Phenotypic diversity of sickle cell disorders: a rebuttal

We read with interest the research communication entitled 'Phenotypic diversity of sickle cell disorders with special emphasis on public health genetics in India' by Balgir[1]. The author has re-emphasized a well-recognized but inadequately understood phenomenon, i.e. why a specific nucleotide replacement (as in sickle cell anaemia) produces diverse clinical phenotypes (epistasis, epigenetics, gene environmental interaction, differential control mechanisms through siRNA, alternate splicing, ribosomal selection, etc.). However, there are some issues with the data reported which merit attention.

A search in PubMed on sickle cell anaemia in India gives over 250 hits. Over the last 58 years several scientists from different parts of the country have contributed in the field of sickle cell anaemia. There have been several population-based studies from Rajasthan, the Nilgiri Hills in Tamil Nadu, Orissa, Madhya Pradesh and Kerala, where the prevalence of sickle cell carriers has varied from 3% to 38% (refs 2–4). Hospital-based screening of anaemia cases in Orissa has shown that around 37% had sickle cell disorders[5].

Extensive clinical studies by Kar in Orissa have shown that attacks of pain, fever and anaemia were the predominant presenting features. These were seen mainly among non-tribal populations[6]. In a later study, he reported 79 deaths among 1800 sickle cell disease patients during a period of 16 years. The main causes of death were pain attacks, hepatic failure, fever, severe anaemia and acute splenic sequestration. The foetal haemoglobin levels in these cases were variable (<5–>25%)[7]. Higher foetal haemoglobin levels have been shown to reduce painful crises[8]. In five autopsy cases of sudden death in Gujarat, vasoocclusion by sickled red blood cells was found to be the factor for terminal events[9]. In Central India, a follow-up of sickle cell disease children, particularly among the Mahars, has shown that the main cause of hospitalization was the need for blood transfusion, painful crises and infections[10]. Among tribal groups as well, painful crises have been universally observed[4], although the clinical presentation is milder among tribals compared to non-tribals, α-thalassaemia being one of the major epistatic factors for amelioration of the disease[11].

Hydroxyurea has greatly benefitted Indian patients with sickle cell disease and sickle β-thalassaemia, where the sickle gene was linked to the Arab–Indian haplotype with high foetal haemoglobin levels. About 78% of patients had no further crises after starting hydroxyurea and the foetal haemoglobin levels showed a significant increase[12].

Balgir[1] writes 'Both sickle cell disease (1–44%) and β-thalassaemia syndromes (3–17%) are prevalent in India'. However, these quoted figures represent carrier frequencies and not the frequencies of the disease or syndrome. The carriers are either not clinically affected or are mildly affected.

In India, β^{++}-thalassaemia is extremely rare. We mainly have β^{+}- or β^{0}-thalassaemia. Balgir has not done any molecular analyses to define the mutation in the β globin gene, but has surmised that >10% Hb A represents β^{++}-thalassaemia, which may be incorrect in the face of his own submission of history of blood transfusion in 34.5% of patients with sickle cell disease and 7.1% of patients with sickle β^{++}-thalassaemia. Transfusions may have led to misclassification.

Typical haemolytic facies were found in 17.2% of patients with sickle cell disease, but only in 10% of patients with sickle cell β-thalassaemia, which is again contrary to the literature because typical haemolytic facies come mainly from inheritance of the β-thalassaemia gene.

Some of the statistical analysis is really surprising. Generally healthy adult males have higher haemoglobin levels than healthy adult females, and the same holds true for sickle cell traits. Age differences seen among male and female sickle cell traits are obvious as many of the heterozygotes were parents of index patients and the father is generally older than the mother in most Indian families.

The reticulocyte counts of the patients are not mentioned. Reticulocyte count along with the haemoglobin level is an important indicator of ongoing haemolysis and ineffective or effective erythropoiesis.

α-Thalassaemia is extremely common in India (average, 13%)[13] and associated α-thalassaemia skews the levels of Hb S in sickle traits. However, this has also been overlooked and not calculated.

There are errors in table 4 of Balgir[1]. How can the mother with a haemoglobin of 12.6 g/dl have a haematocrit of 15.4%? Furthermore, the mother has a SE band on haemoglobin electrophoresis. In such a situation, a Hb A_2 level of 5.7% cannot be reported, as both Hb E and HbA_2 co-migrate on cellulose acetate membranes and co-elute on HPLC. There are only few reports of Hb SE disease in the literature and two cases reported earlier from India have shown that one patient had gallstones, whereas the other was asymptomatic[14].

Sickle cell disease is a major health burden in India and various studies done in different regions of the country have helped understand the clinical diversity and genetic factors contributing to this.

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