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Alpha-thalassaemia trait as a cause of unexplained microcytosis in a South African population

To the Editor: I read the article by Loonat *et al.*[1] with interest. In the early 1980s a study was undertaken at Red Cross War Memorial Children's Hospital, Cape Town, South Africa (SA), to assess the frequency with which a low red cell mean corpuscular volume (MCV) was associated with the presence of thalassaemia or an abnormal haemoglobin.[2] Between January 1979 and December 1980, 730 patients with an MCV of ≤60 fl were investigated. Forty-six (6.4%) were found to carry a β-thalassaemia gene and 20 (2.7%) had an abnormal haemoglobin, most commonly Hb E. The prevalence of thalassaemia was highest in individuals of mixed ethnic origin, and abnormal haemoglobins were found exclusively in this population, although the numbers of white and black patients were much smaller in comparison. Alpha-thalassaemia was not tested for, as the technology was unavailable at the time owing to cost constraints. Nevertheless the findings confirmed that patients with persistent unexplained microcytosis/hypochromia should be screened for thalassaemia and haemoglobin variants.

A further survey of blood donors of mixed racial origin was undertaken to determine the prevalence of inherited haemoglobin disorders in this population more accurately.[3] Globin synthesis studies and DNA analyses were performed in donors with microcytosis or hypochromia or both associated with normal ferritin, Hb A_2 and Hb F levels. DNA was analysed by Southern blotting and hybridisation with an α-globin complementary DNA probe and a γ-globin genomic probe. In 989 donors screened, Hb S and E were the commonest structural variants detected, each with a prevalence of 1%. Hb C was detected in just 1 donor. Seven donors had β-thalassaemia trait (0.8%) and 2 had hereditary persistence of fetal haemoglobin. A total of 45 donors had DNA analyses. Thirty-three were documented as having α-thalassaemia, the majority (n=24) of whom were heterozygous for the α^+ (–α/) haplotype, with an observed frequency of 0.023.

I am not clear whether other haemoglobin variants, in particular Hb E, were screened for in the study by Loonat *et al.*[1] Hb E was first described in Thailand and is common in South-East Asia. Many South-East Asians who were brought to the Cape in the early years of settlement were from Indonesian islands, and presumably this accounts for the presence of Hb E in the mixed-race population of the Western Cape. The heterozygous and homozygous states for Hb E are benign conditions clinically, but individuals often have red cell microcytosis and/or hypochromia.[4] The β^E gene results in inefficient synthesis, as borne out by studies that show decreased β^E globin chain synthesis,[5] and there is also evidence that the β^E messenger RNA is relatively unstable.[6] It therefore appears that the β^E gene leads to a mild form of β-thalassaemia. The double heterozygous condition of Hb E/β-thalassaemia is, however, a major public health hazard in the Far East, India, Pakistan and Bangladesh, with a clinical picture akin to that of thalassaemia major. Milder forms of Hb E/β-thalassaemia have also been described and are perhaps the result of Hb E interaction with β^+-thalassaemia.

With regard to α-thalassaemia, other studies in southern Africa include those of Ramsay and Jenkins,[7] Mathew *et al.*[8] and Rousseau and Mathew.[9] The former studied a group of San in the Kalahari region of Namibia and found the –α/ determinant to occur at a frequency of 0.06. They postulated that the –α/ haplotype has a significant protective effect against malaria. Rousseau and Mathew[9] performed follow-up DNA analyses on neonates with Hb Bart's detected in cord blood samples. The –α/ determinant was the most frequent haplotype and the observed frequency was very similar to that in the donor study. Krause *et al.*[10] summarised their 30-year experience in testing for haemoglobinopathies in Johannesburg: five common α-globin deletions were identified with 10 genotypes. The most common deletion identified was $-\alpha^{3.7}$ in individuals of different ethnicities.

Red cell microcytosis/hypochromia is most commonly caused by iron deficiency and chronic inflammatory or infectious disorders. However, in patients with persistent unexplained microcytosis and/or hyopchromia following a thorough haematological assessment, a full investigation for the presence of a haemoglobinopathy is warranted. Haemoglobinopathies are not the most common monogenic disorders in SA, but from the data summarised above it is clear that they do occur at significant frequencies in high-risk minority groups, and when detected appropriate genetic counselling can be offered. It is also important that these patients are identified, since they may receive inappropriate chronic therapy such as iron medication.

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