Case Report: Hurler syndrome (Mucopolysaccharidosis Type 1) in a young female patient [version 1; peer review: 3 approved with reservations]

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Abstract
Hurler syndrome is a rare autosomal recessive disorder of mucopolysaccharide metabolism. Here, we present the case of a young female patient who presented with features of respiratory distress. In addition, the patient had gingival hypertrophy, spaced dentition, misaligned eruptive permanent dentition, microdontia, coarse facial features, low set ears, depressed nasal bridge, distended abdomen, pectus carinatum, umbilical hernia and J-shaped Sella Turcica on an X-ray of the skull. A diagnosis of Hurler syndrome (Mucopolysaccharidosis Type 1) was made. The patient was kept on ventilator support from the third day; however, she died on the fifth day of admission. Enzyme replacement modality of treatment can increase a patient’s survival rate if an early diagnosis can be made. To the best of our knowledge, only a few cases of Hurler syndrome have been reported in Pakistan.

Keywords
Hurler syndrome, mucopolysaccharide, enzyme, genetic
Introduction
Mucopolysaccharidosis (MPS) represent a set of metabolic disorders, which are autosomal inherited disorders. MPS are lysosomal storage disorders that occur as a result of the deficiency of one group of enzymes, which degrade three classes of mucopolysaccharides: heparan sulphate, dermatan sulfate, and keratan sulfate. MPS occurs due to mutations in the gene encoding human α-L-iduronidase. Glycosaminoglycans (GAGs) accumulate chronically and progressively in the lysosomes of the cells throughout the body. Such accumulation of GAGs leads to multiorgan dysfunction and significant morbidity. Patients with Hurler’s syndrome (MPS Type 1) experience progressive debilitation of the musculoskeletal, cardiorespiratory, and central nervous systems, leading to death before 10 years of age if they remain untreated. There are very few cases of Hurler syndrome reported in Pakistan especially in last few years. Here, we present the case of Hurler’s syndrome in a young female patient.

Case report
An 8-year-old female patient was referred to the Children’s Hospital, Faisalabad, Pakistan with complaints of respiratory distress, massive abdominal distension, and generalized body swelling. According to her parents, developmental milestones slowed down at the age of 1.5 years with gradual mental decline expressed in terms of lost physical skills. The parents mentioned multiple joint stiffnesses and that the patient was having difficulty in walking for last few years and was unable to walk in the last year of her life. Though they were unaware of any hearing difficulties in the patient, they reported that she was not able to speak. The patient had noisy breathing noticeable since the third day of birth. In the past few years, the patient had multiple chest infections and had been constipated for around the last 3–4 months before hospital admission. Family history revealed that the parents had a consanguineous marriage (first cousins), and the patient had one older brother who had no obvious mental and physical abnormalities. This was the patient’s first tertiary hospital visit.

Clinical findings
General physical examination revealed coarse facial features, hirsutism, low set ears, depressed nasal bridge, rotated legs, talipes varus, short neck, distended abdomen, pectus carinatum, thick short claw-like hands, umbilical hernia, and kyphosis. Abdominal examination revealed massive hepatosplenomegaly. On cardiac auscultation, a murmur was not heard but loud P2 was audible. Moreover, on chest auscultation, bilateral crepitations were present. On oral examination, gingival hypertrophy, spaced dentition, misaligned eruptive permanent dentition, microdontia, delayed eruption of the permanent tooth and delayed shedding of the deciduous tooth were observed.

Figure 1. General examination revealed umbilical hernia (yellow arrow) and pectus carinatum (red arrow).

Figure 2. Oral examination revealed gingival hypertrophy, spaced dentition, misaligned eruptive permanent dentition (yellow arrow), microdontia, delayed eruption of the permanent tooth and delayed shedding of deciduous tooth.
Chest X-ray showed cardiomegaly and oar shaped ribs (Figure 3). X-ray of the patient’s skull showed J-shaped Sella Turcica (Figure 4), while X-ray of her hand showed proximal pointing of metacarpals (Figure 5), and X-ray of the lumbosacral spine showed inferior beaking of vertebrae (Figure 6). The patient’s echocardiogram showed normal left ventricular function, and hematological investigations were all in the normal range.

A differential diagnosis of Hunter syndrome (MPS Type II; MPS-II) and Sly syndrome (MPS-VII) was made. However, after clinical analysis and imaging findings, a provisional diagnosis of Hurler syndrome was made. The patient’s MPS urine was 1673 mL MPS/g creatinine (normal levels, 116.4–324.4 mL MPS/g creatinine). The patient’s α-L-iduronidase activity in the leukocytes was non-detectable (normal levels, 0.105–0.327 µmol phenol per 18 hours per mg protein). A final diagnosis of Hurler syndrome (MPS-I) was confirmed after the result of urinary excretion of MPS and an enzyme assay.

**Therapeutic interventions**

On arrival the patient was having difficulty breathing. She was supplied with oxygen through nasal prongs and was managed conservatively. On the third day, the patient was intubated and kept on ventilatory support. On diagnosis of Hurler...
syndrome (MPS-I), the patient’s parents were advised for further management; however, they denied further management because of socio-economic reasons. The patient died on her fifth day of hospital stay.

**Discussion**

Hurler syndrome manifests as an autosomal recessive disorder of mucopolysaccharide metabolism. There is an excess accumulation of lipids in the central nervous system as well as other viscera. This condition manifests in early infancy. Patients have developmental retardation, an expressionless face, and increase in the size of the head with deformed shape. They also have various skeletal abnormalities, contracture on flexion, hernias, and an increase in the size of the liver and spleen. Corneal clouding can be found in some patients. Hurler syndrome is a metabolic disorder of mucopolysaccharide metabolism to defect in lysosomal degradation pathways. It is seen in approximately 1:100,000 live births.

Hurler syndrome is diagnosed based on the reduced level of α-L-iduronidase activity in leukocytes or cultured fibroblasts. Prenatal diagnosis is confirmed by the presence of unusual glycosaminoglycan components in the amniotic fluid, or abnormal metabolic activity in cultures amniotic fluid cells, and a deficiency of the lysosomal enzyme α-L-iduronidase in these cell homogenates. Along with symptomatic treatment, enzyme replacement therapy with α-L-iduronidase, as well as bone marrow transplantation, increases the probability of life expectancy. Couples who have a positive family history must be provided with genetic counseling and testing.

**Conclusion**

Hurler syndrome is a rare genetic disorder of mucopolysaccharide metabolism and is caused by a defect in lysosomal degradation pathways. For patients with MPS-I, enzyme replacement modality of treatment can increase the patient’s survival rate if an early diagnosis can be made.

**Consent**

Written informed consent was obtained from the father of the patient for the publication of this case report and associated images.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.

**References**

Open Peer Review

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The authors describe a case of Hurler syndrome in an 8-year-old girl. The clinical description is good and well supported by the images. It may be useful to index this article, but it is necessary to make some corrections.

In the Introduction the authors describe mucopolysaccharidosis in an incomplete way, neglecting the recessive X-linked transmission form (MPS II), and stating that they are due to mutations in the gene encoding for alpha-L-hyduronidase, which only concerns MPS I. Furthermore, no mention is made of the subdivision within MPS I into a severe form (Hurler syndrome) and an attenuated form (Hurler-Scheie syndrome and Scheie syndrome). The distinction is important because it reflects on the therapeutic choices.

For the definitive diagnosis of MPS I it is sufficient to demonstrate the enzymatic deficit, but it would be appropriate to add also the molecular examination of the IDUA gene, as the results would also be useful in the family for the prevention of the risk of recurrence. Since the test was not performed on the patient, it would be appropriate to perform it on the parents, and then extend it to family members, starting from those of first degree.

In the Discussion the authors cite outdated methods of prenatal diagnosis. Currently Prenatal testing is possible for pregnancies at increased risk for MPS I by measuring α-L-iduronidase enzyme activity in cultured cells obtained by amniocentesis (usually performed at ~15-18 weeks' gestation) or CVS (at ~10-12 weeks' gestation). Difficulty with prenatal diagnosis for MPS I may result from the low α-L-iduronidase enzyme activity in normal chorionic villi; however, difficulties in interpreting borderline low α-L-iduronidase enzyme activity can be overcome by assaying enzyme activity in cultured rather than uncultured CVS cells, provided analysis for possible maternal contamination is performed.

With regard to treatment options, the authors correctly cite enzyme replacement therapy, while hematopoietic stem cell transplantation is preferred to bone marrow transplantation cited by the authors.
Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical genetics, Molecular genetics, Prenatal diagnosis, Genetic counseling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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The article is devoted to one of the most common forms of storage diseases - mucopolysaccharidosis type I - Hurler syndrome. The authors note that for the Pakistani population, Hurler syndrome is a rare disease, and on this basis, the publication of this case is undoubtedly relevant.

In the introduction, the authors give literary information about this form of mucopolysaccharidosis.
The clinical results describe in great detail the patient's phenotype and the data of the clinical, laboratory and X-ray examinations. The results obtained are perfectly illustrated by the attached figures, which undoubtedly increases the practical significance of the article. However, there are a number of remarks to the scientific fragment of the article: the authors note that the diagnosis was confirmed on the basis of a study of the GAG fractionation indices and the activity of the lysosomal enzyme alpha-L-iduronidase, but the results of urinary glycosaminoglycan excretion were not presented in the article.

It is regretful that molecular genetic studies have not been carried out, namely the search for mutations in the IDUA gene. Previous articles by Pakistani authors indicate a high frequency of occurrence of the variant p. L490P among the Pakistani population, and it has even been suggested that this option be included in Pakistan's newborn screening program. If possible, the authors of the article should be advised to conduct a molecular genetic examination of the parents and siblings of the dead girl. These data will undoubtedly increase the scientific value of the article.

In the Discussion section, which provides data on the prenatal diagnosis of Hurler syndrome, the authors cite outdated methods of antenatal diagnosis. Currently, all over the world, methods of DNA diagnostics of chorionic biopsy performed at 10-11 weeks of gestation are used. The advantage of this method is in the early diagnosis of pathology, when the pregnancy can still be terminated (at the request of the parents) by means of medical abortion, and not premature birth.

Thus, the peer-reviewed article is especially relevant for practitioners, and in the current version can be published in the section titled "Notes and observations from practice."

Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Partly

Is the case presented with sufficient detail to be useful for other practitioners? Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: hereditary diseases, storage diseases

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.
Case report is well written besides few lacuna.
1. The authors have diagnosed the case with urinary test and demonstration of enzyme deficiency, but could not do genetic testing. This can be mentioned.

2. In the discussion a general description about Hurler syndrome is given, but nothing has been mentioned about the present case like whether the case has classical presentation or any other deviation.

3. The authors have mentioned about bone marrow transplantation, but actually nowadays stem cell transplantation is the treatment of choice which should be done early preferably before 2.5 years.

The case report can be accepted with corrections.

**Is the background of the case's history and progression described in sufficient detail?**
Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**
Partly

**Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**
Partly

**Is the case presented with sufficient detail to be useful for other practitioners?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Pathology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
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