Hemoglobin H-constant spring in North America: an alpha Thalassemia with frequent complications

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Hemoglobin H-constant spring (Hb H-CS), the most common nondeletional alpha thalassemia in Asia is increasingly recognized in North America due to shifts in immigration patterns. In California, alpha (α)-thalassemia syndromes are the second most frequent finding among newborns screened for hemoglobinopathies with a two-fold increase compared to a decade earlier [1,2]. Though known to have a more severe anemia than Hb H disease, the other clinical findings of Hb H-CS are not well described. Moreover, beneficial therapies that have become available in the last decade are often not applied to their care.

This analysis of 46 patients enrolled in the Thalassemia Clinical Research Network (TCRN) age 13+/- 10 years old, with Hb H-CS revealed moderate anemia (mean 8.7 ± 1.5 g/dl), regular transfusion therapy in 24% of patients, and splenomegaly or prior splenectomy in one-third of them. Serum transferrin receptor (sTfr), was elevated; (44.4 ± 18 mcg/ml normal range 2.9-8.3 mcg/ml), reflecting ineffective erythropoiesis, which in turn leads to high iron absorption and increased ferritin levels in younger (median 187 ng/ml) and older (median 465 ng/ml) nontransfused patients. These findings along with moderate growth delay and low bone mass were more prevalent in Hb H-CS patients compared to deletional Hb H disease. Our results highlight the required monitoring of the extent of anemia, growth, splenomegaly, iron overload, gallstones, bone density and assessment of need for transfusions and specific treatments for disease complications.

The constant spring (CS) termination codon mutation (α142 STOP→G; TAA→CAA), is the most prevalent nondeletional α globin mutation in Southeast Asia (SEA) and southern China. DNA diagnosis of Hb H-CS, a combination of two α's α-gene deletions and one CS deletion is often required because the Constant Spring, a slow moving band produced in small quantities, can be missed by electrophoresis. It is inadvertently mistaken for the more common, three α-gene deletion—Hb H disease—typically a milder type of α thalassemia. In North America, clinical data on α thalassemia, in particular concerning Hb H-CS is lacking. Moreover, recent advances in technology for diagnosis and treatment of thalassemia-induced complications are therefore rarely considered for this patient population. We sought to characterize the clinical and hematological findings in patients with Hb H-CS in North America, addressing findings that can impact on their clinical care. Genotyping of 836 thalassemia patients identified 106/836 (12.7%) with Hb H (three gene deletion) and 46/836 (5.5%) that can impact on their clinical care. Genotyping of 836 thalassemia patients.

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The compound heterozygocity for a deletional mutation in combination with the CS mutation results in less α-globin mRNA production by the remaining functional α-gene in comparison to a three α-gene deletion. Therefore more αβ imbalance occurs and more Hb H (α4 tetramers) pre-
Pathology is induced by dysfunction and shortened RBC survival [4]. In addition, direct membrane precipitates in the cell causing local oxidative damage, membrane scores in subjects while normal in Hb H patients. 

Figure 1. Height Z score grouped by age in Hb H and in Hb H-CS patients. 

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Descriptive statistics were reported as number and percent or mean and standard deviation (SD). Differences in categorical variables were tested by Chi-square or Fisher’s exact test and differences in continuous variables were tested by Student’s t-test. Ferritin level was not normally distributed and log-transformation was used. All analyzes were performed at the Data coordinating center (New England Research Institutes, Watertown, MA) with SAS statistical software (9.2, SAS Institute, Cary, NC). P-values less than 0.05 were considered statistically significant.

References