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Original Article

Hemoglobin H Disease and Growth: A Comparative Study of DHbH and NDHbH Patients

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Abstract. ***Background:*** **Hemoglobin H disease *(*HbH*)*, a hemoglobinopathy resulting from abnormal alpha globin genes, is classified into two categories: deletional HbH *(*DHbH*)* and non-deletional HbH *(*NDHbH*)*. The alpha-mutation genotypes exhibit a range of clinical anemias, which differentially impact patient growth.**

Objectives: **This retrospective study assessed the growth of HbH patients at Siriraj Hospital, Mahidol University.**

Methods: **Patients diagnosed with HbH between January 2005 and April 2021 were analyzed using growth standard scores of the Thai Society for Pediatric Endocrinology (2022 version) and BMI-for-age Z scores of the World Health Organization. Growth failure was defined as a patient's height for age exceeding two standard deviations below the mean.**

Results: **Of the 145 HbH patients, 75 *(*51.7*%)* had NDHbH, with --^{SEA}/α^{CS}α being the most common genotype *(*70 patients; 93.3*%)*. The mean baseline hemoglobin level was significantly lower in NDHbH patients than in DHbH patients (8.16 ± 0.93 g/dL vs. 9.51 ± 0.68 g/dL; *P* < 0.001*)*. Splenomegaly and growth failure prevalences were higher in NDHbH patients (37.3*%* vs. 0%, with *P* < 0.001, and 22.7% vs. 8.6%, with *P* = 0.020, respectively). Multivariable analysis revealed splenomegaly > 3 cm was associated with growth failure (OR = 4.28; 95% CI, 1.19–15.39; *P* = 0.026).**

Conclusions: **NDHbH patients exhibited lower hemoglobin levels and more pronounced splenomegaly than DHbH patients. Growth failure can occur in both HbH types but appears more prevalent in NDHbH. Close monitoring of growth velocity is essential, and early treatment interventions may be required to prevent growth failure.**

Keywords: Alpha-thalassemia; Genotypes; Growth failure; Hemoglobin H disease.

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Introduction. The hemoglobin (Hb) protein is composed of two alpha globin chains (α chains) and two beta-globin chains (β chains), arranged in a tetramer of α2β2. Usually, each chromosome 16 contains two alpha

genes, composing four alpha genes per genome.[1] Natural mutations, mainly deletion of the alpha globin gene, lead to alpha thalassemia. Hemoglobin H disease (HbH), the most common form of alpha thalassemia syndrome, results from compound heterozygosity of α^0 thalassemia due to a loss of two linked alpha globin genes and either single alpha gene deletion (deletional HbH; DHbH) or a non-deletional mutation (non-deletional HbH; NDHbH) on the other alleles. Therefore, HbH can be classified into two types, i.e., DHbH and NDHbH.[2,3]

The genetic mutations of HbH vary among ethnicities. For instance, the deletional mutations ($--^{MED}$) and ($-\alpha^{20.5}$) are commonly found in the Mediterranean region, whereas ($--^{SEA}$), ($--^{FIL}$), ($--^{THAI}$), ($-\alpha^{-3.7}$), and ($-\alpha^{-4.2}$) are prevalent in Southeast Asia. The Hb Constant Spring (CS) variant (α2 codon 142 TAA>CAA) is the most common NDHbH. Other non-deletional types include Hb Quang Sze (α2 codon 125 CTG>CCG), Hb Paksé (α2 codon 142 TAA>TAT), Hb Q Thailand (α2 codon 34 GAC>CAC), Hb Saun Dok (α2 codon 109 CTG>CGG), α2 codon 59 (GGC>GAC), α2 codon 0 Δ1bp (-T), α2 codon 30 Δ3bp (-GAG), and α2 codon 35 (TCC>CCC).[4-6]

The prevalence ratio of DHbH to NDHbH is varied. Although DHbH was found to be more prevalent in several studies,[3,7,8] NDHbH was more prevalent in some studies from Thailand.[9-11] In the United States, Hong Kong, and Canada, the majority of DHbH cases have genotypes of $--^{SEA}/-\alpha^{-3.7}$ (55%), $--^{SEA}/-\alpha^{-4.2}$ (12%), and $--^{FIL}/-\alpha^{-3.7}$ (11%), while NDHbH is caused mainly by the $--^{SEA}/\alpha^{CS}\alpha$ genotype (10%).[6] In Thailand, the genotypic distribution of HbH is $--^{SEA}/-\alpha^{-3.7}$ (33.3%–57.5%) and $--^{SEA}/\alpha^{CS}\alpha$ (53%–55%).[10,12]

The severity of the disease is contingent upon the specific alpha-thalassemia type involved, with NDHbH generally presenting greater clinical severity than DHbH.[10,13] Most patients with HbH have mild anemia; a few patients may require transfusion ranging from occasional transfusion to regular transfusion.[10] Some patients who occasionally have received blood transfusion support may also develop complications, particularly during adolescence. These complications may be delayed growth and puberty and reduced final height,[14] mainly due to chronic anemia and gonadal dysfunction.[15]

In HbH patients, growth development during the first ten years of life is typically normal.[12] However, some patients, especially those with severe anemia, may experience abnormal growth during pre-adolescents. Moreover, NDHbH patients may experience growth retardation at a young age.[6]

Although abnormal growth can significantly impact patients with HbH, there is currently a scarcity of studies investigating this topic. Therefore, our study aimed to identify factors associated with growth retardation and other relevant complications in HbH patients. The information gathered from this study may help physicians improve treatment outcomes for individuals with HbH.

Materials and Methods. This retrospective study was conducted on patients aged 1 month to 18 years diagnosed with HbH at the Department of Pediatrics, Siriraj Hospital, Mahidol University, Thailand, between January 2005 and April 2021. All included neonate patients previously presented with anemia or neonatal jaundice and were subsequently diagnosed with HbH.

The data collected by this study were the frequency of hemolytic crises, the number of occasional transfusions since diagnosis, history of splenectomy, and age of growth failure. The genotypes of alpha globin mutations were also recorded. To assess patients' health status, hemoglobin level, red blood cell indices, reticulocyte count index, and serum ferritin were measured at three consecutive follow-up visits while the patients were not experiencing acute hemolytic episodes.

Serum ferritin and vitamin D levels were also assessed. Vitamin D status was evaluated according to the Thai Society for Pediatric Endocrinology's 2023 guidelines. Serum levels of 25-OHD less than 12 ng/mL, 12 to 20 ng/mL, and more than 20 to 100 ng/mL were defined as indicating vitamin D deficiency, insufficiency, and sufficiency, respectively.

Patients' weight and height were collected at each clinic visit. Height was measured in the morning by a trained nurse using a wall-mounted stadiometer. Patients' longitudinal growth record data were assessed using the growth standard score established by the Thai Society for Pediatric Endocrinology in 2022. Body mass index (BMI) was calculated as BMI = weight (kg) ÷ height^2 (meters). Growth failure was diagnosed by a decline in height-for-age greater than two standard deviations from the mean during follow-up.

Patients with periodic anemic symptoms or hemoglobin less than 8 g/dl received occasional transfusions, whereas those with chronic severe anemia received regular transfusions to maintain pre-transfusion hemoglobin more than 9 g/dl. The transfusion and chelation protocol of our institute was previously described.[16]

The Institutional Review Board authorized the study protocol (approval number 127/2565 [IRB1]).

Statistical analysis. Statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp, Armonk, NY, USA). Mann–Whitney, chi-square, Fisher's exact, and independent t-tests were used as appropriate to assess the association between patient characteristics and growth failure. Logistic regression analysis was also conducted to identify significant factors associated with growth failure. A probability (*P*) value < 0.05 was considered statistically significant.

Table 1. Baseline characteristics of HbH disease patients.

Characteristics	Total (n=145)	Non-deletional HbH (n=75)	Deletional HbH (n=70)	*P*
Age (years) (median, inter-quartile range)	8.7 (7.3)	9.1 (6.8)	8.15 (8.0)	0.333
Age of diagnosis (years) (median, inter-quartile range)	1.9 (3.0)	1.6 (2.0)	2.4 (7.0)	0.060
Sex (n,%)				0.353
Male	75 (51.7)	36 (48.0)	39 (55.7)	
Alpha globin genotype (n,%)				
Non-deletional	75 (51.7)			
$--^{SEA}/\alpha^{CS}\alpha$		70 (93.3)	-	
$--^{SEA}/\alpha^{PS}\alpha$		3 (4.0)	-	
$--^{THAI}/\alpha^{CS}\alpha$		2 (2.7)	-	
Deletional	70 (48.3)			
$--^{SEA}/-\alpha^{-3.7}$		-	67 (95.7)	
$--^{SEA}/-\alpha^{-4.2}$		-	3 (4.3)	
Type of thalassemia (n,%)				0.002
NTDT	132 (91)	63 (84.0)	69 (98.6)	
TDT	13 (9)	12 (16.0)	1 (1.4)	
Age of first blood transfusion (years) (median, inter-quartile range)		2.2 (2.2)	3 (5.3)	0.318
Total number of occasional transfusion since diagnosis (n,%)				<0.001
No transfusion	81 (55.9)	17 (22.7)	64 (91.4)	
Transfusion 1-10 times	45 (31.0)	40 (53.3)	5 (7.2)	
Transfusion >10 times	19 (13.1)	18 (24.0)	1 (1.4)	
Frequent hemolytic crisis (n,%)				0.029
<3 times/year	139 (95.9)	69 (92.0)	70 (100.0)	
≥3 times/year	6 (4.1)	6 (8.0)	0 (0.0)	
Significant splenomegaly (n,%)				<0.001
<3 cm	117 (80.7)	47 (62.7)	70 (100.0)	
≥3 cm	28 (19.3)	28 (37.3)	0 (0.0)	
Splenectomy (n,%)	13 (8.97)	13 (17.3)	0 (0.0)	<0.001

CS, Constant Spring; HbH, hemoglobin H disease; NTDT, non-transfusion dependent thalassemia; PS, Paksé; SEA, Southeast Asian; TDT, transfusion-dependent thalassemia.

Results. The study included 145 patients, 75 (51.7%) with NDHbH and 70 patients with DHbH (48.3%). Among patients with NDHbH, most genotypes were the Southeast Asian (SEA) deletion, followed by the THAI deletion. The Constant Spring (CS) variant was the most common (96%), followed by Paksé (PS; 4%).

Most NDHbH patients were compound heterozygous for the SEA type and the Constant Spring variant ($--^{SEA}/\alpha^{CS}\alpha$). In contrast, most DHbH patients were compound heterozygous for the SEA type and the 3.7-kb deletion of the α globin gene ($--^{SEA}/-\alpha^{-3.7}$).

Table 1 presents the baseline clinical characteristics of the 145 HbH patients included in this study. Of these patients, 23 (15.9%) had growth failure, with a higher prevalence in NDHbH patients (17/75 patients; 22.7%) than in DHbH patients (6/70 patients; 8.6%). DHbH patients had an earlier onset of growth failure, with a median age of onset of 1.6 (0.6–8.3) years compared to 7.4 (1–13.1) years for NDHbH patients.

Table 2 displays the laboratory findings of HbH patients. Of the 81 patients with available vitamin D data, 74 (91.3%) had low levels, comprising 50 (61.7%) with vitamin D insufficiency and 24 (29.7%) with vitamin D deficiency. There was no significant difference in the prevalence of low vitamin D between NDHbH and DHbH patients ($P = 0.242$).

Table 3 demonstrates that NDHbH patients had lower weight for age, height for age, and weight for height than DHbH patients.

Table 4 shows the correlation between clinical factors and growth failure. The genotype most strongly associated with growth failure was $--^{SEA}/\alpha^{CS}\alpha$ (69.6%), followed by $--^{SEA}/-\alpha^{-3.7}$ (26.1%) and $--^{SEA}/\alpha^{PS}\alpha$ (4.3%). Multivariable analysis revealed that only splenomegaly was significantly associated with growth failure (95% CI, 1.19–15.39; $P = 0.026$).

Table 2. Baseline laboratory findings of HbH disease patients.

Characteristics	Total (n=145)	Non-deletional HbH (n=75)	Deletional HbH (n=70)	*P*
Mean Hb level baseline (n,%)				0.004
<7 g/dl	8 (5.5)	8 (10.7)	0 (0.0)	
≥7 g/dl	137 (94.5)	67 (89.3)	70 (100.0)	
Mean Hb level baseline (g/dl) (mean ± SD)	8.81 ± 1.06	8.16 ± 0.93	9.51 ± 0.68	<0.001
Mean Hct base line (%) (mean ±SD)	30.23 ± 3.17	28.82 ± 3.12	31.74 ± 2.47	<0.001
Mean Reticulocyte count base line (%) (mean ± SD)	3.43 ± 1.98	4.73 ± 1.81	2.03 ± 0.91	<0.001
Ferritin (ng/ml) (mean ± SD)	289.84 ± 32.68	409.39 ± 51.24	150.36 ± 29.39	<0.001
Vitamin D status*	**n=81**	**n=47**	**n=34**	0.242
Normal	7 (8.6)	6 (12.8)	1 (2.9)	
Insufficiency	50 (61.7)	29 (61.7)	21 (61.8)	
Deficiency	24 (29.7)	12 (25.5)	12 (35.3)	

* Data available for 81 patients. Hb, hemoglobin; HbH, hemoglobin H disease; Hct, hematocrit; SD, standard deviation.

Table 3. A comparison of growth status of non-deletional HbH and deletional HbH patients.

Growth status	Non-deletional HbH (n=75)	Deletional HbH (n=70)	*P*
Weight for age (Z-score)			0.483
<Z-2	0 (0)	1 (1.4)	
≥Z-2	75 (100.0)	69 (98.6)	
Height for age (Z-score)			0.020
<Z-2	17 (22.7)	6 (8.6)	
≥Z-2	58 (77.3)	64 (91.4)	
BMI (Z-score)			1.000
<Z-2	4 (5.3)	3 (4.3)	
≥Z-2	71 (94.7)	67 (95.7)	

HbH, hemoglobin H disease; Z, standard score.

Table 4. Correlation of characteristics of the growth-failure and normal-height groups.

Characteristics	Alpha thalassemia			*P*	Unadjusted OR (95% CI)*	*P*	Adjusted OR (95% CI)#
	Total (n=145)	Growth failure (n=23)	Normal height for age (n=122)				
Sex (n,%)							
Female	70 (48.3)	10 (43.5)	60 (49.2)	0.616	0.80 (0.32-1.95)	-	-
Male	75 (51.7)	13 (56.5)	62 (50.8)		1.00		
Mean Hb level baseline (n,%)							
<7 g/dl	8 (5.5)	3 (13.0)	5 (4.1)	0.114	3.51 (0.78-15.86)	-	-
≥7 g/dl	137 (94.5)	20 (87.0)	117 (95.9)		1.00		
Frequent hemolytic crisis (n,%)							
≥3 times/year	6 (4.1)	3 (13.0)	3 (2.5)	0.011	8.93 (1.64-48.53)	0.363	2.31 (0.38-14.01)
<3 times/year	139 (95.9)	20 (87.0)	119 (97.5)		1.00		1.00
Significant splenomegaly (n,%)							
≥3 cm	28 (19.3)	11 (47.8)	17 (13.9)	<0.001	11.97 (3.91-36.62)	0.026	4.28 (1.19-15.39)
<3 cm	117 (80.7)	12 (52.2)	105 (86.1)		1.00		1.00
Total number of occasional transfusion since diagnosis (n,%)							
Transfusion >10 times	19 (13.1)	7 (41.2)	12 (9.4)	<0.001	6.77 (2.18-21.03)	0.730	1.28 (0.32-5.16)
Transfusion ≤10 times	126 (86.9)	10 (58.8)	116 (90.6)		1.00		1.00

CI, confidence interval; Hb, hemoglobin; OR, odds ratio.

Discussion. NDHbH was the most prevalent genotype in our study, accounting for 51.7% of cases. This finding differs from other studies, but it is in agreement with several studies conducted in tertiary care centers in Thailand. [9-11] A possible explanation for this discrepancy is that our center is a tertiary care referral center, with more severe cases, including those with NDHbH, referred to our institution. Furthermore, this finding may underscore that NDHbH has more severe anemia and may require treatment intervention.

In Thailand, the $--^{SEA}/\alpha^{CS}\alpha$ genotype variant was found to be the most prevalent among NDHbH patients, while the $--^{SEA}/-\alpha^{-3.7}$ genotype variant was the most common among DHbH patients. This finding is consistent with other studies conducted in Thailand[11,12,15] and an investigation by Chao et al.[17] in Taiwan. However, our result differs from a survey by Shamoon et al.[18] in Iraq, which identified $--^{MED}/-\alpha^{-3.7}$ as the most common genotype. These genotypic differences are likely related to ethnicity.

The clinical severity of HbH disease can vary widely. This study found that NDHbH was more severe than DHbH, consistent with other research.[10,12] Specifically, NDHbH had lower mean hemoglobin levels and higher mean reticulocyte counts at baseline than DHbH, as reported by Lal.[3] Furthermore, in our cohort, NDHbH patients had a higher frequency of hemolytic crises, a greater incidence of splenomegaly, and more transfusions than DHbH patients. Approximately 9% of HbH patients in this study underwent splenectomy, and all of them were NDHbH patients. This finding is consistent with another study of Thai patients, which reported a prevalence of splenectomy of 5%–8%.[10,12]

The role of vitamin D in bone health and mineralization is critical.[19] Adolescents commonly exhibit low levels of vitamin D.[20] This study found a high prevalence of vitamin D insufficiency and deficiency among alpha-thalassemia patients during clinical follow-up. This result is consistent with other studies showing high rates of vitamin D deficiency in thalassemia patients.[21,22] This highlights the importance of monitoring vitamin D levels in this patient population. Factors associated with decreased vitamin D levels include avoidance of sun exposure, poor nutrition,[21] inadequate physical activity, and defective hydroxylation of vitamin D due to hepatic dysfunction.[23] Health education, food fortification policies, and early detection monitoring are necessary to mitigate the risk of vitamin D deficiency and promote bone health and growth in thalassemia patients.[21]

Growth failure in thalassemia may be attributed to economic status[24] and clinical factors such as the degree of chronic hypoxia, iron overload, several micronutrient deficiencies, and parental height.[25,26] In this study, the prevalence of growth failure was 15%, consistent with other studies (13%–21%),[10,12] with the failure more pronounced among our patients with NDHbH.

Previous research has shown that HbHCS is linked to more severe anemia and growth failure that starts during infancy and early childhood, requiring transfusions in children under the age of 6.[3] The $--^{SEA}/\alpha^{CS}\alpha$ genotype has also been reported to have a significantly higher prevalence of growth failure.[20] Therefore, patients with HbHCS should be closely monitored for growth delay.

In our study, the BMI of thalassemia patients, both DHbH and NDHbH, was normal, as in another study.[20] This finding highlights that monitoring growth in these patients should rely on several parameters, not just BMI. In our cohort, splenomegaly was also associated with growth failure, and patients with NDHbH or splenomegaly should be closely monitored for growth. Early treatment interventions such as regular transfusion and splenectomy may be required to prevent growth failure.

There were some limitations to our study. First, as growth is a dynamic process, factors such as parental height, micronutrient levels, and another endocrine parameter for evaluated growth may have confounded our results. These factors could have acted as confounding variables. Another limitation of our study is that it was retrospective, which meant that some data were missing and could have introduced bias into our analyses. Finally, since our center is a tertiary care referral center, the generalizability of our findings to other centers may be limited.

Conclusions. Growth failure is common among patients with HbH, particularly NDHbH. Close monitoring and multidisciplinary care are essential to improve the quality of care for these patients.

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