Mucopolysaccharidosis Type II: A Kenyan Case Series

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1.Introduction

Mucopolysaccharidosis type II (Hunter syndrome or MPS2) is an X-linked disorder caused by a deficiency in the lysosomal enzyme iduronate-2-sulfatase (I2S) leading to the accumulation of glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate. Accumulation of GAGs within lysosomes leads to progressive cellular damage, subsequent organ failure, and reduced life expectancy [1]. Its incidence is 0.3–0.71 per 100,000 live births [2]. MPS2 presents as either severe or attenuated form depending on the degree of central nervous system involvement. Death of patients with the severe form usually occurs in the first or second decade of life mostly due to cardiopulmonary complications. Mild or attenuated Hunter syndrome is characterized by preservation of intelligence, somatic involvement, and survival into adulthood [3, 4].

The MPS2 patients experience a spectrum of progressive, multiorgan clinical symptoms. The age at presentation and progression of disease can vary. They can have respiratory symptoms in the first months of life but usually present between 2 and 4 years of age. They have an inguinal or umbilical hernia, short stature, coarse facial facies, enlarged tongue, and gum hypertrophy. Other symptoms they can present with are recurrent ear and respiratory infections, obstructive sleep apnoea, dysostosis multiplex, macrocephaly, kyphosis, thickening of the long bone diaphysis, and barrel chest. They also have hepatosplenomegaly, hearing loss, and cardiomyopathy [1, 5].

About two-thirds of patients have psychomotor retardation, behavioral disturbances, and developmental regression. Patients with attenuated form present later in life with minimal neurological dysfunction [1, 2, 6]. They have normal intelligence and can survive into adulthood. The patients with the severe, neuropathic form of Hunter
syndrome may have a primary disease with parenchymal
neural cognitive impairment due to deposition of GAGs in
neural tissue and from other pathophysiologic, neurotoxic,
and inflammatory disease mechanisms [7, 8].

Analysis of urine GAGs can be used to confirm the
suspicion of Hunter syndrome. Excess urinary excretion of
dermatan sulfate and heparan sulfate is a characteristic of
Hunter syndrome but not diagnostic as these GAGs can also
be elevated in other types of mucopolysaccharidoses. Thus,
measurement of I2S enzyme activity is necessary to confirm
the diagnosis. Absent or low I2S activity in males is diag-
nostic of MPS2, but absolute enzyme activity is unable to
predict phenotype severity [2, 9, 10]. Genetic testing of IDS
allows the prediction of the phenotype and confirms MPS2
in males [5]. Mutations resulting in the complete absence of
IDS or its activity are associated with MPS2 with neurologic
involvement [2].

Kenya, like many sub-Saharan countries, does not
routinely screen for metabolic diseases. Therefore, with a
paucity of data on MPS2 in the majority of these countries,
most of the patients with severe Hunter syndrome die early
before the diagnosis is made.

To our knowledge, no published data exist on MPS2
from Kenya and sub-Saharan Africa. In this paper, we
present 6 confirmed cases of MPS2 and describe the clinical
characteristics. This preliminary analysis will aid in
informing Kenyan healthcare professionals on the presence
of MPS2 patients among patients who report having had
male relatives who died of similar illness without a diagnosis.
It will also form a basis for a larger study among MPS2
patients.

2. Methods

This is a descriptive case series of patients receiving care for
MPS2 at Kenyatta National Hospital (KNH), the main re-
referral hospital in Kenya. This case report is part of a larger
ongoing study seeking to identify the MPS2 carrier rate
among relatives of patients with mucopolysaccharidosis type
II. Records of patients who had been screened for inborn
errors of metabolism and other genetic mutations were
retrieved. Data on sociodemographic characteristics, clinical
history, and genetic analysis information were extracted and
tabulated. A description of the patient characteristics was
also conducted.

3. Results

Out of the total of 17 children that were reviewed, 6/17
(35.3%) patients had pathogenic variants in the IDS gene
associated with X-linked recessive mucopolysaccharidosis
type II. They were all symptomatic with mainly neurological,
musculoskeletal, and respiratory symptoms. The mean age at
diagnosis was 7.5 years with a range of 3–13 years. The
guardians noted the first early symptoms at an average age of
two years. The six patients were from a total of four families
with some being siblings. From the genetic analysis, three
different gene mutations were found among the 6 patients.
Three of the patients had nonsense mutations, two had
missense mutation, and one patient had frameshift
mutation.

3.1. Case 1. The boy had a missense type of mutation with a
severe type of MPS2. He developed the symptoms of noctur-
nal snoring by age 4 years and then progressively had
regression of milestones, and by the age of ten years, he was
defead, could only mumble some things, was hyperactive, and
could not follow any instructions. He was snoring when both
awake and asleep. He could neither feed nor dress himself.
Though he could not be toilet trained, he remained am-
bulant. He had dysostosis multiplex, hepatomegaly, large
umbilical hernia, enlarged tongue, and coarse facial facies.
He had macrocephaly, macroglossia, and gingival hyper-
trophy. There was no history of similar illnesses in the
family.

3.2. Case 2. He had a severe form of MPS2 with a similar
mutation as in case 1. He started snoring while asleep at the
age of 3 years. Though he could pronounce some words at
the age of 1.5 years, he had regression of speech develop-
ment, and by 3 years, he could only communicate by
pointing at things. He was partially deaf by 5 years of age
with dysostosis multiplex. He had the diagnosis confirmed at
the age of five years. Though he progressively became ag-
gressive and hyperactive by 7 years of age, he could feed and
dress by himself. An older brother with a similar condition
had died at 13 years, and from the extended family, 12 boys
had died before 15 years of age.

3.3. Cases 3, 4, and 5. They were three siblings. They had the
same nonsense mutation. Though the enzyme activity for the
three patients was the same, the first born had a severe form
of the disease with deafness and poor cognitive function. The
second sibling was deaf but had good cognitive functions
with good school performance. The third sibling was still
young and, by the time of diagnosis, had no obvious central
nervous system manifestations of the disease. All three had
short stature with dysostosis multiplex. They all had course
features. Despite being siblings with the same mutation, they
had different forms of central nervous system involvement.
A maternal uncle had died at 20 years with similar illness.

3.4. Case 6. Patient number 6 was an older boy. He had the
flame shift type of mutation. By the time the diagnosis was
confirmed, he was both mentally and physically incapac-
tated. He could neither feed himself nor walk. He had signs
and symptoms of severe disease. He presented with respira-
tory symptoms characterized by dyspnoea at rest and sleep
obstructive apnoea. An older brother and two maternal
cousins had died of similar illnesses at the age of 13 and 14
years.

An older brother with a similar condition had died at 13
years, and from the extended family, 12 boys had died before
15 years of age (Table 1).
Table 1: Clinical characteristics of mucopolysaccharidosis type II patients at Kenyatta National Hospital.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years when the guardian noted symptoms</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age in years at diagnosis</td>
<td>10</td>
<td>5</td>
<td>15</td>
<td>13</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CNS symptoms and signs</td>
<td>Hyperactivity, poor cognitive function, irritability, not talking</td>
<td>Hyperactivity and irritability, poor cognitive function, mumbles things</td>
<td>Attention-deficit, poor cognitive function, language intact</td>
<td>Very intelligent despite being deaf, good school performance</td>
<td>Functionally normal</td>
<td>Severe CNS dysfunction</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Enlarged tongue, gum hypertrophy, dyspnoea, sleep apnoea</td>
<td>Enlarged tongue, gum hypertrophy, dyspnoea, sleep apnoea</td>
<td>Enlarged tongue, gum hypertrophy, dyspnoea, sleep apnoea</td>
<td>Enlarged tongue, gum hypertrophy, dyspnoea, sleep apnoea</td>
<td>Snoring when asleep</td>
<td>Enlarged tongue, gum hypertrophy, dyspnoea, sleep apnoea</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Umbilical hernia, hepatomegaly</td>
<td>Umbilical hernia, hepatomegaly</td>
<td>Umbilical hernia, hepatomegaly</td>
<td>Umbilical hernia, hepatomegaly</td>
<td>Umbilical hernia, hepatomegaly</td>
<td>Umbilical hernia, hepatomegaly</td>
</tr>
<tr>
<td>Ears</td>
<td>Recurrent otitis media and deaf</td>
<td>Recurrent otitis media and deaf</td>
<td>Recurrent otitis media and deaf</td>
<td>Recurrent otitis media and deaf</td>
<td>None</td>
<td>Recurrent otitis media and deaf</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Carpal tunnel syndrome, multiple joint contractures</td>
<td>Carpal tunnel syndrome, multiple joint contractures</td>
<td>Carpal tunnel syndrome, multiple joint contractures</td>
<td>Carpal tunnel syndrome, multiple joint contractures</td>
<td>Carpal tunnel syndrome</td>
<td>Carpal tunnel syndrome, multiple joint contractures</td>
</tr>
<tr>
<td>Iduronate-2-sulfatase level, ref ≥5.6 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
<td>&lt;0.8 μmol/L/h</td>
</tr>
<tr>
<td>Gene mutation type</td>
<td>Missense</td>
<td>Missense</td>
<td>Nonsense</td>
<td>Nonsense</td>
<td>Nonsense</td>
<td>Frameshift</td>
</tr>
</tbody>
</table>

4. Discussion

The three siblings with a nonsense mutation had IDS variant. This was previously described as a mutation that causes mucopolysaccharidosis II [9, 11, 12]. Cases 1 and 2 had missense mutation, and case 6 had frameshift mutation. This is similar to other MPS2 studies. In 2016, Kosuga et al. analyzed mutations in the IDS gene of 65 patients suffering from MPS II in the Japanese population. They were diagnosed with both the accumulation of urinary glycosaminoglycans and a decrease in their IDS enzyme activity. Among the samples examined, they identified different mutations: 33 missense, 8 nonsense, 7 frameshift, and 4 intronic changes. Consistent with the previous studies, the Japanese study showed that most of the attenuated phenotypes were derived from the missense mutations of the IDS gene, whereas mutations associated with a large alteration which included splicing, frameshift, and nonsense mutations were linked to the severe phenotype of MPS II [9].

The three siblings had varying clinical presentations. This has been found in other studies where they looked at sibling pairs. Ficioglu et al. looked at the data in the Hunter Outcome Survey to study the intrafamilial variability in the clinical manifestation of MPS II in 2017. They found that a majority of sibling pairs had a similar phenotypic presentation. However, there was discordance in some areas; out of 28 sibling pairs, four had different intelligent quotient that was used to measure the cognitive function. The mental function was rated as normal or borderline, educable, trainable, or profound. They also found differences in regression in walking in 8 pairs, speech in 8 pairs, dress alone in one pair, and toilet training regression in 1 pair. This has been suggested for the differences between siblings. After looking at the clinical presentations at different ages, Ficioglu et al. concluded that the chronological age difference between siblings may not have been the cause of discordance [13]. In our study, the sibling who was least affected was the youngest at 3 years. The oldest sibling was the most affected. He was not able to learn which may have been affected by the loss of hearing. However, the middle sibling was also deaf but was able to overcome it by using his eyes to follow the teacher. Clinical variability among siblings with the same condition has been found in other lysosomal storage diseases (LSDs) such as Pompe disease, Fabry disease, and Sanfilippo syndrome. There have been suggestions to indicate that epigenetic and genetic may be the cause [14–17].

The two patients with a missense mutation, that is, cases 1 and 2, presented with rapidly progressing severe type of MPS2. This is contrary to the Japanese study where the patients with similar mutations had the attenuated form of MPS2. Case 6 presented at 13 years of age when he was already moribund. He had a neuropathic form of the disease with severe somatic symptoms. He snored while awake and asleep and was not aware of his surroundings. The Japanese study associated frameshift mutation with severe disease [13].
5. Conclusion

Our patients had varying clinical presentations, similar to patients in previous studies. The 6 cases in our study are too few to conclude on the clinical presentations and types of mutations; however, they give an idea of the local phenotype and IDS gene mutations in Kenyan MPS2 patients.

Data Availability

The laboratory reports and photos of patients data used to support the findings of this study have not been made available because of patient privacy.

Ethical Approval

Approval to conduct this study was issued by Kenyatta National Hospital-University of Nairobi ethics research committee (P140/02/2020).

Disclosure

The funders had no role in study design, data collection and analysis, or preparation of the manuscript. The views expressed in this publication are those of the authors and not necessarily those of the Wellcome Trust, NIHR, or the UK government.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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