Genetic Diseases in Arabia—A Model for National Awareness and Care Programme

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The report of the sickle cell gene in 1963 from the eastern province of Saudi Arabia set in motion a cascade of studies of the red cell genetic disorders in the Arabian peninsula. Screening programmes supported by King Saud University, and later by King Abdulaziz City for Science and Technology (KACST), were initiated at the College of Medicine, Riyadh in the early 1970s. A high frequency of sickle cell disease, α- and β-thalassaemias and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, hexokinase and glutathione reductase deficiency genes were encountered in several regions of Saudi Arabia. Studies at the national level demonstrated extensive heterogeneity both in the clinical presentation and molecular pathogenesis of these disorders. A need for better understanding, accurate diagnosis, appropriate management and prevention of these diseases induced the formation of the Sickle Cell and Allied Syndromes (SAS) Study Group in King Saud University. Consequently coordinated efforts at the national level thrived and resulted in the formation of the National Working Group composed of physicians drawn from related medical disciplines and comprised a network of three interconnected organizational levels i.e. the primary care, the regional hospitals and the National Referral and Consulting Unit. This endeavour was complemented by the designation of the Medical Biochemistry Department as the World Health Organization (WHO)
Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies. A complementary proposition involving a WHO Eastern Mediterranean Regional Office is currently planned in order to further regional interactions and integrate similar experiences.

Against this background and in an attempt to improve patients’ management and adoption of standardized measures for control and prevention of these disorders, a National Awareness and Care Programme was initiated. This embraces physicians, patients and family awareness strategies. We outline the steps adopted and the scheme of the programme as a model to provide comprehensive care and to lighten the burden inflicted by these genetic blood disorders on patients, their families and the National Health Service. In its totality, the national programme is coordinated with global initiatives in order to further its cause and to share experience and expertise.

Abnormal variants of human haemoglobins were known to physicians at the Diharan Health Centre in the eastern province of Saudi Arabia as early as 1957 and were first reported by Lehmann and coworkers in 1963.1 This discovery initiated comprehensive studies that resulted in the identification of sickle cell haemoglobin (Hb S), \( \alpha \) - and \( \beta \) -thalassaemias, glucose-6-phosphate dehydrogenase (G-6-PD), pyruvate kinase, hexokinase and glutathione reductase deficiency (Fig. 1) in different regions of Saudi Arabia.2–9 Screening and studies into clinical and laboratory aspects followed, supported by King Saud University and King Abdulaziz City for Science and Technology, Riyadh. A brief outline of the history of the progress in the study of red cell genetic disorders in Saudi Arabia is presented in Table 1. The investigations have shown that the gene frequencies of Hb S, \( \alpha \) - and \( \beta \) -thalassaemias, G-6-PD deficiency and other enzymopathies varied significantly in different regions and correlated positively to the malaria endemicity.3–8

Studies on the natural history of these disorders, particularly Hb S homozygosity showed that sickle cell anaemia (SCA) was mainly mild in the eastern province and mainly severe in all other regions.14,17–19 Varied clinical pictures were found with \( \alpha \) - or \( \beta \) -thalassaemia in combination with Hb S. Hb S/\( \beta \) \( \alpha \) –thalassaemia double heterozygotes occurred at a high frequency and presented with severe manifestations that required constant medical attention.28

It was soon revealed that a better understanding of the pathophysiology, diagnosis, management and prevention of these disorders was essential in order to reduce the burden on health care services and to minimize psychosocial problems faced by these patients and their families.

Conception of Sickle Cell Anaemia and Allied Syndrome Study Group

Early in the 1980s the idea of establishing the Sickle Cell Anaemia and Allied Syndromes (SAS) Study Group was conceived at the College of Medicine, King Saud University, Riyadh. Clinical and laboratory staff at the College of Medicine formed the group and formulated the objectives presented briefly in Table 2. The members are specialists from different disciplines including internal medicine (pulmonary, cardiology, nephrology, haematology) radiology, clinical pathology, obstetrics and gynaecology, biochemistry and community medicine. A comprehensive health care programme was drawn up to cover all aspects of clinical evaluation and management. A starting point was patient and family education with the specific aim of reducing the sufferings of the patients, both physical and psychosocial. Meetings were held with patients and their families, and pamphlets in simple laymen’s language were distributed to give information about the disease, its inheritance, complications, care and home management.

Strategies for comprehensive health care were individualized where each patient was followed regularly at various out-patient clinics nationwide, and the signs, symptoms and complications were recorded to determine the clinical severity of the disease. Haematological, biochemical and radiological evaluations of the patients were carried out and further clinical analyses were suggested. Studies at the molecular level were conducted to identify molecular defects. Depending on the severity of their disease, patients were enrolled in health programmes.

It is hoped that these strategies will be successful and lead to improvement of management and patient care and will be reflected in a decrease in the morbidity of these disorders.

National Working Group

In an attempt to establish a comprehensive health care programme in all regions of Saudi Arabia, the National Working Group was established. It comprised clinicians and other members of the
Figure 1. Sketch map of Saudi Arabia showing the frequency of abnormal genes in different regions.

Table 1

Milestones in the study of haemoglobinopathies, thalassaemias and enzymopathies in Saudi Arabia

<table>
<thead>
<tr>
<th>Findings</th>
<th>Year</th>
<th>Ref</th>
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<tbody>
<tr>
<td>A new sickling disorder due to α-thalassaemia in SCA</td>
<td>1969</td>
<td>[7]</td>
</tr>
<tr>
<td>α-Thalassaemia in CP</td>
<td>1975</td>
<td>[11]</td>
</tr>
<tr>
<td>Hb Bart's in Saudi Arabia</td>
<td>1975</td>
<td>[12]</td>
</tr>
<tr>
<td>Hb S in SWP of Saudi Arabia</td>
<td>1976</td>
<td>[10]</td>
</tr>
<tr>
<td>β-Thalassaemia in SWP, NP</td>
<td>1976</td>
<td>[10]</td>
</tr>
<tr>
<td>G-6-PD deficiency in SWP</td>
<td>1976</td>
<td>[10]</td>
</tr>
<tr>
<td>Study of natural history of sickle cell disease in EP</td>
<td>1978</td>
<td>[14]</td>
</tr>
<tr>
<td>Hb S, α-thal., β-thal., G-6-PD deficiency in different regions</td>
<td>1982</td>
<td>[4]</td>
</tr>
<tr>
<td>Identification of hexokinase and glutathione reductase deficiency</td>
<td>1982–to date</td>
<td>[9,16–30]</td>
</tr>
<tr>
<td>Identification of phenotypes of red cell enzymes</td>
<td></td>
<td></td>
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<tr>
<td>Identification and characterization of the two clinical forms of SCA</td>
<td></td>
<td></td>
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<tr>
<td>(benign and severe) in the Saudi population</td>
<td></td>
<td></td>
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<tr>
<td>Studies at the molecular level</td>
<td></td>
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<tr>
<td>Studies of gene–gene interactions</td>
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<tr>
<td>Identification of several Hb variants</td>
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<td></td>
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<tr>
<td>Initiation of experimental therapy</td>
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</tbody>
</table>

EP = eastern province.
CP = central province.
NP = northern province.
SWP = south western province.
Table 2
The main objectives of the Sickle Cell Anaemia and Allied Syndromes Study Group and the National Working Group

Improvement of health through a multidisciplinary approach to patient care by:

i. Monitoring the clinical presentation in individual patients
ii. Identification of risk factors leading to crisis
iii. Identification of complications and establishment of therapy
iv. Identification of long-term complications of the current therapeutic measures
v. Adoption of a multidisciplinary approach to problems of the individual patient.
vi. Monitoring of clinical and laboratory investigations during steady state and in the state of crisis
vii. Education of patients and families
viii. Identification of social problems and exploring ways of finding solutions
ix. Implementation of preventive measures through:
   patient education
   vaccination
   antibiotic prophylaxis
   pharmacological manipulations, etc
x. Promulgation of family screening and genetic counselling programmes

Enhancement of education of health care personnel through:

i. Establishment of educational programmes both theoretical and practical, for undergraduate and postgraduate students of medicine and paramedical disciplines
ii. Initiation of a newsletter for publication of recent advances in the management, therapy, prevention, prophylaxis, genetic counselling etc. of sickle cell disease and allied disorders
iii. Organization of seminars, workshops and symposia

Achieving a better understanding of the pathophysiology and improvement of methods of treatment by conducting research into various aspects of patient care, particularly:

i. Identification of new anti-sickling agents and agents for control of pain
ii. The feasibility of bone marrow transplantation and gene therapy

health team in different parts of the country. The main objectives of this study group are:

(i) Provision of diagnostic services.
(ii) Preparation of regional registries and hence a National Registry.
(iii) Adoption of comprehensive management and therapeutic protocols for proper health care.
(iv) Prevention of these disorders by proper genetic counselling.

Three interconnected organizational levels, i.e. the primary care, the regional hospital and the national referral unit, were endorsed. The responsibilities of each level are presented in Table 3.

At the primary care level, routine analyses are carried out, signs, symptoms, complications and physical and medical history of the suspected patients are recorded. For further comprehensive studies the patient is forwarded to a regional hospital. There are eight regional hospitals in the different regions of the country. Routine haematological analysis and electrophoresis are carried out and a provisional diagnosis is made for definitive diagnosis, the patient is directed to the Referral Unit, where genetic studies are carried out to establish accurate diagnosis. The full support of Ministry of Health of Saudi Arabia has played a significant role in successful implementation of these objectives. Yearly meetings of the members of the National Working Group take place under the auspices of the Ministry of Health and College of Medicine, King Saud University.

WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies
In January 1991, the World Health Organization designated the centre at the Department of Medical Biochemistry, College of Medicine, King Saud University as the WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies. This recognition follows the longstanding services that have been offered by this centre for the study of genetic blood disorders. The responsibilities assigned to the centre are listed in Table 4. The implementation of these responsibilities
Table 3

The National Scheme of Care for Blood Genetic Disorders in Saudi Arabia—An outline of the tasks of the complementary organizations

National Referral and Consulting Unit:

Establishing the definitive diagnosis
Maintaining a National Registry of SCA, thalassaemias and enzymopathies
Provision of management consultation
Provision of information on SCA, thalassaemias and enzymopathies to the general public through:
   lectures
   pamphlets
   videotapes
Organization of meetings between:
   physicians in different regions
   patients families and health care providers
   families and families
Organizing national, regional and international symposia
Organizing national, regional and international training workshops
Communication and back-up support for physicians at Primary Health Centres and Hospitals

Regional Hospitals (King Fahad or Equivalent):

Provision of diagnostic support
Provision of patient care and follow-up
Maintaining regional records of SCA, thalassaemia and enzymopathy patients
Provision of health counselling
Provision of social support
Communication with other hospitals and the National Referral and Consultant Unit

Primary Health Centre (PHC):

Making professional diagnosis
Maintaining record of SCA, thalassaemia and enzymopathy patients
Provision of health counselling
Provision of patient care and follow-up
Communication with regional hospitals and the National Referral and Consulting Unit

SCA = sickle cell anaemia.

Table 4

The responsibilities of the Medical Biochemistry Department as the WHO Collaborating Centre for Haemoglobinopathies, Thalassaemias and Enzymopathies

To develop further the approaches for improvement of delivery of thalassaemia control services to the community
To investigate community knowledge and attitude to the control of hereditary disorders
To assist in the development of training aids for programmes for the control of hereditary disorders
To assist in training for population screening and fetal diagnosis of hereditary anaemias
To develop and improve diagnostic methods for haemoglobinopathies, thalassaemias and enzymopathies
To investigate further structural, functional and genetic aspects of haemoglobinopathies, thalassaemias and enzymopathies

have been initiated and steps have been adopted for the improvement of delivery of health care services through appropriate education of clinicians, patients and their family members. The programme allows development of patient, parent and community education and awareness. Training programmes for clinicians and laboratory workers have been organized and it is expected to improve health care to lighten the burden created by these disorders.
Table 5

Proposed key tasks of the regional office of the WHO Eastern Mediterranean group on haemoglobin disorders and red cell enzymopathies

To describe the regional epidemiology of haemoglobin disorders
To describe the relevant services, the needs and the resources—both current and targeted
To enhance the concept of community genetics, aiming at reducing the genetic contribution to disability, morbidity and mortality
To devise appropriate control programmes that are applicable to the countries in the region
To develop a regionally applicable approach to the management of haemoglobin disorders
To develop and disseminate educational aids and augment the awareness and counselling programmes

![Flowchart]

**Regional and Universal Linkage of the National Programme**

It is pertinent to consider other activities, at regional and universal levels, that are expected to advance our services. The establishment of a regional office for the Eastern Mediterranean Working Group to form one of the international regional chains of WHO working groups on haemoglobin disorders is of obvious relevance. The regional office will comprise members from different countries in the East Mediterranean region. The ultimate goal of the office is the improvement of the delivery of health care in the region. The main specific objectives are outlined in Table 5. A complementary scheme for the interrelation and exchange of experiences are outlined in Fig. 2. Because of their wide geographic spread genetic disorders of blood have attracted cooperation and coordination of complementary efforts between various regions all over the world. Ideally, effective learning experiences and exchange of thoughts need to be a collective effort and to have input from the patient, his family and the community at large. More recently this has become of obvious value and has proved to be applicable at the country level, as well as at the regional level and world wide.

The doctors—patients association, one of the activities of the Thalassaemia International Federation (TIF), has confirmed the value of this method of improving health care delivery and the alleviation of physical and mental sufferings of affected individuals.
Acknowledgement
This work was supported partially by King Abdulaziz City for Science and Technology (Project No. AT-4-074) and partially by King Saud University. I am grateful to members of the SAS and the National Working Groups for their constructive suggestions.

References