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Clinically diverse sickle cell disease influenced by genetic factors

Różnice w obrazie niedokrwistości sierpowatokrwinkowej w zależności od czynników genetycznych

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Dear Editor,

I have a particular interest in the article recently published in your journal related to haemoglobinopathies. I appreciate the quality of the information provided regarding sickle cell disease (SCD).

As we know, sickle cell disease is one of the significant hereditary monogenic disorders, with a global health burden as well as in India. Pain is the main sign in SCD, generally experienced in the initial phase of life. Reflection of pain may relate to an array of genetic and environmental factors such as anxiety, depression, climatic changes, or a socio-economic burden which directly or indirectly is involved in response to treatment in patients [1]. Over the last two decades, several studies have focused on the clinical, biochemical and haematological aspects of SCD. Researchers are suggesting that the clinical manifestations of SCD might be related to variations in foetal haemoglobin levels (HbF) among different geographic regions. Previously we have reported a global HBB haplotype study with diverse clinical manifestations such as splenomegaly, painful crises, and renal failure. In our analysis, we found a high prevalence of atypical haplotypes with higher HbF levels in the Indian population [2].

The clinical severity of pain perception seems to involve a variety of genetic approaches with a number of pro-inflammatory cytokine genes such as tumour necrosis factor (TNF), interleukin 8 (IL-8), endothelin 1 (ET-1) and endothelial nitric oxide synthase (eNOS) gene polymorphisms being associated with SCD patients [3, 4]. However, recent results have contradicted the previous report [5]. Structural evidence-based studies suggest that the mutations sickle-β^+-thalassemia (HbSβ^+) and sickle-β^0-thalassemia (HbSβ^0) are responsible for the severity of clinical manifestation in SCD, and this complication may vary in the same family member due to alterations in the genetic makeup and a contributory role for genetic heterogeneity.

Further, the variation in levels of HbF is associated with multiple QTLs linked to the *HBB* gene cluster, such as XmnI polymorphism (upstream position of the γG-globin gene), *HBS1L-MYB* gene polymorphism (6q22), and *BCL11A* gene polymorphism (2p16.1) [6]. Besides, the co-inheritance of alpha-thalassemia deletion and SCD is associated with improved clinical aspects with better survival [7]. This genetic modulation could explain why carriers of a beta-globin gene mutation may have different clinical severities.

The opportunity for SCD research expanded in the late 1990s to comprehend vascular biology. Remarkably the endothelium-derived nitric oxide provides the vital determinant of vaso-occlusion *in vivo* of SCD.

I would like to draw your attention to the highly versatile experimental methods in SCD that represent potential new therapeutic tools. These include haematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling, genetic manipulation for HbF induction, gene addition strategies (CRISPR/Cas9 gene-editing system), developing β-globin expressing vectors, site-specific gene correction, and improved stem

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cell function by the use of lentiviral vectors, long terminal repeats and self-inactivating vectors. Furthermore, the findings of biochemical markers for a new pharmacological target like N-acetyl-cysteine (NAC), L-glutamine is essential for the reduction of anti-oxidant systems in SCD. The overall letter indicates that the genetics of SCD require a multidisciplinary approach for effective therapy.

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