The (--SEA) α-thalassemia (SEA) deletion ameliorates the clinical phenotype of β⁰/β⁺ but not necessarily that of β⁰/β⁰ thalassemia

Among 108 Chinese patients who showed two β-thalassemia alleles on genotyping, five out of six β⁰/β⁰-thalassemia patients who co-inherited the SEA deletion showed β-thalassemia major phenotype, whereas all five patients with β⁰/β⁺-thalassemia and concurrent SEA deletion showed β-thalassemia intermedia phenotype. The SEA deletion therefore ameliorates the clinical phenotype of β⁰/β⁺ but not necessarily that of β⁰/β⁰ thalassemia.

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While it is well known from early family studies that co-inheritance of α-thalassemia determinants significantly ameliorates the phenotype of severe β-thalassemia, the molecular heterogeneity of α- and β-thalassemia alleles results in a wide range of clinical outcomes. Co-inheritance of two α-globin gene deletions (usually in the form of -α/-α) or a non-deletional α2-globin gene mutation in β⁰-thalassemia homozygotes is more likely to produce the clinical phenotype of thalassemia intermedia, whereas the co-inheritance of a single α-globin gene deletion in the same group of patients is usually associated with thalassemia major phenotype.[1-4] In homozygosity or compound heterozygosity for β⁺-thalassemia, co-inheritance of a single α-globin gene deletion is sufficient to produce an amelioration effect.[5,6] It should be noted that analysis of specific interactions is hampered by small patient numbers in each category, so that α-thalassemia as a modulating factor is not evident in every study.[7] Different populations, moreover, may show variations. For example, it has recently been described in Thai patients that co-inheritance of α-thalassemia alleviates the disease severity of severe beta-thalassemia only in the presence of at least one β⁺-thalassemia allele.[8] We analyze the interaction between α-thalassemia and two β-thalassemia alleles in Chinese patients with severe β-thalassemia.

The clinical features of thalassemia patients followed up at the Departments of Medicine and Pediatrics from two regional hospitals in Hong Kong were reviewed, and results were correlated with genotypic data. Determination of β-thalassemia genotype was performed by standard mutation detection techniques. The α-thalassemia deletions were identified by a polymerase chain reaction (PCR)-based strategy and the configuration of the α-globin locus was determined by Southern blot hybridization with probes specific for α- and ζ-globin genes. The Xmn-I $^{G}\gamma$ promoter polymorphism at position –158 was determined by PCR restriction analysis. The β-thalassemia intermedia phenotype was defined in accordance with published criteria.[7-9]

There were 108 patients who showed two β-thalassemia alleles, comprising 63 patients with β⁰/β⁰ and 45 patients with β⁰/β⁺-thalassemia (Table 1). The β⁰-thalassemia alleles detected were codons 41-42 (-CTTT), IVSII-654 (C→T), codon 17 (A→T), codons 71-72 (+A), codons 14-15 (+G), codon 43 (G→T), codons 27-28 (+C), ATG→AGG at the initiation codon, IVSI-1 (G→T) and IVSII-2 (-T). The β⁺-thalassemia allele detected was nt –28 (A→G) in all but one patient who showed nt –29 (A→G). Five out of six β⁰/β⁰-thalassemia patients who co-inherited SEA deletion showed β-thalassemia major phenotype, whereas all five patients with β⁰/β⁺-thalassemia and concurrent SEA deletion showed β-thalassemia intermedia phenotype (Fisher's exact test, $p = 0.015$). Four out of five patients in the latter group never required blood transfusion. In comparison, only 13 out of 39 (33%) patients with β⁰/β⁺-thalassemia and normal α-globin genes showed β-thalassemia intermedia phenotype (Fisher's exact test, $p = 0.0079$). The single patient with β⁰/β⁰-thalassemia and concurrent SEA deletion who showed a β-thalassemia intermedia phenotype had a genotype of compound heterozygosity for IVSII-654 (C→T) and codons 27-28 (+C), and was heterozygous for Xmn-I $^{G}\gamma$ promoter polymorphism. The three patients

Table 1. The effect of α-thalassemia on the clinical phenotype of Chinese patients with severe β-thalassemia.

Category	*Clinical phenotype*	*Number*	*Xmn-I $^{G}\gamma$ heterozygosity*	*Age at diagnosis* (years)*	*Age at first transfusion* (years)*	*Frequency of transfusion (times per year)*	*Lowest or steady state hemoglobin* (g/dL)*
β⁰/β⁰ thalassemia		63					
αα/αα	Major	52	1	0.5±0.06	0.9±0.2	12	5.6±0.4
	Intermedia	2	1	2.7 (mean)	5.3 (mean)	2–12	5.5 (mean)
--SEA/αα	Major	5	0	0.8±0.1	0.9±0.3	6–12	4.5±0.6
	Intermedia	1	1	7	10	0	9.0
-α/αα	Major	3	1	1.3±0.3	1.7±0.7	12	4.3±0.3
	Intermedia	0	NA	NA	NA	NA	NA
β⁰/β⁺ thalassemia		45					
αα/αα	Major	26	1	0.8±0.1	1.5±0.6	12	4.9±0.9
	Intermedia	13	0	2.5±0.7	7.6±3.0	Variable	7.9±0.2
--SEA/αα	Major	0	NA	NA	NA	NA	NA
	Intermedia†	5	0	9.0±3.8	10 (one patient)	4 (one patient)	9.1±0.5
-α/αα	Major	0	NA	NA	NA	NA	NA
	Intermedia	1	0	2	Never transfused	Never transfused	9.0

**Value expressed as mean±standard error (unless otherwise stated); †four out of the five patients were never transfused; NA, not applicable.*

with β^0/β^0-thalassemia and co-inheritance of a single α-globin gene deletion all showed the β-thalassemia major phenotype, while β^0/β^+-thalassemia and co-inheritance of a single α-globin gene deletion, observed in only one patient, was associated with a β-thalassemia intermedia phenotype.

Our results show that co-inheritance of the SEA deletion ameliorates the clinical phenotype of β^0/β^+ but not necessarily that of β^0/β^0-thalassemia in Chinese patients with severe β-thalassemia. However, no definite conclusion is warranted about the phenotypic effect of a single α-globin gene deletion in view of the many fewer cases than the SEA deletion. This conclusion has two clinical implications. First, we propose that the presence of SEA deletion should be routinely determined in couples at risk of conceiving a fetus affected by β^0/β^+-thalassemia (i.e. parents who are discordant carriers of β^0- and β^+-thalassemia mutations), so that this information may be incorporated into the genetic counseling of such couples. Based on prevalence figures of β-thalassemia alleles[10] and assuming 70,000 live births annually, this amounts to eight pregnancies ($0.004 \times 0.027 \times 70{,}000$) per year. As Hb H inclusion bodies are typically absent in subjects who are heterozygous for both β-thalassemia mutation and SEA deletion, the presence of SEA deletion must be detected by PCR-based techniques.[10] Second, at prenatal diagnosis, a genotype of β^0/β^+-thalassemia and SEA deletion for the fetus is predictive of β-thalassemia intermedia, whereas the same cannot be said for compound heterozygous β^0/β^+-thalassemia only or β^0/β^0-thalassemia in association with SEA deletion.

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References

1. Furbetta M, Tuveri T, Rosatelli C, Angius A, Falchi AM, Cossu P, et al. Molecular mechanism accounting for milder types of thalassemia major. J Pediatr 1983; 103:35–9.
2. Wainscoat JS, Kanavakis E, Wood WG, Letsky EA, Huehns ER, Marsh GW, et al. Thalassaemia intermedia in Cyprus: the interaction of α and β thalassaemia. Br J Haematol 1983; 53:411–6.
3. Thein SL, Hesketh C, Wallace RB, Weatherall DJ. The molecular basis of thalassaemia major and thalassaemia intermedia in Asian Indians: application to prenatal diagnosis. Br J Haematol 1988; 70:225–31.
4. Galanello R, Dessi E, Melis MA, Addis M, Sanna MA, Rosatelli C, et al. Molecular analysis of β^0-thalassemia intermedia in Sardinia. Blood 1989; 74:823–7.
5. Weatherall DJ, Pressley L, Wood WG, Higgs DR, Clegg JB. Molecular basis for mild forms of homozygous β-thalassaemia. Lancet 1981; 1:527–9.
6. Gringras P, Wonke B, Old J, Fitches A, Valler D, Kuan AM, et al. Effect of α thalassaemia trait and enhanced γ chain production on disease severity in β-thalassaemia major and intermedia. Arch Dis Child 1994; 70:30–4.
7. Ho PJ, Hall GW, Luo LY, Weatherall DJ, Thein SL. β-thalassaemia intermedia: is it possible consistently to predict phenotype from genotype? Br J Haematol 1998; 100:70–8.
8. Winichagoon P, Fucharoen S, Chen P, Wasi P. Genetic factors affecting clinical severity in β-thalassemia syndromes. J Pediatr Hematol Oncol 2000; 22:573–80.
9. Rund D, Oron-Karni V, Filon D, Goldfarb A, Rachmilewitz E, Oppenheim A. Genetic analysis of β-thalassemia intermedia in Israel: diversity of mechanisms and unpredictability of phenotype. Am J Hematol 1997; 54:16–22.
10. Ma ESK, Chan AYY, Ha SY, Chan GCF, Lau YL, Chan LC. Screening for ($--^{SEA}$) α-globin gene deletion in β-thalassemia carriers and prevention of hydrops fetalis. Haematologica 2000; 85:991–3.

Clinical characteristics of and risk factors for herpes zoster after hematopoietic stem cell transplantation

One hundred and eighty-three varicella-zoster virus seropositive patients after stem cell transplantation were reviewed. Herpes zoster developed in 41 patients (22.4%), at a median of seven (2-33) months post-transplantation. Stem cell transplantation from an allogeneic donor was the most significant risk factor (p<0.01) for the development of herpes zoster.

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Herpes zoster (HZ) occurs in 17-52% of patients after hematopoietic stem cell transplantation (SCT).[1] Most patients are seropositive for varicella zoster virus (VZV), indicating past infections. Despite treatment with high dose acyclovir, most patients suffer from complications including post-herpetic neuralgia, corneal ulceration, superimposed bacterial infection and viral dissemination.[2] We evaluated the clinical characteristics of HZ in a cohort of SCT patients treated at a single center, with a view to defining the clinical characteristics of and risk factors for this post-transplantation complication.

One hundred and ninety-four consecutive adult patients undergoing SCT in the Queen Mary Hospital and surviving more than two months were reviewed. Eleven patients were seronegative for VZV at transplantation and were excluded from subsequent analysis. The demographic characteristics of the remaining 183 patients are shown in Table 1. Acyclovir (5 mg/kg every 8 hours, conditioning to day 30) for prophylaxis against herpes simplex infection was used in autologous and allogeneic SCT from HLA identical siblings. In SCT from matched unrelated donors (MUD), high dose acyclovir (10 mg/kg every 8 hours) was given from conditioning to engraftment, followed by ganciclovir (5 mg/kg) three times a week until day 120, for prophylaxis against cytomegalovirus (CMV) infection. Pre-emptive ganciclovir was administered, when two consecutive polymerase chain reactions (PCR) for CMV were positive, to 6/55 autologous and 68/125 allogeneic SCT recipients. The duration of ganciclovir therapy, however, was subject to the discretion of the attending physicians and therefore not included in the analysis. HZ was defined clinically as the presence of a vesicular rash over one or more dermatomes. Treatment comprised high dose intravenous acyclovir (10 mg/kg every 8 hours) for 5-7 days followed by oral acyclovir (800 mg five times per day) or valacyclovir (1