Opinion

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Scalar Scoring in Thalassemia Genotype: As a New Overview

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Introduction

One of the most complex subjects of Hematology is thalassemia and hemoglobinopathy genotype interpretation and phenotype determination as well as their clinical symptoms and electrophoresis. Therefore, establishing a logical digital relationship between the above-mentioned items can contribute to the understating of this subject.

In this opinion article, we present a new digital scoring method for genotype and predicting phenotype and some CBC indexes based on estimated genotype score. This method in Hematology might facilitate the complexity of medical patients, but it may not be possible to justify all existing details in these patients.

Material and Methods

Focusing on down table: For example, a 6-year-old patient with $\beta^A/\ \beta^+$ genotype is a minor β thalassemia case and he has β score=4 and α score=6 and total score=10 in our scoring. In this method, we attribute his minimum Hb as a sum of α score and β score equal 10 and his minimum MCV=76. Also, in this patient because of β thalassemia minor, genotype is asymptomatic with predictable Hb electrophoresis.

The thalassemia has Mendelian inheritance and it has inherited autosomal recessive; therefore, people with 50% healthy alleles have thalassemia trait and they are not patients, but the people with 100% involved alleles of α or β genes have thalassemia disease and they are patients. Thalassemic patients have organomegaly, anemia, and ineffective erythropoiesis with objective and subjective symptoms (fatigue, pallor, jaundice) and abnormal Hb electrophoresis and CBC, but thalassemia trait persons just have abnormal Hb electrophoresis and CBC without clinical symptoms **(Figure 1)**.

In this method, we attributed β chain score equal 3.

β^A, β^+, β^0 and 6 compound genotypes derive from this three conditions. Every healthy β chain gets the score +3: HbA has $\alpha_2\beta_2$ combination; therefore, a healthy person with two healthy β chains in hemoglobin A is shown as β^A/β^A has β score=+6, So: **(Figure 2a-c).**

Hemoglobin Lepore is a chimeric protein, which is resulted from a fusion gene (adherence of β gene to Δ). Therefore: **(Figure 3).**

Based on the above description, Lepore trait has β score=+4; therefore, the patient has minor thalassemia and Lepore homozygous patient has β score=+2 and the patient has intermediate thalassemia. With the same method composition of β^{lepore} with other β gene variations such as β^E, β^C, β^S, β^D produced other β thalassemia and hemoglobinopathies genotypes and phenotypes.

Exception 1: $\beta^{lepore}/\ \beta^{lepore}$ (homozygote Lepore or Lepore disease) is one of exceptions, which has maximum 20-25% Lepore Hb with score=2. Therefore, he is an intermediate β thalassemia phenotype or disease. This patient has 75-80% HbF. People with Lepore heterozygote genotype such as $\beta^{lepore}\ \beta^A$ have score=4; therefore, they are β variant thalassemia trait and have no disease. In these cases, HbA1 and HbA2 do not exist and remaining Hb chains are 75-80% δ chains that present with HbF.

Note: Second interesting genotype in β thalassemia is co-deletion of β gene and $^{\Delta}$. One of this genotypes is $(\Delta\beta)^+/(\Delta\beta)^+$. This person has β score=+2 and he is β thalassemia intermediate with low HbA2, HbA1. $(\Delta\beta)^+/A$ is heterozygous with score=+4; therefore, he is a case of β thalassemia trait or minor β thalassemia with low HbA2.

THALASSEMIA	GLOBIN GENOTYPE	FEATURES	EXPRESSION	HEMOGLOBIN ANALYSIS
α-THALASSEMIA				
1 gene deletion	-,α/α,α	Normal	Normal	Newborn: Bart's 1-2%
2 gene deletion trait	-,α/-,α -, -/α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart's: 5-10%
3 gene deletion hemoglobin H	-,-/-,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart's: 20-30%
2 gene deletion + Constant Spring	-,-/α,α Constant Spring	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2-3% Constant Spring, 10-15% hemoglobin H
4 gene deletion	-,-/-,-	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89-90% Bart's with Gower 1 and 2 and Portland
Nondeletional	α,α/α,α variant	Microcytosis, mild anemia	Normal	1-2% variant hemoglobin
β-THALASSEMIA				
β^0 or β^+ heterozygote: trait	β^0/A,β^+/A	Variable microcytosis	Normal	Elevated A_2, variable elevation of F
β^0-Thalassemia	β^0/β^0, β^+/β^0, E/β^0	Microcytosis, nucleated RCB	Transfusion dependent	F 98% and A_2 2% E 30-40%
β^+-Thalassemia severe	β^+/β^+	Microcytosis nucleated RBC	Transfusion dependent/thalassemia intermedia	F 70-95%, A_2 2%, trace A
Silent	β^+/A	Microcytosis	Normal with only microcytosis	A_2 3.3-3.5%
β^+/β^+	Hypochromic, microcytosis	Mild to moderate anemia	A_2 2-5%, F 10-30%	
Dominant (rare)	B^0/A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$-Thalassemia	$(\delta\beta)^0$/A	Hypochromic	Mild anemia	F 5-20%
$(\delta\beta)^+$-Thalassemia Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	Lepore 8-20%
Lepore	$\beta^{Lepore}/\beta^{Lepore}$	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%

Figure 1 Genotype and phenotype of β thalassemia and clinical features.

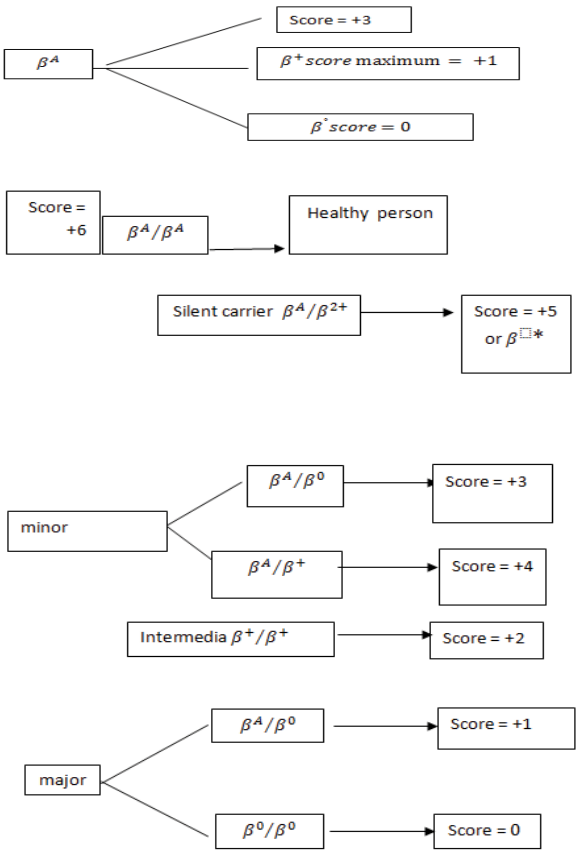

Figure 2 (a-c) Healthy person with two healthy β chain in hemoglobin A shown as β^A/β^A has β^ score=+6.

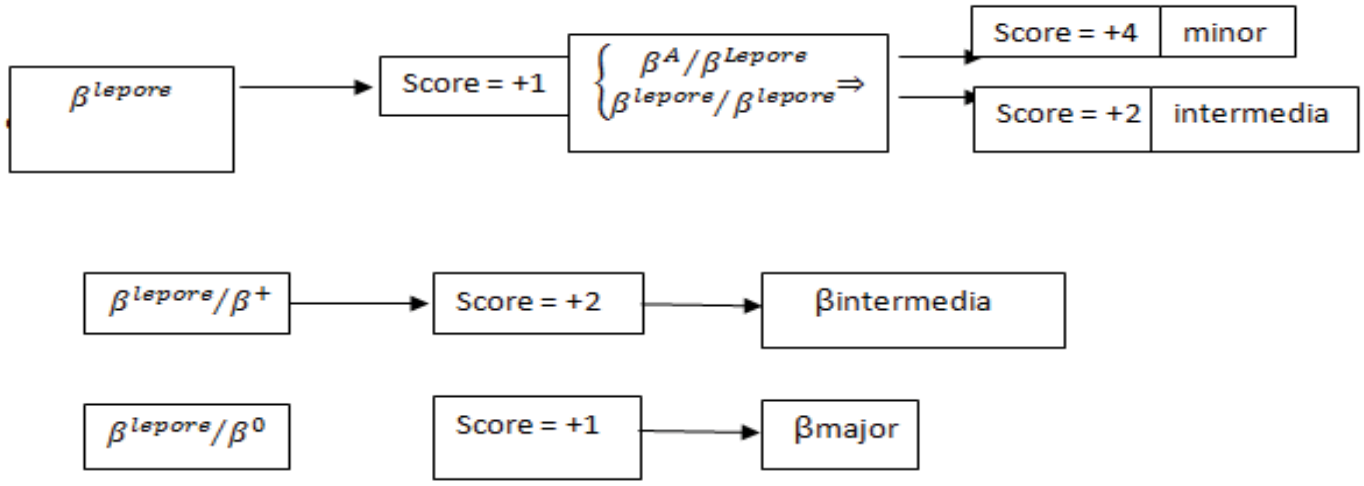

Figure 3 Scoring of Lepore trait.

Gen/genotype	β^{A}	β^{2+}	β^{+}	β^{o}	β^{lepore}
β^{A}	$\beta^{A}\ \beta^{A}$	$\beta^{A}\ \beta^{2+}$	$\beta^{A}\ \beta^{+}$	β^{A}	$\beta^{A}\ \beta^{lepore}$
β^{2+}	$\beta^{2+}\ \beta^{A}$	$\beta^{2+}\ \beta^{2+}$	$\beta^{2+}\ \beta^{+}$	β^{2+}	$\beta^{2+}\ \beta^{lepore}$
β^{+}	$\beta^{+}\ \beta^{A}$	$\beta^{+}\ \beta^{2+}$	$\beta^{+}\ \beta^{+}$	β^{+}	$\beta^{+}\ \beta^{lepore}$
β^{o}	$\beta^{o}\ \beta^{A}$	$\beta^{o}\ \beta^{2+}$	$\beta^{o}\ \beta^{+}$	β^{o}	$\beta^{o}\ \beta^{lepore}$
β^{lepore}	$\beta^{lepore}\ \beta^{A}$	$\beta^{lepore}\ \beta^{2+}$	$\beta^{lepore}\ \beta^{+}$	$\beta^{lepore}\ \beta^{o}$	$\beta^{lepore}\ \beta^{lepore}$

Figure 4 Matrix of possible β thalassemia genotype.

Gen/genotype	β^{A}	β^{2+}	β^{+}	β^{o}	β^{lepore}
β^{A}	6	5	4	3	4
β^{2+}	5	4	3	2	3
β^{+}	4	3	2	1	2
β^{o}	3	2	1	0	1
β^{lepore}	4	3	2	1	2

Figure 5 Matrix of score of β thalassemia genotype.

Gen/genotype	β^{A}	β^{2+}	β^{+}	β^{o}	β^{lepore}
β^{A}		Silent Carrier β	minor β	minor β	minor β
β^{2+}	Silent Carrier β	minor β	minor β	β intermediate	minor β
β^{+}	minor β	minor β	β intermediate	β major	β intermediate
β^{o}	minor β	β intermediate	β major	β major	β major
β^{lepore}	minor β	minor β	β intermediate	β major	β intermediate

Figure 6 Matrix of possible β thalassemia phenotype.

Genotype and phenotype multiplication table: In summary, if we put all β genes situations in horizontal and vertical column, we assess all probable β genotypes. **Figure 1** shows possible genotypes with β gene variations, **Figure 3** shows possible

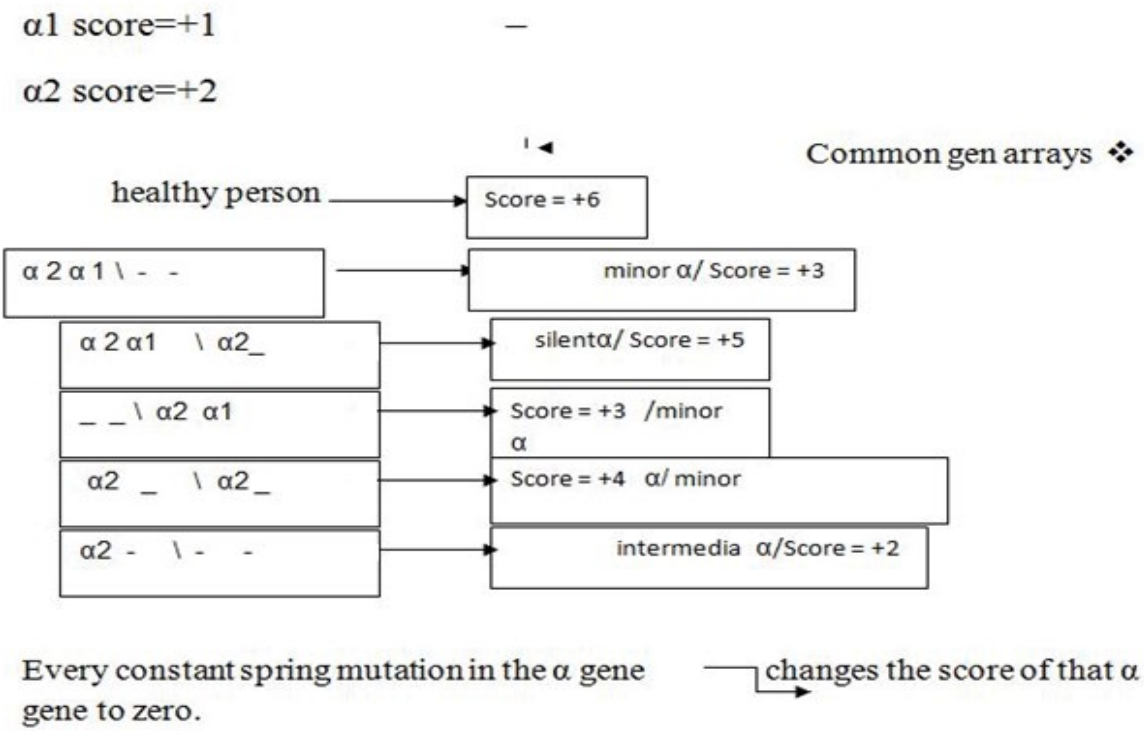

Figure 7 α genes placement and the score in αthalassemia.

genotypes score in our scalar scoring, and **Figure 4** shows possible clinical situations compatible with genotype and score. For example, patient with β^+/β^+ in matrix home 4 x 4 has β thalassemia intermediate genotype and β score=+2 in our scoring **(Figures 4-6)**.

α genes placement and the score in αthalassemia: There are two types of α genes: α1 and α2 genes and they are not equal regarding their ability for producing α chains. Therefore, they have 2 different scalar scores in our scoring system. In healthy persons, α genes composition is α2 α1\α2 α1. If we attribute α1 score=+1 and α2 score=+2 in scoring, they have 2 different genotypes with α genes in α thalassemia setting: **(Figure 7).**

This method is extended about α variants hemoglobinopathies such as Constant Spring Hemoglobin and other deletional and non-deletional genotypes:

α CS score has value 0 in our scoring system, for example: α2 _ \ α CS_ has score=+2, therefore, he is intermediate α thalassemia.

Estimation of complex genotype clinical manifestations: In complex genotype such as α thalassemia intermediate with β thalassemia minor scor α=+2 and β thalassemia minor score=+3 or +4 and α/β ratio=2/3 or 4. In pure genotype such as α thalassemia intermediate with β normal scor α=+2 and β score=+6 and α/β ratio=2/6. In comparison of two patients, α/β ratio nearer to 1 (normal genotype score in healthy person) clinical manifestations would be better.

Conclusion

Our new and simplified method in interpreting thalassemia genotype, phenotype, and clinical symptoms well based on the scoring method. Therefore, it is an effective applied method for learning, interpreting, and simplifying complicated concepts of thalassemia syndromes. We think that using simple language is most important factor for effectiveness of this course and this method similar case based bedside teaching provides active learning in real context observes students skills, increases learners' motivation and professional thinking, integrates clinical, communication, problem solving, decision making and ethical skills [1-5].

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