Challenges of diagnosis and management of Hunter syndrome in a resource-constrained setting: a case series of two siblings in Nigeria

Amalachukwu Okwukweka Odita[1*], Ekene Fidelis Enema[2], Ngozi Ojinnaka[3]

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ABSTRACT

Hunter syndrome (HS) (MPS-II) is a rare X-linked lysosomal storage disorder caused by iduronate-2-sulfatase deficiency, resulting in glycosaminoglycan (GAG) accumulation and multisystem dysfunction. It predominantly affects males, leading to skeletal deformities, neurocognitive decline, organomegaly, and distinctive facial features. The impact of HS in Nigeria and resource-limited settings is far-reaching due to diagnostic obstacles, underreporting, and limited access to specialized care. This report elucidates the clinical presentation, diagnostic difficulties, and management of two siblings (10 years, 6 years) diagnosed with HS in Southeast Nigeria years after the onset of symptoms. Their clinical histories, physical examinations, laboratory investigations, and treatment modalities were systematically documented and analyzed. Both siblings displayed characteristic clinical features of HS: coarse facial features, macroglossia, skeletal deformities, hepatosplenomegaly, and developmental regression. The older sibling had a more severe expression of the disorder. Urinary GAG levels, particularly heparan sulfate, were elevated with significantly reduced iduronate-2-sulfatase levels. Cranial imaging showed cerebral atrophy, hydrocephalus, and multi-suture synostosis. With financial constraints, confirmatory genetic testing, enzyme replacement therapy (ERT), and gene therapy were not accessed, leading to symptomatic management instead. HS is underdiagnosed and underreported in Nigeria, primarily due to insufficient clinical awareness, lack of newborn screening, and financial barriers to diagnostic and therapeutic access. This case series highlights the urgent necessity for enhanced awareness among healthcare providers, early identification of clinical features, and advocacy for accessible genetic testing and ERT. International collaborations are essential for optimizing care and improving outcomes for individuals affected by rare genetic disorders in low-resource environments.

Keywords: Hunter syndrome, mucopolysaccharidosis type II, low-resource setting, enzyme replacement therapy, case series

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Correspondence to: Amalachukwu Okwukweka Odita
*Department of Paediatrics, Nnamdi Azikiwe University, Awka, Nigeria
Email: ao.odita@unizik.edu.ng
Full list of author information is available at the end of the article.

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Background

Hunter syndrome (HS) also known as mucopolysaccharidosis type II (MPS II) is a rare X-linked lysosomal storage disorder caused by a deficiency of the enzyme iduronate-2-sulfatase (I2S). This enzyme is responsible for the degradation of glycosaminoglycans (GAGs), specifically dermatan sulfate and heparan sulfate. The enzyme deficiency results in the progressive accumulation of GAGs in various tissues, leading to multisystem dysfunction [1]. HS primarily affects males and manifests with a broad spectrum of clinical features, including coarse facial features, hepatosplenomegaly, joint contractures, developmental delay, and progressive neurodegeneration in severe cases [2]. Depending on the genetic variations in mutation on the long arm of chromosome X, two main phenotypes of HS have been described which are "Severe" and "Attenuated" phenotypes with varying presentations existing in a spectrum between these two phenotypic ends. About 60%-75% of affected people have the severe phenotype of the disease, and they often develop normally within the first 2-4 years before the onset of cognitive decline, behavioral changes, hearing loss, speech delay, and epileptic seizures. Patients with the attenuated phenotype of the disease have less prominent clinical manifestations and have the neurological system preserved. These patients often present before the age of 10 years [1].

The global prevalence of HS is estimated to range from 1 in 100,000 to 1 in 170,000 live male births [3]. However, a recent study reported an incidence as high as 1 in 73,290, suggesting that MPS II may be more common than previously recognized, with a higher prevalence of attenuated cases [4]. The prevalence of HS varies from country to country depending on genetic predisposition, consanguinity, access to testing, accurate diagnosis, and reporting. With the introduction of mucopolysaccharidosis into the newborn screening programs in some developed countries like the US, more cases have been identified [4,5]. Data on its epidemiology in sub-Saharan Africa are scarce with

few reported cases in Kenya [6], Zambia [7], Tunisia [8], and Nigeria [9-11]. Limited awareness, lack of diagnostic facilities, and the absence of newborn screening programs contribute to underdiagnosis and delayed identification of affected individuals in low-resource settings. Additionally, many children with HS experience significant morbidity and early mortality due to the lack of access to definitive enzyme replacement therapy (ERT) and supportive multidisciplinary care [6].

The diagnosis of HS is primarily clinical, supported by biochemical assays measuring urinary GAG levels and enzyme activity in leukocytes or fibroblasts. Genetic testing provides a confirmatory diagnosis, but its availability in many developing countries remains a challenge [7,11]. ERT with idursulfase has been shown to improve somatic symptoms and quality of life in affected individuals when introduced early [12], but it remains prohibitively expensive and inaccessible to most patients in resource-limited settings such as Nigeria. Another limitation of the use of intravenous ERT is that it does not cross the blood-brain barrier. Regrettably, clinical studies that explored the intrathecal ERT administration and intracerebroventricular ERT despite having better CNS penetration did not produce significant improvement on cognition [13,14], so where available, hematopoietic stem cell transplantation (HSCT) is preferred to ERT as a treatment option for the neuronopathic form of MPS II with documented improvements in cognitive, language, and motor skills over time [15,16]. Another novel treatment strategy, with ongoing clinical trials, is brain-targeted hematopoietic stem cell gene therapy (HSCGT), which involves the insertion of a functional copy of the missing IDS gene (responsible for the disease) into the patient's bone marrow stem cells. These modified cells can produce the deficient enzyme, which crosses the blood-brain barrier with promising results in addressing the neuropathological consequences of the condition [14,17].

This article presents a case series of two siblings diagnosed with HS in a tertiary hospital in southeastern Nigeria. It highlights the clinical presentation, diagnostic challenges, and management limitations faced in a low-resource setting. Informed consent and ethical approval (FMC/OSHA/ETH.C/073/010) were obtained. By documenting these cases, we aim to raise awareness among healthcare professionals and advocate for improved diagnostic and treatment strategies for lysosomal storage disorders in Nigeria and other low-income regions.

Case Series

This is a descriptive case series of two siblings with MPS type II. Data on sociodemographic characteristics, clinical history, examination findings, investigation results, and management are described below and summarized in Table 1.

Case 1

Sibling A, a 10-year-old male from non-consanguineous parents, presented at 4 years with a large head, abnormal limb development, and frequent respiratory infections. The mother observed that he differed from his siblings and was underperforming academically. His pregnancy and neonatal history were unremarkable, with no similar symptoms in his two female siblings and no family history of such features. Key examination findings included coarse facial features, normal height, prominent chest wall, hepatomegaly, umbilical hernia, and widely spaced lower jaw teeth (Figure 1).

Investigations, including thyroid function tests and imaging, yielded normal results except for dysostosis on X-ray. The child defaulted from follow-ups for three years, during which his condition deteriorated, leading to his transfer to a special needs school and exploration of various therapies, which were ineffective. A brain CT scan revealed significant cerebral abnormalities and hydrocephalus.

After a year of lost follow-up while institutionalized, at age 8 years, he remained incontinent, exhibited limited speech capabilities, and developed hearing impairment. Additional examinations indicated macroglossia, drooling, below-average height, and cognitive impairment, ultimately resulting in a referral to a pediatric neurologist who made the diagnosis of mucopolysaccharidosis.

Urinary mucopolysaccharide screening indicated elevated GAG levels, predominantly heparan sulfate, alongside reduced iduronate-2 sulfatase levels. Attempts to initiate enzyme replacement therapy with Elaprase were unsuccessful due to availability and cost constraints, worsening symptoms over the subsequent two years including progressive hearing loss and mobility issues. He is currently receiving symptomatic management and is being connected to Hunter syndrome support groups, with counseling provided regarding prognosis and treatment alternatives.

Case 2

Sibling B, a 6-year-old male, exhibited developmental similarities to his older brother, presenting with various physical and cognitive impairments. He demonstrated coarse facial features, thickened nostrils and lips, joint stiffness, skin thickening, urinary incontinence, academic difficulties, and speech defects. In contrast, his older female siblings exhibited normal development, with no familial history of similar conditions.

The mother observed abnormal forearm curvature at 10 months, with joint stiffness and delayed grasping noted by 1 year. Concurrently, he displayed macrocephaly and skin thickening, alongside underdeveloped, slurred speech, academic struggles, and delayed continence. There was no indication of hearing loss, and the pregnancy and neonatal periods were uneventful.

Table 1*. Comparison of features in both siblings.*

	SIBLING A	SIBLING B
Age at onset	Mother was not sure	10months
Age at diagnosis	8 years	4 years
Current age	10 years	6 years
Key clinical features Speech	Poor speech development. Currently unable to talk	Higher word count and can engage in minimal conversation though speech is slurred
Height for age (z-score)	Unable to read or write	Can chant nursery rhymes and write 1-10
	–3 (less than 3rd percentile)	–1 (25th percentile)
BMI (z-score)	1	>2
Diagnostic milestones Brain CT scan	Bilateral multifocal encephalomalacia, cerebral volume loss, communicating hydrocephalus, multi-suture synostosis	Multifocal encephalomalacia, Hypoplastic inferior cerebellar vermis, sagittal suture synostosis
Screening urine test	Markedly elevated urinary GAGs 26.7mg/mmol/ creatinine	Markedly elevated urinary GAGs 32.8mg/mmol/ creatinine
Diagnostic urine test	Predominantly heparan sulfate	Heparan sulfate
Enzyme assay	Reduced iduronate-2 sulfatase level 5.2µmol/l (13.8 -25.4)	Low serum iduronate-2 sulfatase
Genetic testing	Not available	Not available
Management approaches	Counselling, symptomatic treatment, ERT (unavailable, not affordable), attempts to link parents to support groups in developed countries	Counselling, symptomatic treatment, ERT (unavailable, not affordable), attempts to link parents to support groups in developed countries
Disease progression	Withdrawn from conventional school and institutionalized	Withdrawn from school temporarily because of bullying but currently back to conventional school
	Easy fatigability	Activity level: fair
	Difficulty walking and unable to feed self due to stiff joints	Walks unaided
	No seizures	No seizures
	Hearing impairment	Can hear
	Prolonged episodes of fever and recurrent respiratory infections	

Clinical examination revealed coarse facial features, frontal bossing, a broad nasal bridge, macroglossia, spaced teeth, brachydactyly , and limited joint movement (Figure 2). He presented with abdominal distension, hepatosplenomegaly, and an umbilical hernia, while height-for-age measurement was initially normal. EEG results indicated generalized seizure activity, but clinically there were no seizures. Urinary mucopolysaccharide screening showed elevated GAG levels, particularly heparan sulfate.

A multidisciplinary approach was adopted, involving genetic counseling, social support, physiotherapy, and management of complications. Parents received guidance on prognosis and reproductive options due to concerns about future male offspring. Financial limitations hindered access to genetic testing and ERT.

Discussion

This is the first case series of HS in Nigeria, and incidentally, it involves two siblings. There have been 3 other case reports within the last 20 years [9-11]. The absence of a national newborn screening program, poor awareness among health workers, lack of specialized diagnostic facilities, and early mortality from complications may account for underdiagnosis or misdiagnosis of affected patients. Cultural beliefs about the causes of "strange" diseases influence parents to seek traditional care or exorcism as was the case here until a definitive diagnosis was made.

The index case series describes two siblings with HS who presented with classical clinical features of coarse facial features, skeletal dysostosis, hepatosplenomegaly, and neurodevelopmental delays which align with previously reported cases [6,10]. However, while both siblings exhibited features of the severe phenotype, their presentations varied in severity. The older sibling experienced profound cognitive impairment, poor communication, and incontinence, while the younger sibling demonstrated comparatively milder neurocognitive involvement. Such variability within affected individuals has been well-documented and is attributed to the spectrum of mutations affecting the IDS gene [1,3,8,18].

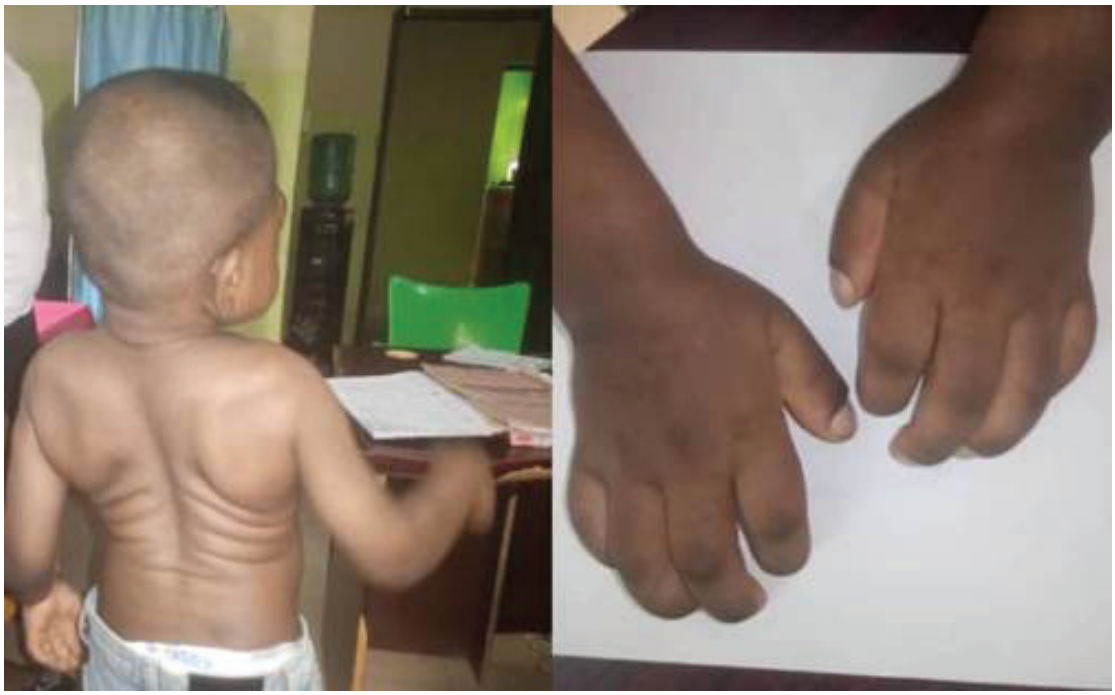

Figure 1. *Displaying characteristic features of macrocephaly, thickening of the scalp with pebble-like nodules, short stature with a broad chest, and claw-shaped hands (joint stiffness and contractures) in HS.*

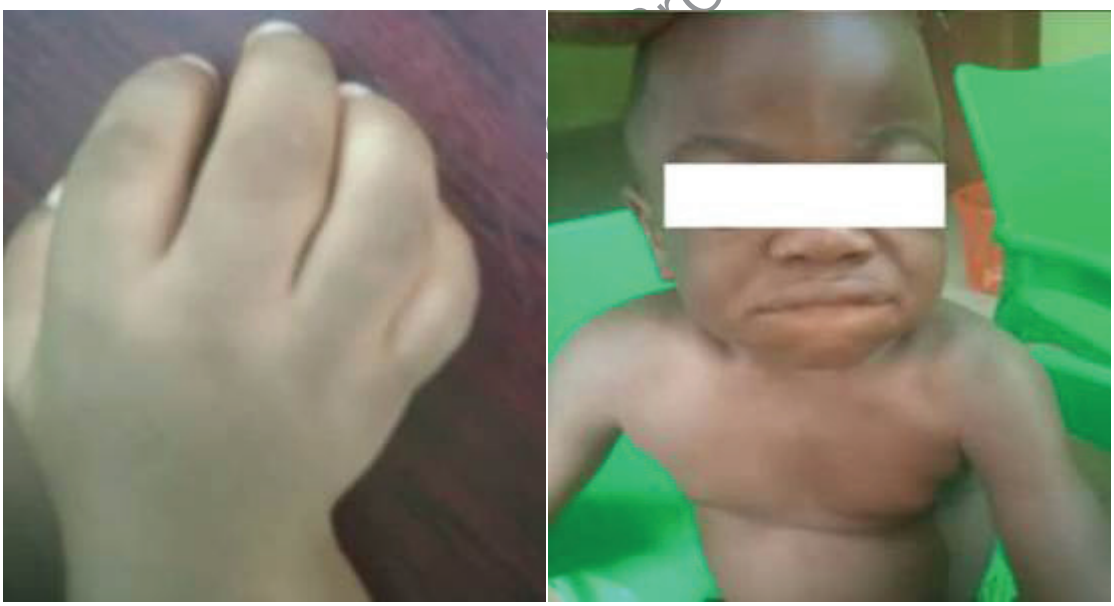

Figure 2. *A child with HS with coarse facial features, frontal bossing, thickened lips, and a broad nose, exhibiting claw-like hand deformities due to joint stiffness.*

The diagnosis of HS remains challenging in resource-constrained settings. The first sibling was initially misdiagnosed with rickets and subsequently hypothyroidism. Getting a definitive diagnosis was delayed for 8 years. This reflects the broader diagnostic difficulties in settings where metabolic disorders are rarely considered differential diagnoses due to poor awareness and limited access to diagnostic facilities. The second sibling's diagnosis was made more readily due to heightened clinical suspicion due to the occurrence of similar symptoms exclusive to males in the family. This highlights the need for carrier screening and early detection of affected individuals. Usually, the diagnosis of mucopolysaccharidoses II is made on demonstrating deficient iduronate-2 sulfatase (I2S) activity and genetic testing [1]. In the index cases, iuronate-2 sulfatase was very low, while urinary GAG levels were elevated, with a predominance of heparan sulfate which was consistent with HS. Although genetic testing would have provided a confirmatory diagnosis, it was not performed due to financial constraints, unavailability of

the service locally, and caregiver fatigue. Currently, there are no facilities offering genetic testing partnerships with international organizations at subsidized prices in the region. This mirrors the challenges faced in resource-poor settings where definitive biochemical and molecular diagnostics remain largely unavailable or unaffordable [7,11].

The mainstay of treatment of the affected children was symptomatic and other supportive therapies such as physiotherapy to improve joint mobility, reduce respiratory complications, and optimize the quality of life. NSAIDs have also been shown to help in managing musculoskeletal complications as they inhibit the production of inflammatory mediators, thus preventing degenerative joint changes. ERT with recombinant idursulfase (Elaprase) was sought but was not available in Nigeria. The cost of importation was over 7 million naira per vail. Elaprase is designated an orphan drug and is ranked among the 10 most expensive medications. At the price of $4,215 per vial (6mg), the annual treatment for a child that weighs 35kg is estimated at $657,000 which is prohibitive and not sustainable in resource-constrained communities [19]. Moreso, because Elaprase does not cross the blood-brain barrier, it only ameliorates the somatic manifestations without significant neurocognitive benefits [12]. HSCT, which offers the potential to prevent neurodegeneration if performed early, is also largely inaccessible in many low-income countries due to cost and infrastructure limitations [13,16].

Conclusion

This case series underscores the urgent need for increased awareness, early diagnosis, and improved access to confirmatory diagnostic tools and therapies for HS in Nigeria. Establishing newborn screening programs and expanding access to genetic testing will facilitate early detection and intervention, potentially improving outcomes for affected children. Advocacy through international collaborations by reputable organizations such as the National Organization for Rare Disorders (NORD) and Rare Diseases Clinical Research Network (RDCRN) as well as support of pharmaceuticals that produce orphan drugs such as Elaprase can enhance diagnostic and therapeutic capacity in low- and middle-income countries.

Recommendations

Considering the high socioeconomic burden, supporting families of children with Hunter syndrome in Nigeria requires a multi-faceted approach.

1. Develop national rare disease policies to improve diagnosis, treatment, and care.
2. Establish national rare disease registries to track rare cases and to facilitate research and international collaboration.
3. Include orphan drugs, e.g., ERTs for HS on essential medicine lists to ensure access to life-saving treatments.
4. Provide genetic counselling services and multidisciplinary care teams.

What's new?

Hunter syndrome is underdiagnosed in Nigeria due to poor clinical awareness, lack of newborn screening, and limited access to diagnostics and therapy. This first Nigerian case series involving two siblings highlights the urgent need for early recognition, multidisciplinary care, and equitable access to ERT. Strengthening rare disease infrastructure is essential for improving outcomes in low-resource settings.

List of abbreviations

ERT	Enzyme replacement therapy
GAGs	Glycosaminoglycans
HSCT	Hematopoietic stem cell transplantation
HS	Hunter syndrome
I2S or IDS I	duronate-2-sulfatase
MPS-II	Mucopolysaccharidosis type II

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the parent for publication.

Ethical approval

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Author details

Amalachukwu Okwukweka Odita[1], Ekene Fidelis Enema[2], Ngozi Ojinnaka[3]

1. Department of Paediatrics, Nnamdi Azikiwe University, Awka, Nigeria.
2. Mango Specialist Children Hospital, Onitsha, Nigeria.
3. University of Nigeria, Nsukka, Nigeria.

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Summary of the case

1	Patients (gender, age)	8 years, male; 4years, male
2	Final diagnosis	Mucopolysaccharidosis type II (MPS II)
3	Symptoms	Coarse facial features, macroglossia, skeletal deformities, hepatosplenomegaly, developmental regression and neurodevelopmental disabilities.
4	Medications	Symptomatic treatment given. Enzyme replacement therapy with Elaprase was not affordable
5	Clinical procedure	Diagnostic tests, Genetic counselling, Definitive treatment, Genetic tracing by testing other family members
6	Specialty	Paediatric Neurology