Striking a delicate balance: ethical considerations and promising advances in timely diagnosis and patient safety for Hunter syndrome

Najia Sadiq[1], Osaid Ahmed[2], Fareeha Ubaid[3]

Abstract

Hunter syndrome (HS) is a rare X-linked lysosomal storage disease that poses a significant challenge to affected individuals and healthcare professionals. HS is characterised by MRI scans that often show extensive white matter changes as well as dilated perivascular spaces, despite apparently normal intellectual skills. HS requires early diagnosis to initiate enzyme replacement therapy and potential improvements in patients' outcomes. However, using intrusive methods to diagnose patients has serious ethical problems. Seeking early diagnosis and effective treatment for HS necessitates a careful balancing act among the advancement of medical research, the prioritisation of patient safety, comfort, and resolving moral dilemmas. We can give these individuals hope and improved outcomes by creating non-invasive biomarkers, improving upon existing diagnostic methods, and looking into novel treatment approaches. Programmes that prioritise early identification and screening in underserved areas, raise awareness and ensure equitable treatment for all HS-affected individuals can also help close the gap.

Keywords: Biomarkers, Hunter's syndrome, Mucopolysaccharidosis II, Enzyme Replacement Therapies, Ethical Issues.

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Introduction

Hunter syndrome (HS) or mucopolysaccharidosis type II (MPS II) is an X-linked lysosomal storage disorder caused due to deficiency of iduronate-2-sulfatase (IDS), leading to accumulation of glycosaminoglycans in tissues and organs.[1] HS poses a significant challenge to affected individuals, as well as for researchers and medical practitioners. Considering how severely life is gradually worsened and overshadowed by the unrelenting advancement of symptoms, such as coarse facial features, nervous system abnormalities, breathing issues, and so on. Individuals and families impacted by HS suffer this painful reality. However, using intrusive methods to diagnose patients has serious ethical problems.

HS primarily affects males meaning that the faulty gene responsible for the disease is located on the X chromosome, having an incidence rate in males ranging from 0.38 to 1.09 per 100,000 live male births.[2] This leads to the accumulation of complex sugars called dermatan sulphate and heparan sulphate in cells throughout the body. Heparan sulphate tends to damage the central nervous system (CNS), whereas dermatan sulphate is responsible for connective tissue damage.[3] This gradual accumulation of sugars disrupts normal cellular function and causes a variety of symptoms that worsen over time. Characteristic signs and symptoms of the early severe MPS-II phenotype usually develop between 18 months and four years of age and include inguinal and umbilical hernia, frequent respiratory infections that lead to hearing impairment, macrocephaly, macroglossia, coarse facial features, bone dysplasia with joint stiffness, and claw-like shaped hands.[4]

Regarding the epidemiology of HS, it is known that Saudi Arabia provided the highest frequency of overall MPS because of regional or consanguineous marriages (or founder effect), followed by Portugal, Brazil, the Netherlands, and Australia.[5] Early diagnosis is crucial for initiating enzyme replacement therapy and potential improvements in patient outcomes. However, there are a few issues with the gold standard for diagnosis, which uses a bone marrow sample to analyse enzyme activity. Given the discomfort of the procedure and the risks of bleeding and infection, there are moral concerns regarding the patient's well-being.

It could be necessary to screen siblings in families with a history of HS for carriers or potential cases. When a healthy child undergoes an invasive surgery, there exists a grave ethical quandary since there exists a possibility

[1,2]4th Year MBBS Student, Jinnah Sindh Medical University, Karachi, Pakistan.
[3]Department of Obstetrics and Gynaecology, Dow University of Health Sciences, Karachi, Pakistan.
Correspondence: Osaid Ahmed **Email:** osaid.ahmed803@gmail.com
ORCID ID: 0009-0001-5623-9577

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that the risks associated with the diagnostic process will exceed the benefits of early detection. The issue exacerbates and worsens when one considers the potential for diagnosing children who are not affected. In families with a history of HS, there might be a need to screen siblings to identify carriers or potential patients. Subjecting a healthy child to an intrusive procedure creates a significant ethical dilemma.

Hunter Syndrome must be diagnosed as soon as possible in order to start the right treatment and enhance recovery outcomes for betterment of the patient. However, diagnosis presents significant challenges because of lack of testing facilities in developing countries like Pakistan. Even in patients with attenuated diseases, cranial magnetic resonance imaging (MRI) scans are often grossly abnormal, with extensive white matter changes as well as dilated perivascular spaces, despite apparently normal intellectual skills.[6] Furthermore, the gold standard for diagnosis, which involves taking a bone marrow biopsy to measure enzyme activity, is invasive, risky and fraught with ethical issues. With the recent development of new medications for HS, improved and favourable outcomes are anticipated. In 2006, the US Food and Drug Administration (FDA) approved intravenous (IV) infusion of idursulfase (Elaprase), Shire Human genetic therapies (HGT) for enzyme replacement therapy (ERT) in confirmed MPS-II patients 5 years and older.[7] ERT is a remarkable form of treatment in which patients receive I2S, an enzyme that may be missing or malfunctioning in HS. Enzyme replacement therapy has produced good results in terms of lowering certain symptoms and improving overall quality of life. Another innovative therapeutic strategy is gene therapy, which addresses the underlying genetic problem by giving the patient's cells, functional copies of otherwise damaged genes. The encouraging results obtained allowed the realisation of many preclinical studies investigating the utilisation of gene therapy vectors in animal models of MPS-II, together with a phase I clinical trial approved for Hunter patients affected by the mild form of the disease.[8] Researchers are also looking into chaperone therapy, which stabilises the defective enzyme and improves its function using microscopic molecules. These state-of-the-art treatments hold great potential for treating the underlying cause of HS and improving patients' long-term outcomes. However, more research, clinical studies, and regulatory clearances are needed to demonstrate their efficacy, safety, and long-term benefits.

HS must be combatted using an array of strategies. Minimising patient discomfort and potential injury throughout the diagnostic process is equally critical as early diagnosis. Research on non-invasive biomarkers must be funded, and current techniques need to be continuously improved. Only then will it be possible to swing the odds in favour of these defenceless patients. Disease manifestations progress over time, leading to significant morbidity and early mortality.[9,10]

There is potential for addressing the shortcomings of the existing diagnostic techniques through the search for non-invasive biomarkers. Blood or urine sample analysis is being investigated by researchers, which could lead to sooner and less stressful diagnoses. Diagnosis of the disease is usually by clinical presentation and skeletal survey.[11] This method is also invasive for patients and not as reliable compared to biopsy as appearance changes appear later. For guaranteed accuracy, these methods still need to be further validated and studied as they are still in their infancy phase and not that reliable.

Apart from non-invasive biomarkers, exploring alternative methods such as needle aspiration or specific blood cell analysis could offer a middle ground between accuracy and patient safety. Striking a delicate balance between diagnostic precision and minimising patient distress is paramount in the pursuit of ethical healthcare practises.

Discussion

Hunter syndrome's treatment accessibility and cost concerns must be addressed even in the case of promising advancements. For patients and their families, the exorbitant expense of enzyme replacement therapy and other cutting-edge treatments can be a major obstacle and hindrance. It is imperative that healthcare practitioners, pharmaceutical corporations, and legislators collaborate to guarantee that individuals in dire need get access to these life-changing treatments. In addition, programmes aimed at raising awareness, prioritising early detection and screening in marginalised areas can aid in closing the gap and guaranteeing fair treatment for all those impacted individuals by HS.

Abbreviations: Hunter syndrome (HS), mucopolysaccharidosis type II (MPS II), iduronate-2-sulfatase (IDS), magnetic resonance imaging (MRI), Food and Drug Administration (FDA), enzyme replacement therapy (ERT), Human genetic therapies (HGT).

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