Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Prevalence of Thalassemia among Newborns: A Re-visited after 20 Years of a Prevention and Control Program in Northeast Thailand

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Competing interests: The authors have declared that no competing interests exist.

Abstract. ***Background.*** **To provide accurate prevalence information of thalassemia in northeast Thailand, authors performed thalassemia screening in newborns after 20 years implementation of a prevention and control program.**
Methods. **Study was done on 350 cord blood specimens collected consecutively at Maternal and Child Hospital, Regional Health Promotion Center 7, Khon Kaen, Thailand. All kinds of α- and β-thalassemias were identified using combined hemoglobin (Hb) and DNA analyses.**
Results. **Among 350 newborns examined, subjects with thalassemia genes were identified in 184 (52.6%) cases with as many as 22 different genotypes. The most prevalent one was Hb E (39.1%). The incidence of 3.1% α^0-thalassemia, 25.9% α^+-thalassemia, 5.4% Hb Constant Spring and 1.4% of Hb Paksé were encountered. Heterozygous β-thalassemia was found in 2 cases (0.6%). Hb capillary electrophoresis could demonstrate Hb E in all cases with Hb E and detected different levels of Hb Bart's for different α-thalassemia genotypes but not in all cases with α-thalassemia. No newborn with severe thalassemia diseases was encountered.**
Conclusion. **This study reveals that α-thalassemia, β-thalassemia, and Hb E carriers as well as complex thalassemia syndromes are still prevalence and indicates a need for continuing a prevention and control program in the region.**

Keywords: Thalassemia, Newborn screening, Prevention, Control program.

Citation: Chaibunruang A., Sornkayasit K., Chewasateanchai M., Sanugul P., Fucharoen G., Fucharoen S. Prevalence of thalassemia among newborns: a re-visited after 20 years of a prevention and control program in northeast Thailand. Mediterr J Hematol Infect Dis 2018, 10(1): e2018054, DOI: http://dx.doi.org/10.4084/MJHID.2018.054

Published: September 1, 2018 **Received: April 27, 2018** **Accepted: July 28, 2018**

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Introduction. Thalassemia and hemoglobinopathies are very heterogeneous and are major public health problems in Southeast Asian countries. In Thailand, the prevalence based statistically on phenotype has been estimated at 2.5-10% for α^0-thalassemia ($--^{SEA}$ and $--^{THAI}$), 1-8 % for hemoglobin (Hb) Constant Spring and Hb Paksé and 15-20% for α^+-thalassemia ($-\alpha^{3.7}$ and $-\alpha^{4.2}$) and 3-9% for β-thalassemia. Hb E can be found between 30-50% especially in the northeastern part of the country.[1,2] It is estimated that around 1% of the Thai population has thalassemia disease and each year there are more than 12,000 new births with thalassemia

syndromes. With the high prevalence and diverse heterogeneity of thalassemia and hemoglobinopathies, around 60 thalassemia syndromes are encountered in Thailand.[3] Accordingly, the national prevention and control program has been established throughout the country under the support of the National Health Security Office (NHSO). Under this program, all pregnant women and their husbands can have thalassemia screening and diagnostics at the government hospitals for free. However, with the reasons on clinical severity and budget for treatment of each thalassemia syndrome and limited laboratory facilities and economic resources, the program has been focused mainly on the three severe thalassemia diseases including homozygous α^0-thalassemia (Hb Bart's hydrops fetalis), homozygous β-thalassemia and Hb E-β-thalassemia.[4] The main objective of the program is to prevent births of new cases with these three severe thalassemia diseases. Carrier screening, genetic counseling, and prenatal diagnosis are offered to couples at risk of having fetuses with these three severe thalassemia syndromes.[5,6] At our center in northeast Thailand, this prevention and control program has been implemented since 1993. A retrospective analysis to evaluate the overall performance of the prevention and control service at the center during 1993-2008 has demonstrated a satisfactory prevention outcome.[7] To provide accurate data on the current prevalence of thalassemia after 20 years of a prevention and control program, we have now looked prospectively on 350 newborns and determined thalassemia genotypes using complete Hb and molecular investigations.

Materials and Methods. *Subjects.* The study protocol was approved by our institutional review board (IRB) of Khon Kaen University, Khon Kaen, Thailand (HE 542253). Informed consent was obtained from the parents. Based on the prevalence of thalassemia found in the region,[8] the sample size was estimated at 334.[9.] Therefore, cord blood specimens (n=350) anti-coagulated with EDTA were consecutively collected from babies delivered at the Maternal and Child Hospital, Regional Health Promotion Center 7, Khon Kaen province, Northeast Thailand during January to May 2012. Before collection, the umbilical cord was wiped with gauze to reduce maternal blood contamination. Preterm newborns and newborns with other abnormalities were excluded.

Hb analysis and DNA analysis. Hb fractions and quantifications were performed using automated capillary electrophoresis (CE) (Capillarys 2 Flex Piercing: Sebia, Lisses, France), applying the manufacturer protocol.[10] Genomic DNA was prepared from leukocytes using the standard method. Identification of the α^0-thalassemia ($--^{SEA}$ and $--^{THAI}$) and α^+-thalassemia (3.7 and 4.2 kb deletions) were routinely performed in our laboratory using gap-PCR. Hb Constant Spring and Hb Paksé were identified using multiplex allele-specific PCR.[2,7,11,12,13] Screening for α-globin gene triplication ($\alpha\alpha\alpha^{anti3.7}$) was done using a PCR method as previously described.[14] Common β-thalassemia genes found in Thailand were examined using allele-specific PCR assays.[15]

Results. Among the 350 babies examined, no thalassemia was detected in 166 cases (47.4%). Based on Hb and DNA analyses, the remaining 184 cases (52.6%) were found to carry thalassemia genes with as many as 22 thalassemia genotypes including those with double or triple heterozygosities as shown in **Table 1**. However, no case with severe thalassemia diseases targeted in a prevention and control program including homozygous α^0-thalassemia, homozygous β-thalassemia, and Hb E-β-thalassemia was encountered. As expected, the three most common prevalent thalassemias were heterozygous Hb E which was found in 60 cases (17.1%) followed by heterozygous α^+-thalassemia ($-\alpha^{3.7}$) (11.4%) and double heterozygous α^+-thalassemia ($-\alpha^{3.7}$) with Hb E (5.7%). Two cases of heterozygous β^0-thalassemia (codon 17; A-T) were identified. Other genotypes were observed at lower frequencies. The corresponding number of allele detected, gene frequency and incidence of each thalassemic gene is shown in comparison with those described in other areas of Thailand in **Table 2**.[16-18] As shown the table, the overall incidences of 35.8% for all forms of α-thalassemia, 39.1 % Hb E and 0.6% β-thalassemia were encountered in newborns in this study.

Twelve Hb patterns and corresponding genotypes of the newborns are shown in **Table 3**. A normal Hb FA pattern was identified in 183 cases including 145 normal babies, 33 α^+-thalassemia carriers ($-\alpha/\alpha\alpha$), four carriers of non-

Table 1. Thalassemia genotypes found in 350 newborns.

Thalassemia genotypes	Number	%
Non-thalassemia	166	47.4
Heterozygous Hb E	60	17.1
Heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$)	40	11.4
Double heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) with Hb E	20	5.7
Heterozygous Hb Constant Spring	12	3.4
Homozygous Hb E	10	2.9
Heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) with homozygous Hb E	8	2.3
Double heterozygous α^{0}-thalassemia ($--^{SEA}$) with Hb E	5	1.4
Homozygous α^{+}-thalassemia ($-\alpha^{3.7}$)	4	1.1
Heterozygous α^{0}-thalassemia ($--^{SEA}$)	4	1.1
Double heterozygous Hb Paksé with Hb E	3	0.9
Compound heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) and Hb Constant Spring with Hb E	3	0.9
Heterozygous β^{0}-thalassemia	2	0.6
Double heterozygous Hb Constant Spring with Hb E	2	0.6
Heterozygous Hb Paksé	2	0.6
Compound heterozygous α^{0}-thalassemia ($--^{SEA}$) and α^{+}-thalassemia ($-\alpha^{3.7}$) or Hb H disease	2	0.6
Heterozygous α-thalassemia 2 ($-\alpha^{4.2}$)	1	0.3
Double heterozygous α^{+}-thalassemia ($-\alpha^{4.2}$) with Hb E	1	0.3
Homozygous α^{+}-thalassemia ($-\alpha^{3.7}$) with heterozygous Hb E	1	0.3
Double homozygous α^{+}-thalassemia ($-\alpha^{3.7}$) with Hb E	1	0.3
Compound heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) and α^{+}-thalassemia ($-\alpha^{4.2}$) with Hb E	1	0.3
Compound heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) and Hb Constant Spring	1	0.3
Compound heterozygous α^{+}-thalassemia ($-\alpha^{3.7}$) and Hb Constant Spring with homozygous Hb E	1	0.3
Total	350	100

Table 2. Number of allele, gene frequency and incidence of each thalassemia gene observed among 350 newborns.

Thalassemia genes	Number of allele	Gene frequency	95% CI	Incidence of thalassemia			
				This study	Lower Northern Thailand (16)	Northern Thailand (17)	Central Thailand (18)
^{SEA} deletion	11	0.0157	0.008-0.028	3.1	5.2	6.7	4.6
$^{3.7}$ deletion	88	0.1257	0.102-0.152	25.1	19.4*	18.6	17.2*
$-\alpha^{4.2}$ deletion	3	0.0043	0.001-0.012	0.8		0.8	
Hb Constant Spring	19	0.0271	0.016-0.042	5.4	5.2	4.4	5.6
Hb Paksé	5	0.0071	0.002-0.017	1.4	0.5	0	0.5
Hb E	137	0.1957	0.167-0.227	39.1	22.9	11.5	22.7
β-thalassemia	2	0.0028	0.0003-0.0102	0.6	0.5	0.8	0.7

*****Combined α^{+}-thalassemia ($-\alpha^{3.7}$ and $-\alpha^{4.2}$)

deletion α^{+}-thalassemia ($\alpha^{T}\alpha/\alpha\alpha$) and a baby with β-thalassemia heterozygote ($\alpha\alpha/\alpha\alpha$, β^{17}/β^{A}). Hb Bart's was detected in most of the babies with α-thalassemia, i.e., 46 of 48 cases, and in 2 cases of homozygous Hb E. The results showed that the amount of Hb Bart's was increased with the increasing numbers of the defective α-globin genes. Newborns with single α-globin gene defect [(α^{+}-thalassemia; $-\alpha^{3.7}$ or $-\alpha^{4.2}$) or Hb Constant Spring and Hb Paksé] have Hb Bart's at 0.4 ± 0.1% and 0.7 ± 0.1%, respectively. The Hb Bart's levels found in individuals with two α-globin gene defects were 2.6 ± 1.2%, 1.6 ± 0.7% and 6.2 ± 2.1% for heterozygous α^{0}-thalassemia ($--/\alpha\alpha$), homozygotes α^{+}-thalassemia ($-\alpha/-\alpha$) and compound heterozygous α^{+}-thalassemia/Hb Constant Spring ($-\alpha/\alpha^{T}\alpha$), respectively. Newborns with Hb H disease ($--/-\alpha$) (n=2) had Hb Bart's at 21.9% and 18.6%, respectively. These results indicated that while Hb Bart's detected by CE

Table 3. Hemoglobin types and fractions found among 350 newborns in corresponding to genotypes. Values are presented as mean ± SD or as raw data where appropriate.

Hb types (n°)	Genotype (n°)	Hb fraction (%)				
		Hb A_2	Hb E	Hb F	Hb A	Hb Bart's
FA (183)	αα/αα (145)	-	-	84.2 ± 4.5	15.8 ± 4.5	-
	-α/αα (33)	-	-	81.5 ± 5.2	18.8 ± 5.2	-
	α^Tα/αα (4)	-	-	82.9 ± 4.8	17.2 ± 4.8	-
	αα/αα, $\beta^{17}\beta^A$ (1)	-	-	92.9	7.1	-
FABart's (18)	-α/αα (4)	-	-	82.0 ± 1.3	17.6 ± 1.3	0.4 ± 0.1
	α^Tα/αα (6)	-	-	87.6 ± 1.5	11.8 ± 1.6	0.7 ± 0.2
	-α/-α (4)	-	-	79.3 ± 7.2	19.8 ± 7.1	0.9 ± 0.3
	-α/α^Tα (1)	-	-	84.5	9.7	5.8
	--/αα (2)	-	-	83.7, 89.5	14.3, 9.6	2, 0.9
	--/-α (1)	-	-	47.1	30	21.9
FABart'sH (1) *	--/-α (1)	-	-	59.9	21.5	18.6
CSFABart's (1)**	α^Tα/αα (1)	-	-	94.8	4.4	0.6
A_2FA (25)	αα/αα (21)	0.2 ± 0.2	-	75.4 ± 6.9	24.3 ± 6.8	-
	-α/αα (3)	0.4 ± 0.1	-	70.2 ± 8.0	29.4 ± 7.9	-
	αα/αα, $\beta^{17}\beta^A$ (1)	0.2	-	86.8	13	-
A_2FABart's (4)	-α/αα (1)	0.1	-	78.4	21.2	0.3
	α^Tα/αα (1)	0.1	-	80.8	18.4	0.7
	--/αα (2)	0.3, 0.2	-	62.7, 67.7	34.2, 27.9	2.8, 4.1
CSA_2FABart's (2) **	α^Tα/αα (2)	0.3, 0.1	-	71.6, 78.1	27.4, 20.8	0.5, 0.8
EF (14)	αα/αα, $\beta^E\beta^E$ (8)	-	6.5 ± 2.8	93.4 ± 2.9	-	-
	-α/αα, $\beta^E\beta^E$ (6)	0.7 ± 0.7	12.7 ± 8.7	87.0 ± 9.3	-	-
EFBart's (6)	αα/αα, $\beta^E\beta^E$ (2)	0.1, -	8.7, 5.5	91.2, 94.5	-	0.3, 0.4
	-α/αα, $\beta^E\beta^E$ (2)	-	3.7, 3.2	95.9, 96.5	-	0.4, 0.3
	-α/-α, $\beta^E\beta^E$ (1)	-	6.8	90.8	-	2.4
	-α/α^Tα, $\beta^E\beta^E$ (1)	0.4	12.2	83.7	-	3.7
EFA (80)	αα/αα, $\beta^E\beta^A$ (60)	0.4 ± 0.1	3.5 ± 1.3	88.3 ± 4.8	8.2 ± 3.5	-
	-α/αα, $\beta^E\beta^A$ (19)	0.2 ± 0.1	3.5 ± 1.0	86.9 ± 4.5	9.6 ± 3.5	-
	α^Tα/αα, $\beta^E\beta^A$ (1)	-	4.7	82.1	13.2	-
EFABart's (14)	-α/αα, $\beta^E\beta^A$ (2)	0.2, -	3.7, 2.2	81.3, 92.0	14.3, 5.8	0.5, 0.2
	α^Tα/αα, $\beta^E\beta^A$ (4)	-	3.3 ± 0.8	87.5 ± 2.7	8.6 ± 2.1	0.6 ± 0.2
	-α/-α, $\beta^E\beta^A$ (2)	0.4, -	5.2, 5.6	75.8, 87.7	16.8, 8.7	1.8, 1.3
	-α/α^Tα, $\beta^E\beta^A$ (1)	-	1.6	87.1	5.7	5.6
	--/αα, $\beta^E\beta^A$ (5)	-	3.3 ± 0.7	81.5 ± 4.0	12.2 ± 3.6	3.0 ± 1.5
CSEFABart's (2) ***	-α/α^Tα, $\beta^E\beta^A$ (2)	-	2.4, 1.2	84.4, 85.7	8.6, 3.5	4.2, 9.2

α^Tα: α^{CS}α or α^{PS}α. *Level of Hb H fraction = 0.8%. Level of Hb CS fraction: ** = 0.2% in all three cases, *** = 0.4% in both cases.

could be a good marker for α-thalassemia in newborns, it is not sensitive enough since some cases of α^+-thalassemia carriers had no detectable Hb Bart's. In contrast, CE is very sensitive in identifying cases with Hb E in newborns. It could demonstrate Hb E peak in all 116 cases of Hb E carriers, and variable levels of Hb E could be measured in all newborns with β^E-mutation.

Discussion. In Thailand, the national thalassemia prevention and control program has been launched formally since 1993.[3] Two strategies are providing proper treatment of the existing cases and prevention of new births with three severe thalassemia diseases including homozygous α^0-thalassemia (the Hb Bart's hydrops fetalis syndrome), homozygous β-thalassemia and Hb E – β – thalassemia. Step-by-step screening strategy composing of initial screening using combined red blood cell indices, osmotic fragility (OF) test and

dichlorophenolindophenol (DCIP) test followed by Hb analysis and DNA testing are applied.[5,6] The program has been progressed and is active all over the country including northeast Thailand where our laboratory at Khon Kaen University has been recognized as one of the reference centers. We have demonstrated retrospectively on prenatal diagnosis of 756 couples that the overall proportions of affected fetuses, thalassemia carriers and unaffected fetuses were respectively 26.9%, 50.0% and 23.1% which were corresponding quite well with the expected values for a recessive genetic disorder.[7] This indicates that most of the targeted thalassemia diseases in the at-risk couples could be successfully prevented, leading to a substantial reduction in future cost of treatment of the diseases.

Another approach to monitoring the performance of a prevention and control program is to look prospectively at newborns. In this study, we have addressed this in northeast Thailand after 20 years of a prevention and control program. Examination for all thalassemic genes found in Thailand was carried out on 350 cord blood specimens collected consecutively and prospectively at delivery. As shown in **Table 1**, we have noted as many as 22 thalassemia genotypes among 184 of 350 (52.6%) newborns. Moreover, no case with the three severe thalassemia diseases targeted in a prevention and control program was encountered. As shown in **Table 2**, high incidence for all forms of α-thalassemia (35.8%) and Hb E (39.1%) are detected. In contrast, the frequency of β-thalassemia is relatively much lower (0.6 %). This pattern of thalassemia and hemoglobinopathies found in newborns is very similar to those documented in adult population observed in a micro-mapping survey in the region[8] as well as in other areas of Thailand as shown in **Table 2**. Here is indicated effective prevention of new case with severe thalassemia but the corresponding thalassemic genes are still prevalent in the region. In fact, this is not unexpected since by theory allele frequency in the population remains constant from generation to generation.

Taking the data on Hb analysis into diagnostic consideration for the three important thalassemia carriers, we found that Hb Bart's detected by capillary electrophoresis is a very good marker for reporting α-thalassemia in newborns. Different levels of Hb Bart's were detected for different α-thalassemia genotypes and the higher level, the more α-globin gene defect (**Table 3**). However, as also observed in other studies, Hb Bart's may be undetectable in some cases of α-thalassemia especially those with one α-globin gene defect (-α/αα or α^{T}α/αα).[19,20] In contrast, we found that all cases with Hb E, either in heterozygote or homozygote had detectable levels of Hb E on the capillary electrophoresis system. This simple examination should permit making initial recognition of the cases before definite diagnosis by DNA analysis. A problem remains for β-thalassemia. In two cases of β^{0}-thalassemia carriers encountered (αα/αα, β^{17}/β^{A}), we observed the same Hb FA pattern with that of the normal newborns i.e. Hb F (92.9 & 86.8 % *v.s.* 84.2 $\pm$ 4.5 %) and Hb A (7.1 & 13.0 % *v.s.* 15.8 $\pm$ 4.5 %). This confirms that diagnosis of β-thalassemia is relatively difficult in newborns unless DNA analysis is performed.[16,17,20,21]

Nonetheless, our study demonstrates the current prevalence of thalassemia and hemoglobinopathies among newborns in northeast Thailand after a prevention and control program of thalassemia has been launched for more than 20 years. Since the three important thalassemia carriers including α^{0}-thalassemia, β-thalassemia, and Hb E are still prevalence in the population, an effective prevention and control program of thalassemia should be continuously operated in the region.

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