Case Report

Diagnosis of Hunter Syndrome (Mucopolysaccharidosis Type II) in a Resource-Limited Setting: A Case Report from Zambia

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ABSTRACT

Hunter Syndrome [Mucopolysaccharidosis (MPS), type II] is a rare genetic disorder arising from a deficiency in the enzyme Iduronate 2-sulphatase. This deficiency leads to the accumulation of glycosaminoglycans (GAGs) dermatan sulphate and heparan sulphate. The GAGs accumulate both intracellularly and extracellularly, leading to abnormalities in different organ systems in the body. The definitive diagnosis of Hunter Syndrome requires biochemical methods which can be a challenge in resource-limited settings, Zambia included. Presented here is a case of Hunter Syndrome in a 12-year-old male child and highlight clinical acumen plays a big role in making the diagnosis and distinguishing different types.

INTRODUCTION

Mucopolysaccharidoses (MPSs) are inherited metabolic disorders caused by the absence or malfunction of the lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs).[1] Over time, the GAGs collect in the tissues and cause irreversible and progressive cellular damage that results in facial dysmorphism as well as systemic organ changes such as organomegaly, pulmonary dysfunction, myocardial enlargement and neurological impairment that results in impaired learning and intelligence.[2]

Eleven distinct single lysosomal enzyme deficiencies are known to cause seven different and recognised phenotypes of MPS.[3] All of these are inherited as autosomal recessive conditions except for Hunter Syndrome, which is inherited as X-linked recessive.[3] Among this group of disorders, Hunter Syndrome is one of the rare conditions with a prevalence of 1:100 000 to 1:170,000 cases.[2,4,5]

There are two types of Hunter Syndrome. Type A is the severe form with a life expectancy of 14-15 years and a much earlier onset, while type B is mild with a life expectancy of 30-50 years[4]. The syndrome is characterised by decline growth, changes in facial features called "gargoylism", skeletal anomalies (multiple dysostoses), obstructive airway conditions such as obstructive sleep apnoea, hepatosplenomegaly, joint stiffness and progressive conductive or neurosensory deafness.[4] Historically, treatment of MPS Type II has been largely supportive, usually involving a multidisciplinary approach.[2] However, in recent years, the use of enzyme replacement (as weekly or biweekly intravenous injections of recombinant human

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enzyme) has shown some improvement in patients in terms of joint mobility, walking ability as well as respiratory function and overall survival rate. Reported here is a 12-year-old male child with Hunter Syndrome, highlighting its rarity and the definitive features that may be of use in the making of a diagnosis in a resource-limited setting.

CASE PRESENTATION

A twelve-year-old male child referred from a rural area in the Eastern part of Zambia, more than 700 km away from Lusaka, presented with history of poor growth and development, short stature and inability to speak comprehensively. The informants, both parents, cited behavioural challenges like hyperactivity, inattention and wandering about and being lost from home. He had insomnia and snored when sleeping. They were also concerned with the shape of the head.

The patient was born out of a non-consanguineous marriage. Pregnancy, birth and neonatal period were unremarkable. However, the parents had noted a short neck and a big head from his early neonatal age. Apart from head control, which was achieved at six months, all the gross motor developmental milestones had been achieved typically.

By the age of two years, he was noted to have delayed speech and had behavioural problems like crying inconsolably, being aggressive and became destructive and disruptive. He was toilet trained by three years but lost this skill by four years and is now in diapers.

He is the fifth born of eight living children and there is a history of two paediatric deaths. One died from severe dehydration at the age of 2 years and the other died suddenly following a febrile illness at the age of two years. The parents are peasant farmers.

On examination, the height for age and sex was less than -4SD and had dolichocephaly with coarse facial features and prominent large ears (Figures 1 and 2). He had neither pallor nor cyanosis with discoloured carious teeth, bruxism, drooling, and fidgety. He was constantly wailing with no intelligible words and was being restrained by the parents. Eye contact was very brief. Examination of the eyes revealed clear corneas and confrontation test was positive. Distraction test was positive. He had increased tone in his upper limbs with contractures at the elbows and a claw hand deformity on both wrists. The respiratory and cardiovascular systems were unremarkable. The abdomen was protuberant with a huge reducible inguinal hernia, hepatomegaly of 7 cm and splenomegaly of 3 cm below the coastal margin. Other physical findings of note were short neck and chest with horizontally inclined ribs, kyphosis with a gibbus at T10 to L1 (Figure 3).

Full Blood Count revealed a mild microcytic hypochromic picture and HIV test was negative, Chest X-ray showed the oar-like ribs (Figure 4) which are characteristic of the dysostosis multiplex, a typical finding in HS. X-rays of the tibia and fibula revealed early osteofibrous changes (Figures 5a,5b). On Echocardiography, both the anatomy and the function of the heart were normal. Computerized Tomography Scan of the brain showed thickened calvarium and hydrocephalus (Figure 6).

A multidisciplinary approach was used to evaluate and manage the patient and included the otolaryngologists, ophthalmologists and child neurologists. The otolaryngologists reported normal audiometry testing, with obstructive airway disease due to adeno-tonsillar hypertrophy. There was no evidence of corneal clouding and visual acuity was not impaired. The fundi were not examined under anaesthesia as the parents declined. Methylphenidate was prescribed for the inattention and hyperactivity but was unavailable at the time and Haloperidol was prescribed instead with Diazepam for insomnia. By day 2 of taking Haloperidol, he was more settled and began to obey commands. A multidisciplinary intervention assessment was done by the physical, occupational, behavioural and speech and language therapists. An intervention plan was made, but the parents opted to leave the hospital against medical advice. These services are limited outside the capital Lusaka. As in other resource-limited countries, enzyme replacement, stem cell transplant or gene therapy are unavailable in

Zambia.

DISCUSSION

There are two main types of HS, a mild and severe form but in reality, the signs and symptoms observed vary according to disease severity and are best described as a continuum between the two extremes.[7] As it is X-linked, it occurs mostly in males with only a few females, possibly by the process of X-chromosome inactivation. In such females, it occurs with equal severity.[8]

Diagnosis of HS is usually prompted by clinical signs. Children with HS appear normal at birth and onset of symptoms is often insidious with signs and symptoms often overlapping with common childhood conditions. Therefore, early diagnosis before irreversible organ and tissue damage occurs, which is important usually does not happen. Where available early treatment with enzyme replacement therapy results in the greatest benefit in children who receive it before any organ or tissue damage.[9] The average age of onset of symptoms is around 2.5 years for severe forms and 4.3 years for those with less severe disease.[10] Our patient had already started showing features of the disease by 2 years and suggesting that he had severe form of HS. With late diagnosis, some children die without a diagnosis. The parents of this patient lost two children, both male though it is difficult say if these children had HS.

Definitive diagnosis in our case was not done although all clinical features (coarse facial features, typical skeletal anomalies, neuro-degeneration and organomegaly) were suggestive of either MPS I (Hurler Syndrome) or HS. The lack of corneal clouding however made HS more likely. Laboratory diagnosis is based on the presence of urinary GAGS dermatan sulphate and Heparan sulphate. An increased amount is highly suggestive of MPS and definitive diagnosis is made by measuring serum or white blood cell levels of Iduronate 2 sulfatase (I2S). Genetic testing is also definitive but is not available in Zambia. In so far as treatment (enzyme replacement therapy) is concerned, several disadvantages such as the burdensome need for weekly intravenous injections, serious side effects such as inhibitor/antibody formation and anaphylaxis as well as the prohibitive cost make it an impractical choice in everyday clinical practice[6].

The learning points are two-fold: one, it is important for clinicians to have good clinical acumen that will be of use not only in the identification of gross categorizations of disease conditions but also in the knowledge of how specific disease conditions present one from another. This way, the management of patients is minimally affected by the lack of a definitive diagnosis. Secondly, HS is a rare condition requiring multi-disciplinary and highly specialised care. The mission of the Ministry of Health, Zambia, is to provide equitable access to cost-effective quality health care services as close to the family as possible.[12] However, the starting point is for health workers to recognise the rare conditions and refer early.

Therefore, advocacy and sensitisation are needed so that conditions such as HS are recognised and given the attention they deserve in terms of clinical dexterity and human expertise, infrastructure development and medical care advancement. It is hoped that clinicians across the country will take the lead in referring children with peculiar or rare conditions to centres where they would be evaluated further as was in this patient. A national registry of rare conditions is suggested and this can create a need to have basic tests in-country or probably collaborate in a systematic way with international centres.

The challenges faced in resource-limited countries in making diagnosis and treatment of rare conditions are not unique to Zambia.[1,11] In a country such as ours where the heavy burden of diseases like Malaria, HIV/AIDS, tuberculosis and malnutrition take precedence and gobble the bulk of the resources, rare conditions remain uninvestigated. It is therefore very difficult to navigate the terrain with uncommon disease conditions such as HS. Both public and private laboratories were not able to process our requests for urinary GAGs, serum I2S or skin fibroblast levels of I2S. In addition, laboratories

abroad were contacted but this did not result in any positive outcome. Furthermore, the new treatment modalities like enzyme replacement therapies are extremely expensive.

CONCLUSION

This case of HS demonstrates that there are cases of rare diseases and conditions of childhood in sub-Saharan Africa. However, to make the definitive diagnosis while practising in resource-limited countries poses a great challenge and most of these children are without a diagnosis. Clinicians need to have a high index of suspicion and know the clinical symptoms and signs of these rare genetic conditions and put them on a national register. Most patients do not have all the therapies necessary to improve the quality of life, let alone cure patients with rare conditions and HS is one such rare disease. Collaborations between countries and institutions that offer these services need to be enhanced to improve the quality of life of these children.

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CONFLICT OF INTEREST

The authors have no conflicts to declare.

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