Case Series of Homozygous and Compound Heterozygosity of Hb Malay, the Diagnostic Features and Transfusion Requirements

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Hb Malay was first described in 1989 following an investigation of anaemia in a 22-year-old Malay gentleman who was homozygous for this β chain variant. This Hb variant is caused by AAC → AGC mutation at codon 19 of the β globin gene resulting in the substitution of serine for asparagine [1]. The mutation creates cryptic RNA splice site in exon 1 of the β-globin gene leading to an abnormal RNA processing. Thus, this mutation not only produces variant haemoglobin but also a mild β^+ thalassemia phenotype [2].

A retrospective analysis was carried out at the Clinical Haematology Laboratory, Hospital Ampang, Selangor, Malaysia from 2012 to 2015. A total of 12 cases of confirmed heterozygous, homozygous or compound heterozygous of Hb Malay were collected. The diagnostic workups in this centre included complete blood count (CBC), blood smear, haemoglobin analysis and molecular study. Table 1 shows the haematological characteristics of Hb Malay and its combination with other thalassaemia/ haemoglobinopathies. Table 2 shows the clinical features and transfusion requirements of various presentation of Hb Malay.

Table 1: Haematological characteristics of Hb Malay case series

Case	Age	Sex	FBC				Hb Analysis (CE)			
			Hb (g/dL)	RBC (10^6/µl)	MCV (fL)	MCH (pg)	HbA2 (%)	HbF (%)	HbA/Hb Malay (%)	Other Hb (%)
Homozygous Hb Malay										
Case 1	31	F	7.3	3.62	68.2	20.2	3.6	47.4	49	-
Case 2	41	M	7.9	3.60	73.1	21.9	5.0	30.0	65.0	-
Heterozygous Hb Malay										
Case 3	31	F	13.0	6.10	66.6	21.3	4.8	-	95.2	-
HbE/ Malay										
Case 4	29	F	11.4	5.87	57.9	19.4	5.5	3.3	38.6	HB E 52.6
Case 5	26	F	10.2	5.04	57.9	20.2	5.5	15.3	33	HB E 46.2
Hb Malay/Beta$^+$										
Case 6	28	F	7.5	3.58	67.6	20.9	2.2	76.3	21.5	-
Case 7	35	F	8.0	2.98	58.7	17.4	4.3	72.9	22.8	-
Case 8	27	F	8.5	4.27	57.9	19.9	3.8	38.5	57.7	-
Hb Malay/Beta^0										
Case 9	20	F	8.8	4.26	66.7	20.7	2.9	48.1	49.0	-
Case 10	21	M	7.9	3.93	61.8	20.1	4.3	16.2	79.5	-
HbS/ Malay										
Case 11	63	F	4.3	1.47	91.8	29.3	2.9	21.8	25.1	Hb S 50.2
HPFH/Malay										
Case 12	41	F	8.7	4.48	67.2	19.4	3.0	60.8	36.2	-

Table 2: Clinical features and transfusion requirement of homozygous, heterozygous and compound heterozygous of Hb Malay

Types (Number case)	Age of 1st transfusion	Transfusion Dependency	Clinical features
Homozygous Hb Malay (2)	Adulthood	No	Asymptomatic with moderate anaemia. May have tinge jaundice or mild pallor.
Hb Malay Trait (1)	-	No	Asymptomatic with normal Hb.
Hb E /Malay (2)	-	No	Asymptomatic with mild anemia
Hb Malay/β^+ (3)	Teenager	PRN	Moderate anemia. May require transfusion during pregnancy and hospitalisation for acute illness. Splenomegaly
Hb Malay/β° (2)	Childhood	Yes	Moderate anemia. Splenomegaly with 1 case splenectomised.
Hb S/Malay (1)	Adult	PRN	Severe anemia. Recurrent painful crisis.
Hb Malay/ HPFH (1)	Adult	PRN	Moderate anemia. Splenomegaly

The definitive diagnosis of Hb Malay can only be made by molecular analysis. Both reverse phase high performance liquid chromatography (HPLC) for haemoglobin variant and capillary zone electrophoresis (CZE) cannot differentiate between Hb A and Hb Malay as it is co-migrated. Previously, it was reported that there was an increased production of Hb F between 12-32% in cases of homozygous Hb Malay and compound heterozygous Hb E/Malay [3]. In our case, the Hb F levels in homozygous Hb Malay were 47.4% and 30%, respectively (Case 1 and 2). Patients with homozygous Hb Malay were non-transfusion dependent with average haemoglobin of 7 to 8g/dL, whereas in Hb Malay trait the haemoglobin level was normal. The Hb E/ Malay patients were also asymptomatic, although the average haemoglobin was lower (10g/dL) compared to the classical Hb E trait (12.4g/dL) [5]. Hb F level in Hb E/ Malay was reported to be above 12% [3], in one of our cases, the Hb F was only 3.3% (Case 4). Molecular analysis showed this patient was also homozygous for 158 Gγ Xmn polymorphism, as well as -α3.7 deletion. This was rather an interesting finding as this polymorphism was associated with higher level of Hb F [4]. Similarly, the presence of alpha thalassaemia was reported to reduce the Hb E percentage to less than 25%, but in this case the Hb E was 52.6% [5]. Compound heterozygous of Hb Malay/ Beta thalassaemia resulted in thalassaemia intermedia with variable phenotypes depending on the type of mutations. The other 2 combinations of Hb Malay with Hb S and HPFH also presented as thalassaemia intermedia. These findings were in keeping with the phenotype of Hb Malay resembling β^+ thalassaemia.

Keywords: Hb Malay, thalassaemia

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