Sickle Cell Disease in Saudi Arabia: The Asian Haplotype

Reflections on a Meeting at Hofuf, September 2003

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Recent developments in sickle cell disease were reviewed at a research meeting in Hofuf held in September 2003, having been postponed from May 2003 because of events within the region. The meeting brought together speakers and researchers from all over the Kingdom along with visiting speakers from India, Nigeria, Greece, Bahrain, Sudan and Jamaica. Although the emphasis of the meeting was on recent advances, it was a timely reminder of the research opportunities posed by the Asian haplotype of the disease prevalent in the Eastern Province. The Asian haplotype refers to a variant of the DNA structure flanking the β–globin locus (the site of the HbS gene), which is not encountered in African populations and appears to represent an independent occurrence of the HbS mutation. This haplotype is confined to peoples of the Eastern Province of Saudi Arabia and to India, and contrasts with African populations, where the HbS gene is associated with different DNA structures, named Benin, Senegal, and Bantu (or Central African Republic) after the places where they were first described. The interesting feature of the Asian haplotype is the extent to which it modifies the haematological and clinical expression of homozygous sickle cell (SS) disease.

The DNA structure of the Asian haplotype was first recognized in Jamaica in an Indian family with SS disease[1] who also had high levels of fetal haemoglobin (HbF). Early reports from the Eastern Province, especially from the ARAMCO facility in Dhahran reported unusually mild features in SS disease[2-6] and near normal survival.[7] The disease was characterized by high levels of HbF and most cases coincided with α-thalassaemia, both features believed to inhibit intravascular sickling. As a result, splenic architecture and splenic function persisted,[8] minimizing the risk of pneumococcal septicaemia characteristic of African SS disease.[9] Other features of clinical mildness included less frequent acute chest syndrome, leg ulceration and priapism,[10] and less cumulative damage to neurological, pulmonary and renal function, which commonly contributes to death in African disease. The overall impression was of a disease process milder than that of African patients.

However, serious pathology in association with the Asian haplotype has been described. Lack of splenic pathology might be expected to protect against acute splenic sequestration and chronic hypersplenism, but it is clear that these occur.[11] There are insufficient data to determine whether the incidence is similar or less than in African disease. Priapism also occurs and can cause impotence, but its prevalence is unknown. It is also clear that bone pathology continues to cause major symptomatology through painful crises, avascular necrosis of femoral and humeral heads, and osteomyelitis. Data on retardation of physical and sexual development are not yet available and would contribute to the overall picture of disease associated with the Asian haplotype. The Hofuf meeting added further to the catalogue of problems encountered in the 'relatively benign' disease of the Eastern Province, addressing acute chest syndrome, acute splenic sequestration, hypersplenism, priapism, problems in pregnancy, and avascular necrosis of the femoral head, as well as aspects of management such as pregnancy and cholecystectomy.

So where do all these observations lead? Is the Asian haplotype really associated with more mild disease? The truth is that the present data are difficult to evaluate in the absence of true incidence or unbiased prevalence figures. Chronic end-organ damage does appear to be less frequent, serious problems in early childhood less common, and survival is probably increased, but considerable morbidity may occur from recurrent, acute painful crises and from the chronic bone damage of avascular necrosis and osteomyelitis. This may seem a daunting prospect for a disease where median survival may exceed 50 years, but two studies are already underway. From 1982, researchers at King Faisal University, Dammam screened 14 122 births and detected 129 babies with SS disease, most of whom were followed for 5 to 8 years.[8,12,13] Although funding for this study ceased in 1990, it is to be hoped that many participants could still be located, interviewed and followed intermittently with documentation of their clinical course and survival. Another study based at King Faisal University, Dammam, screened births for one year at King Fahad Hospital, Hofuf, several years ago (Dr. Mohammed K. Al-Abdul Aali, personal communication). Although the study contributed

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to prevalence figures, no attempt was made to follow-up these children. If records persist, contact with these subjects now and in the future could provide important data. With so many Saudi doctors interested in sickle cell disease, follow-up of these two populations should have the highest priority.

Sickle cell disease in the Eastern Province provides exciting opportunities for genetic research aimed at understanding the relationship between the Asian haplotype, high levels of HbF and frequent α-thalassaemia. Alpha-thalassaemia is predominantly of the deletional type, and since the responsible gene is on chromosome 16, whereas the HbS mutation resides on chromosome 11, direct linkage seems unlikely. More probable is the simultaneous selection of both genes, HbS and α-thalassaemia, possibly because in the past, both have conferred a survival advantage against malaria in early childhood. In this context, it is interesting that α-thalassaemia is commonly associated with SS disease in almost all populations with the exception of Greek patients.[14] The Eastern Saudi population also provides an opportunity for clarifying the complex interaction of α-thalassaemia and SS disease, which has reached conflicting conclusions elsewhere.[15,16]

Similar opportunities exist for exploring the genetics and clinical effects of high levels of HbF. The general perception that high levels of HbF ameliorate African SS disease is currently supported by limited data,[17-20] and analysis of its effect on survival is confounded by the continuing age-related fall in HbF in older patients. The genetics is even more confusing since definition of the genes for heterocellular hereditary persistence of HbF is not yet possible. At a cellular level, HbF synthesis is elevated in erythroid progenitor cultures from Saudi Arabian patients from the Eastern Province,[21] which is consistent with a genetic mechanism, but a commonly occurring polymorphism at -158 to the cap site of the Gγ gene was not closely linked to HbF levels.[22] These authors did not find elevated HbF levels in sickle cell trait (AS) parents of SS patients with high HbF levels and suggested that the haemolytic stress of SS disease was necessary for the expression of high HbF levels. However, HbF levels were influenced by the HbF level of AS parents in African[23] and Indian[24] patients with SS disease, and in India the HbF level in AS parents of SS subjects was directly related to the number of copies of the Asian haplotype.[24,25] The fact that SS patients homozygous for the Asian haplotype manifest wide variation in HbF levels10,[26] indicates the importance of factors other than the Asian haplotype itself.

Clinically, it is clear that bone pain crises remain a major cause of morbidity and hospital admission. In this context, it is interesting to note that a high haemoglobin level is an important risk factor for bone pain in African SS disease.[19,27] Patients in the Eastern Province manifest high haemoglobin levels and it is important to determine whether this is also a risk factor for bone pain in that area. If confirmed, this would be an opportunity for a trial of venesection in reducing haemoglobin and preventing bone pain, long conjectured in African SS disease but currently based only on anecdotal data.

The conference recently held at Hofuf brought together many Saudi professionals, and illustrated the degree of interest in SS disease and the increasing recognition that SS disease in the Eastern Province is not uniformly benign. The Chairman of the Conference, Dr. Khalifa Nasser K. Al Mulhim, and his organizing committee are to be congratulated on a conference that not only highlighted the problems of the disease, but also emphasized the research opportunities. It is to be hoped that this will act as a stimulus to a concerted, collaborative research programme that will address many of the problems and opportunities detailed above.

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