

EDITORIAL

The odyssey of diagnosing genetic disorders in evolving health services

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The current issue of the Sudanese Journal of Paediatrics (SJP) contains articles contributed by the authors from six countries and three continents. These cover the fields of nutrition, gastroenterology, infectious diseases, nephrology, neonatology and paediatric neurosurgery.

Three articles highlight the evolution of diagnostic approach for genetic diseases in countries with evolving health services. One of these discusses the importance of pedigree analysis in familial neurological disorders, including epilepsy, psychomotor delay and intellectual disability (ID) [1]. The other one highlights that the karyotype analysis may not be helpful to determine the etiology in children with idiopathic ID [2]. Karyotype analysis is usually performed in children with idiopathic ID as the first step test in medical centres with limited laboratory facilities.

The importance of medical genetics and its vital role in paediatric practice have been acknowledged by the pioneer paediatricians in Sudan. The Late Professor Mahmoud Mohamed Hassan [3], the first qualified Sudanese paediatrician, was the first Sudanese doctor to obtain a post graduate MD from the University of Khartoum (U of K) more than 50 years ago (1965) with a thesis on "Genetic Diseases in Sudanese Children" [4]. Using his clinical skills and basic laboratory investigations,

he managed to describe several genetic disorders for the first time in Africa and Arab Region, including Down syndrome, haemoglobinopathies, Hartnup disease, phenylketonuria and vitamin D dependent type 2 rickets. His report on Down syndrome [5] was published 3 years before the identification of trisomy 21 as the cause of Down syndrome by Lejeune et al. [6]. His delineation of a Sudanese family with five children who had vitamin D dependent type 2 rickets came 1 year before the first description of the disease worldwide [4]. Professor Mohamed Ibrahim A. Omer [7], the first Convenor of Postgraduate Board of Paediatrics and later the Director of Postgraduate Medical Studies Board, was also visionary in establishing a curriculum on medical genetics for the local specialty training in paediatrics. He invited the Late Professor Nemat Hashem, one of the founders of medical genetics in Egypt [8], to teach the genetics course for the first batch of postgraduate students who were chosen to start the local training and degree in paediatrics, offered by U of K. Both Authors joined this course which was delivered in several weeks, and enjoyed having this important and exciting avenue being opened for them. One of us (MAMS) had the privilege of publishing a joint study with Professor Nemat Hashem in SJP [9]. He was also sponsored by U of K to spend one

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month in Prof Nemat Hashem's Department of Genetics in Cairo, Egypt to learn how to draw and analyse an extended pedigree of eight generations, with 15 individuals affected with what turned out to be a novel form of muscular dystrophy [10]. The study was in partial fulfilment of M.P.C.H. (Clinical MD, Paediatrics and Child Health) degree, and was supervised by Prof M. I. A. Omer [11,12]. One of the articles in the current issue of SJP [1] emphasises the importance of pedigree analysis in familial neurological disorders to optimise screening and diagnostic testing, and guide genetic counselling.

Neurodevelopmental disorders and ID, which affects 1%–3% of the global population, have tremendous genetic heterogeneity. The presence of additional clinical signs may help the diagnosing paediatrician to identify a known syndrome, such as Down syndrome, the most common form of ID. A standard karyotype, available in most medical centres with limited laboratory facilities, will reveal the underlying cause in this and other chromosomal disorders. Rare ID syndromes and children with non-syndromic ID constitute a diagnostic challenge and require extensive clinical, laboratory and radiological evaluations; and many of these procedures are invasive and costly. To overcome these challenges, the evolving health services in this Region are rapidly implementing the recently available high throughput genomic sequencing techniques, as shown in the third article on genetics in the current SJP issue [13]. It emphasises the advantage of multi-locus analysis provided by next-generation sequencing over conventional single-gene investigations in uncovering dual molecular diagnoses in patients with phenotype pointing to two clinical diagnoses involving two separate genetic loci. Although the risk of harbouring more than one genetic disease is small, it increases through consanguineous marriage which is prevalent in Sudan and the Region [14].

To decipher the genetic causes of ID, collaborations are vital between clinicians, basic researchers, academic institutes and public health officials. An example of such collaboration is evolving in Saudi Arabia. The Saudi Human Genome Program [15], a national project to study the genetic basis of disease in Saudi Arabia and

the Middle East is funded by King Abdulaziz City for Science and Technology, which also provides funds for several research projects in health institutes. Saudi Arabian universities reached out to collaborate with renowned institutions in the United States and Europe in the field of medical genetics [16]. As a part of these activities, Professor James Watson, one of the two co-discoverers of the structure of DNA and a 1962 Nobel Prize winner for Physiology or Medicine, was invited by King Saud University (KSU), Riyadh to give lectures and meet with KSU research committees (Figure 1) [17]. Professor Watson provided KSU researchers, during this visit, with valuable encouragement and told them that their goals in research should be ambitious, to make a difference both locally and worldwide.

These collaborative efforts proved to be quite fruitful and accelerated novel candidate gene discovery in neurogenetic disorders, including ID [18]. In addition to established ID genes [19], novel ID-related variants were also discovered



Figure 1. The International Editor of the Sudanese Journal of Paediatrics (Prof. Mustafa A. Salih) in a discussion with Professor James Watson, one of the two co-discoverers of the structure of DNA and a 1962 Nobel Prize winner for Physiology or Medicine, during a meeting with the College of Medicine Research Center Board. Prof. Watson was invited by King Saud University (KSU), Riyadh, Saudi Arabia to give lectures and meet with KSU research committees in January 2010 [17] (Photo taken by the Audiovisual Unit, College of Medicine, KSU).

[20–23]. Because of its prevalence and the need for demanding support services, ID is an important public health issue. Its management requires early diagnosis to enable condition-specific intervention which can withhold further deterioration in certain conditions [22]. Early diagnosis also leads to timely access to health care and appropriate supports. It also guides appropriate genetic counselling to prevent multiple recurrences of the condition in the family, which is commonly seen in this Region [24]. Identifying pathogenic variants in the family allows for prenatal diagnosis for pregnancies at increased risk and pre-implantation genetic diagnosis leading to a happy end to the odyssey of these families [25]. In Sudan, childhood-onset neurogenetic disorders were investigated using first generation sequencing a decade or earlier ago. This has been through collaborative work between the Department of Paediatrics and Child Health, College of Medicine, the Institute of Endemic Diseases, U of K, and university research centers in Europe. These studies [26–28] had rewarding results leading to the use of appropriate therapies and informed genetic counselling. Human cytogenetic research (cytogenetic and FISH analyses) involving children with dysmorphic syndromes was pioneered by Sudanese researchers in collaboration with the Department of Clinical Genetics, University Hospital, Lund, Sweden [29]. Application of next generation sequencing was later pioneered by the Department of Biochemistry, U of K in collaboration with research centers in France and USA. As a result, the diagnostic odyssey of several familial cases of childhood-onset neurodegenerative disorders came to an end in an ongoing collaborative research with the Department of Paediatrics and Child Health, College of Medicine, U of K [30–32].

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