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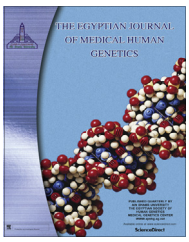

ORIGINAL ARTICLE

Challenges identified in the management of patients with inherited metabolic disorders – A five year experience from Pakistan

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Abstract *Background:* Pakistan is the sixth most populous country in the World. High rates of consanguinity and inter caste marriages have resulted in a substantial burden of inherited metabolic disorders (IMDs). Despite this load, there is a dearth of both medical genetic and clinical metabolic services in Pakistan. There are inadequate numbers of appropriately trained clinicians, ill-equipped laboratories, lack of scientists and technologists equipped with skills to deal with the challenging laboratory investigations involved in IMD and a health care infra-structure unable to support a service.

Aim: We present the first five year experience of the first established metabolic unit at a tertiary care hospital in Pakistan and present the case for screening of parents, parents' siblings and antenatal diagnostic testing in subsequent pregnancies in order that families can make informed choices in preventing recurrence.

Subjects and methods: This retrospective observational study comprising of patients' chart review was conducted in the Department of Paediatrics, AKUH Karachi in Pakistan for patients who presented to the Clinical Genetics unit from January 2008 to December 2012 seeking diagnosis and treatment for the underlying IMD.

Results: We evaluated 426 children, of which, 333 (78%) had consanguineous parents. Most patients, 151 (35%). evaluated for IMD were between 1 year and 5 years of age. Developmental delay, seizures, hypotonia, microcephaly, neuroregression, dystonia, ataxia and encephalopathy

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were the most common reasons for referrals. Only 155 (36%) patients underwent metabolic biochemical testing. Among the investigated group of patients, diagnoses were established for 85 (55%) patients equivalent to only 19.8% of the total.

Conclusion: Neonatal screening for IMDs and their treatment in the current situation is an unaffordable practical option in Pakistan. Screening parents, siblings and subsequent pregnancies, however, is likely to provide a cost effective and acceptable alternative in reducing the burden and enabling early, effective detection of affected progeny before the stage when neurometabolic changes become irreversible in developing countries like Pakistan with very limited resources.

1. Introduction

Inherited metabolic disorders (IMDs) encompass a group of disorders due to defective metabolic processes. The Cumulative incidence of IEMs varies between 1 in 1400 in British Columbia [1] and 1 in 3000 in Germany [2]. The measured prevalence in a particular country depends on the population selected for screening and the method employed for screening for IMDs. With the drop in communicable diseases in developed countries, a demographic switch from communicable diseases to genetic disorders is being observed in many developed countries. However, establishment of programs for the systematic detection of IMDs in developing countries has been a challenging process [3]. Pakistan faces major health challenges with high population growth, fertility, and high infant and under-five mortality. There is uncontrolled burden of communicable diseases with an increasing problem of non-communicable diseases, which comprised 44% of top 10 causes of mortality/-morbidity in 2010 [4]. This has resulted in not only lack of government commitment to invest in this orphan group of diseases but also instilled a belief among physicians in Pakistan that IMDs are rare diseases, which are untreatable and the feeling that creating a service does not represent a good use of already overstretched resources.

The objective of this descriptive study is to report the five year experience of the first established metabolic unit at a tertiary care hospital in Pakistan. We describe the spectrum of IMDs seen, challenges faced in reaching a diagnosis, and difficulties encountered in treatment and follow-up. We also propose some tangible solutions to the unique challenges faced in establishing genetic and metabolic services in Pakistan.

2. Pakistan and its health care structure

Pakistan is a South Asian country and the sixth most populous nation in the World, having a population of over 184 million [5]. The country has four provinces; Punjab, Sindh, Khyber Pakhtunkhwa and Balochistan. The population comprises of six major ethnic subsets including Punjabis 44.68%, Pathans 15.42%, Sindhis 14.1%, Sariakis 8.38%, Muhajirs 7.57%, Balochis 3.57% and others 6.28%. Punjabis and Sariakis are mostly residing in Punjab province, Sindhis and Muhajirs in Sindh province, Pathans in Kyber Pakhtunkhwa and Balochis in Balochistan province [6]. Consanguineous marriages and endogamy are prevalent in Pakistan irrespective of socio-economic and educational background of different ethnicities. Consanguinity is present in 65% of all marriages [7] and is a major contributor to both early and late morbidity and mortality [8].

The WHO has identified Pakistan as one of 57 countries with critical shortages of health care providers across the globe [3]. The physician to 1000 person ratio in Pakistan is 0.8 as compared to 2.4 in USA [9] and the total per capita health expenditure for Pakistan is USD 39 as compared to USD 8895 in USA [10]. Health care management in Pakistan is primarily the responsibility of the provincial government. However, planning and formulation of national health policies are under the federal government's control. The health care system is dichotomized into a small under-utilized public sector financed by the state and a large independent for profit private sector that accounts for 80% of all outpatient health care [11], for which patients have to pay out of pocket. Thirty-four percent of the population is urban having some access to effective health care services [12].

3. Current status of inherited metabolic disorders in Pakistan

Infant and under five mortality rates of Pakistan are 74 per 1000 and 89 per 1000 live births [7]. Birth asphyxia, still birth, pneumonia, diarrhea, sepsis, neonatal tetanus and congenital birth defects are attributed major causes of neonatal and infant mortality in developing countries [13]. Partly as a result of the attention afforded to these problems, IMDs have been relatively ignored by both the government as well as the private sector. There is no national birth defect or metabolic diseases registry established in Pakistan nor is there a newborn screening program for any IMD in any of the four provinces. Before 2013, only rudimentary metabolic testing was available and though this has recently marginally expanded, there is little clinical expertise available for diagnosing and treating patients with IMDs. Treatment options in the form of food for special medical purpose (FSMP) and the availability of orphan drugs is a constant challenge. These factors have resulted in a difficult situation for physicians, parents and families many of whom are faced with a gloomy prognosis when given a diagnosis of a 'non-specific IMD' with little or no counseling about the prognosis or inheritance of the disease. Consequently, most cases are undiagnosed and result in either death or irreversible psychomotor retardation.

In this backdrop, the Clinical Genetics Unit was established by the Department of Paediatrics and Child Health, Aga Khan University in October 2007. Housed with a trained staff geneticist, it is the only nationwide institute providing comprehensive and evidence based medical care to patients with IEMs. The Aga Khan University Hospital (AKUH) is a