

Changes in HbA₂ Levels May Signify Hemoglobin Defects in Infants

To the editor:

The hemoglobin profile has been utilized as a clue for the diagnosis of thalassemia and hemoglobinopathy. Fetal hemoglobin (HbF, $\alpha_2\gamma_2$) is highly expressed as the major functional hemoglobin during the fetal stage. Following hemoglobin switching, HbF declines to less than 1% of the total hemoglobin within one year of age. Adult hemoglobin (HbA, $\alpha_2\beta_2$) therefore predominates over total hemoglobin in combination with 2-3% of HbA₂ ($\alpha_2\beta_2$) and trace amounts of HbF throughout adult life. Hemoglobin can routinely be analyzed using chromatography or electrophoresis. Relative alterations of these hemoglobin types have been shown to be associated with abnormal globin production in adults. For instance, hemoglobin E (HbE, $\alpha_2\beta_2^{26\text{Glu}\rightarrow\text{Lys}}$), the hallmark hemoglobinopathy of Southeast Asia, exists in a range from 25-90% of the total hemoglobin in adults with HbE inheritance; however, HbE levels present less than 25% of total hemoglobin in heterozygous HbE patients who co-inherit with α -thalassemia. Moreover, HbA₂ is markedly raised between 3.5 and 9.9% in adult heterozygous β -thalassemia. In contrast, relative changes in hemoglobin types are unnoticeable by routine hemoglobin analysis in adults with one or two α -globin gene defects. To broaden the knowledge and illustrate the effects of globin disorders on hemoglobin profile in infants, leftover blood samples from 142 unrelated individuals aged between 8 and 12 months with a mean corpuscular volume (MCV) less than 80 fL were subjected to thalassemia screening and diagnosis. Hemoglobin analysis was performed regarding the Rad Variant II Hemoglobin Testing System with β -Thalassemia Short Program (BioRad, Hercules, CA). The diagnosis of α -thalassemia was performed according to standard diagnostic guidelines used in Thailand.²⁻⁴ In addition, common deletion types of α^+ -thalassemia ($-\alpha^{3,7}$ and $-\alpha^{2}$) and α^0 -thalassemia ($--^{\text{SEA}}$ and $--^{\text{THAI}}$) were genotyped as described in previous studies.^{5,6} The protocols in this study were approved by the ethics committee of the Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand (ethical approval reference number AMSEC-63EM-001). The results revealed that 59 (41.5%) were negative for the common thalassemias (hereafter so called normal), 37 (26.1%) were heterozygous for β -thalassemia, 19

(13.4%) were heterozygous for HbE, 18 (12.6%) were heterozygous for α -thalassemia 1, and 9 (6.3%) were deletional HbH disease caused by compound heterozygous α -thalassemia 1 with α -thalassemia 2 (Table 1). Complete blood count (CBC) showed hypochromic microcytic anemia with reduced total Hb level, HbA₂, MCV, and mean corpuscular hemoglobin (MCH) (Table 1). On average, the hemoglobin profile of normal infants was similar to that of normal adults, suggesting that the hemoglobin switching had completed in these subjects. Conversely, significant increase in HbA₂ and HbF levels was observed in infants with heterozygous β -thalassemia and heterozygous HbE (Table 1). The elevated HbA₂ levels were similar to those of adults with heterozygous β -thalassemia. Regardless of age, this suggested that increased HbA₂ levels determine the inheritance of β -thalassemia. Interestingly, elevated HbF levels were absent in adults with either heterozygous β -thalassemia or heterozygous HbE,^{7,8} suggesting a developmental stage-specific effect. This finding is comparable to previous studies in which the delayed HbF to HbA switching is remarkably shown in infants with β -globin defects.^{9,10} Although the mechanisms underlining HbF to HbA switching are unclear, the prolonged HbF levels in infants with a β -globin defect maybe due to the primary compensation of β -like globin gene expression and total hemoglobin during development in affected infants. Similar to those of adults with homozygous β^0 -thalassemia and compound heterozygous β^0 -thalassemia with HbE disease, the increase in γ -globin gene expression has been shown to associate with milder clinical manifestations as it is able to substitute for the inadequate β -globin gene expression and yields increased HbF levels. In contrast to β -globin gene defects, heterozygous α^0 -thalassemia demonstrated comparable hemoglobin types to the normal in our finding. Despite insignificance, infants with two α -globin gene defects displayed reduced HbA₂ and modestly increased HbF levels in the previous study.⁹ The decrease in HbA₂ levels was clearly noticed in infants with three α -globin gene defects or deletional HbH disease in our study. Together, the results suggested that HbA₂ levels may be considered as valuable markers for the inheritance of globin gene defects in infants.