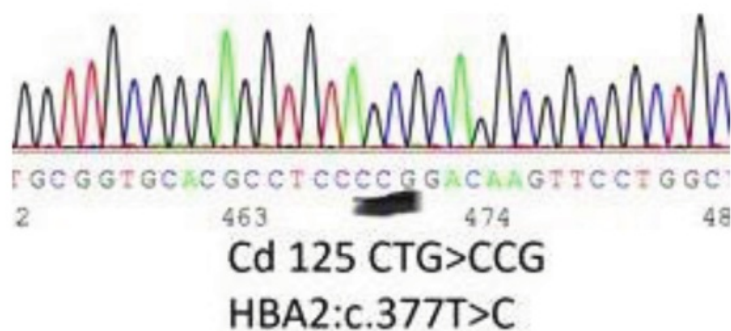


Figure 5 DNA sequencing (electropherogram) shows mutation on c.377T>C in the α globin gene. DNA examination using sequencing techniques on the α globin gene reveal a non-deletional mutation in α_2 globin gene (HbA2; c.377T>C), i.e. Hb Quong Sze (Figure 5).

DISCUSSION

The main defect in alpha thalassemia is the reduction of alpha globin chain output, causing an imbalance synthesis of globin tetramer and increase unpaired beta globin chains. Unpaired beta globin chains deposit in the precursor of red blood cells in the bone marrow and peripheral blood, disrupting the maturation of the erythroid precursor, ineffective erythropoiesis and shortened red blood cell survival.^{2,4}

Hb Quong Sze is a very unstable Hb variant that cannot be detected in thalassemia screening using hemoglobin electrophoresis or High-Performance

Liquid Chromatography (HPLC) method. In heterozygous conditions, Hb Quong Sze is asymptomatic - without clinical symptoms - and only mild anemia with mild microcytic changes in erythrocytes noticeable. However, the Hb Quong Sze compound heterozygosity with deletions of two Southeast Asian type globin alpha genes (SEA) will result in HbH disease with manifestations of hemolytic anemia.^{6,12,13}

Anemia in Hb H disease is caused by ineffective erythropoiesis associated with shortening of the red blood cells survival due to the detrimental effect of the interaction between the excess beta globin chain and the red blood cell membrane. It combined with a physical barrier that is passed by aged red blood cells that have HbH precipitates (beta globin chain tetramers) as they pass through the microcirculation in the spleen.^{2,4,6} Generally HbH patients are asymptomatic and do not require therapy when they are in a steady state condition.

Excess unpaired beta globin chains form tetramers of beta globin chain (i.e., HbH). Higher levels of HbH were found in non-deletional HbH disease compared to deletional type ($12.1 \pm 5.5\%$ vs. $7.9 \pm 4.2\%$). HbH is hemoglobin that is relatively unstable and can be oxidized to form intracellular precipitates (HbH inclusion bodies/golf ball cells). Multiple intraerythrocytic inclusions can be detected using incubated staining of methylene blue or Brilliant Cresyl Blue. HbH inclusion bodies were more commonly found in deletional HbH disease than in deletional type ($77 \pm 10\%$ vs. $66 \pm 11\%$). Formation of HbH inclusion bodies will rapidly increase if the patient had a fever and can lead to sudden severe anemia and hemolytic crisis. Infection can also cause severe anemia and jaundice. Management of hemolytic crisis requires appropriate and immediate action using blood transfusion along with infection control and rapid normalized of body temperature to prevent the increased formation of HbH inclusion bodies.⁶

Proper diagnosis and understanding of the clinical phenotype of HbH disease are crucial, because without understanding the variation of the HbH disease phenotype leading to inappropriate assessment.

CONCLUSION

Highly unstable α -globin chains in Hb Quong Sze make this Hb variant undetectable by routine Hb electrophoresis and accurate diagnosis requires molecular techniques. Accurate detection of non-deletional HbH disease is necessary as these disorders have been associated with more severe phenotypes compared to the deletional forms. The

incidence of Hb Quong Sze in Indonesia is maybe higher than reported due to lack of awareness and the limitations of genetic laboratory facilities. Accurate diagnosis and understanding of gene interactions are vital in the management, genetic counseling, and prevention of thalassemia.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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