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Medicine

MULTIDISCIPLINARY APPROACH TO DIAGNOSIS AND MANAGEMENT OF MUCOPOLYSACCHARIDOSIS TYPE VI: A CASE STUDY

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ABSTRACT:
MUCOPOLYSACCHARIDOSIS TYPE VI, ALSO KNOWN AS MAROTEAUX-LAMY SYNDROME IS A RARE GENETIC DISORDER THAT IMPAIRS THE BODY'S ABILITY TO BREAK DOWN GLYCOSAMINOGLYCANS, LEADS TO VARIOUS SYMPTOMS SUCH AS SKELETAL ABNORMALITIES, JOINT STIFFNESS, VISION AND HEARING PROBLEMS, AND HEART AND LUNG COMPLICATIONS. WE REPORT A CASE OF A 15-YEAR-OLD FEMALE PATIENT WITH MAROTEAUX-LAMY SYNDROME, PRESENTING WITH DECREASED HEIGHT, SQUINTING, AND DIFFICULTY WALKING. IMAGING STUDIES REVEALED SEVERAL SKELETAL ABNORMALITIES, AND THE PATIENT'S ACTUAL BONE AGE CORRESPONDED TO THAT OF A THREE-YEAR-OLD FEMALE. ENZYME REPLACEMENT THERAPY AND PHYSIOTHERAPY LED TO CONSIDERABLE IMPROVEMENT IN MOBILITY, DISEASE PROGRESSION, AND BONE GROWTH. THIS CASE REPORT EMPHASIZES THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT IN MANAGING MAROTEAUX-LAMY SYNDROME.

KEY WORDS: MUCOPOLYSACCHARIDOSIS, PEDIATRICS, STORAGE DISORDER, LYSOSOMAL DISEASE

INTRODUCTION

Mucopolysaccharidoses are a group of rare lysosomal storage diseases caused by genetic defects that lead to a lack of enzymes required for the degradation of glycosaminoglycans (GAGs) [1]. These long, unbranched polysaccharides are involved in

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processes such as cell adhesion and cellular signaling. Maroteaux-Lamy syndrome, also known as type VI mucopolysaccharidosis, is a rare inherited autosomal recessive lysosomal storage condition that results from decreased or absent arylsulfatase-B activity, caused by mutations in the ARSB gene, most commonly in the form of a missense mutation [2]. This deficit leads to chondroitin sulfate buildup in numerous tissues, causing cell and tissue damage that ultimately progresses to organ failure [3]. The classical clinical features of Maroteaux-Lamy syndrome include a significant impairment of the osteoarticular system, with dysostosis multiplex, short stature, and motor dysfunction [4]. Depending on the symptoms, treatment options include enzyme replacement therapy (ERT) or bone marrow transplant, and symptomatic management of the various clinical features [5]. In this report, we describe a rare case of Maroteux Lamy syndrome with unique radiological features.

CASE REPORT

A 15-year-old female was admitted to a tertiary care hospital with a history of stunted height, squinting, and increasing difficulty in walking over the past three years. Upon physical examination, the patient presented with hand contractures and short, stubby fingers, as well as a kyphotic spinal deformity and dysplastic teeth. Notably, her height was found to be 4 standard deviations below the mean. Further investigation into her family history revealed a paternal relative with similar symptoms, and consanguineous marriage was ruled out as a possible cause. In addition to these skeletal abnormalities, the patient displayed signs of coarsening facies, including thickened lips, an enlarged tongue, and a prominent forehead. However, there was no evidence of cardiac involvement or spinal compression.

The patient underwent several imaging tests, including a skeletal survey. The results showed various abnormalities, such as mild microcephaly, hypoplastic maxilla with abnormal dentition, short scapula and high-riding, thickened, and short clavicles, and "oar-shaped" ribs. Abdominal X-ray showed hepatomegaly, confirmed by ultrasonography. X-ray spine revealed moderate to severe platyspondyly with rectangular vertebrae, over faced pedicles, and widened inter-pedicular distance.

Pelvic X-ray showed broad flared ilia, shortened greater sciatic notches, and inferior tapering. Both upper and lower extremities had shortened long bones with irregular and hypoplastic long bone epiphyses, and premature degenerative changes. Arm radiographs showed evidence of terminal deformities of both radii, representing a Madelung deformity. Both hands also showed brachydactyly. Bone age calculated by the Greulich and Pyle method corresponded to a 3-year-old female, as opposed to her chronological age of 15 years. These findings were strongly suggestive of dysostosis multiplex and Maroteaux Lamy syndrome.

The patient underwent several tests, including a quantitative GAG analysis, qualitative GAG analysis, and enzyme assay to evaluate arylsulfatase-B enzymatic activity on leucocytes or fibroblasts. The screening tests showed elevated levels of total urinary GAGs, and qualitative testing revealed dermatan sulfate levels to be the most prominently deranged. The genetic testing identified multiple genetic variants of the ASRB gene, and molecular testing for the respective patient's parents confirmed the presence of defective variants of the gene on opposite chromosomes in the patient's genetic pool. The c.629A>G and c.944G>A alleles were reported in testing.

A novel finding in this case with respect to Maroteaux-lamy syndrome was flares of shortness of breath whenever the patient would undergo some physical exertion, and fatiguability was observed commonly throughout the week whenever the patient would perform day to day tasks which required some physical effort, like hanging clothes or mopping the floor, and required taking a break. The flares for dyspnea usually lasted for 5

minutes with increased and deep breathing, which would resolve on rest. The patient categorized this exertion by providing examples of 15 minutes of slow walking, 5 minutes of brisk walking, or 30 seconds of climbing stairs. Earliest episode was described to have occurred at 10 years of age and has worsened gradually over time but did deteriorate more severely after a chest infection 6 months ago, with 1 episode averaging around every week on admission. According to the prescription brought in, the chest infection was treated with acetaminophen, loratadine and azithromycin. The patient's complete blood count and iron profile tests were requested on 2 different occasions with a 1-month gap. The blood count displayed an average of 86 fl mean corpuscular volume of erythrocytes, while the iron profile was within range. The patient was never taken to a doctor since the parents did not consider it to be significant enough. Further investigation was required to establish the underlying disease or mechanism for this condition, but anemia of chronic disease, aplastic anemia, a lesion leading to destruction of bone marrow to mild degree, a lung disease or hypersensitivity abnormality was suspected.

The patient's management was done through a multidisciplinary approach, including ERT, joint replacement surgery, physiotherapy, speech therapy, and occupational therapy. ERT was started in the form of weekly intravenous infusions with recombinant human ASB after discussion of potential risks and benefits with the family. Joint replacement surgery was being considered to improve the patient's joint deformities and quality of life. Physiotherapy, speech therapy, and occupational therapy were also recommended to improve the patient's mobility and independence. Regular appointments with a primary care physician were advised to monitor the patient's cardiac, respiratory, and neurological function and optimize the outcome.

The patient showed progress in recovery with increased capability in performing day-to-day activities due to ERT combined with physiotherapy. Regular check-ups for vitals, bone marrow density test, serum electrolyte levels and urea creatinine levels were performed monthly to check for the status of recovery, and additional tests were arranged when required. These tests are then compared to the those conducted prior to treatment and the most recent one. The patient was compliant and adherent to their medications and physiotherapy and began to exhibit a greater degree of bone growth as a result of ERT combined with physiotherapy. The patient underwent a six-month follow-up with a multidisciplinary approach involving orthopedics, neurology, and genetics. The follow-up included assessments of the patient's motor function, cognitive function, and cardiac function. The patient was also monitored for any progression of skeletal deformities and joint contractures. Overall, the patient showed mild improvement in motor function, while cognitive function and cardiac function remained stable. No significant progression of skeletal deformities or joint contractures was observed.

In summary, a 15-year-old female with stunted height, squinting, and increasing difficulty walking was diagnosed with Maroteaux Lamy syndrome through several imaging and testing methods. The patient's management was done through a multidisciplinary approach, including ERT, joint replacement surgery, physiotherapy, speech therapy, and occupational therapy, resulting in progress in recovery with increased capability in performing day-to-day activities.

DISCUSSION

Mucopolysaccharidoses (MPS) are a group of rare metabolic lysosomal storage disorders that affect the breakdown of glycosaminoglycans (GAGs), leading to their accumulation in various organs. This results in multisystem symptoms, such as

organomegaly, skeletal abnormalities, short stature, and cardiac and neurological problems [6]. MPSs are inherited as autosomal recessive disorders, except for MPS II, which is X-linked.

There are 13 types of MPS, with MPS I (Hurler syndrome) being the most common, although the incidence varies among different populations [7]. MPS VI, or Maroteaux Lamy syndrome, is a rarer type of MPS with a global incidence of around 1 in 20000 [8]. However, the incidence differs in different countries, with one study reporting MPS VI to be around 3% of all MPS cases [9]. MPS VI is caused by a deficiency of the enzyme arylsulfatase B (ARSB), which is essential for the breakdown of certain complex sugars called glycosaminoglycans (GAGs) in the body. Without this enzyme, GAGs accumulate in various tissues and organs, leading to the characteristic features of MPS VI [10]. MPS VI is inherited in an autosomal recessive manner, meaning that a person must inherit two copies of the mutated ARSB gene (one from each parent) to develop the condition [11]. The patient's family history suggests that this may be the case, as a paternal relative had similar symptoms. However, the patient's parents did not undergo consanguineous marriage, which reduces the likelihood of both parents carrying the same ARSB mutation. Patients with MPS VI have varying clinical features, with some having mild symptoms noticed at later ages, while others have more severe symptoms with earlier onset.

Despite the variability, patients with MPS VI generally have severe generalized disability by their second decade of life. However, they are normal from an intellectual and mental development perspective. Symptoms of MPS VI include skeletal abnormalities, termed “dysostosis multiplex”, that affect various bones, leading to short stature, gait abnormalities, joint contractures, and degenerative joint disease at early ages [12]. Other common features include dysplastic facies, corneal clouding, retinal and optic nerve abnormalities, hearing loss, cardiac sequelae, and visceromegaly [13].

The diagnosis of MPS VI is made through urine GAG analysis, enzyme studies in cultured fibroblasts, or genetic analysis. Imaging plays an important role in detecting the disease, with skeletal abnormalities, kyphoscoliosis, and atlantoaxial instability suggestive features on radiography and echocardiography used to evaluate cardiac anomalies [14]. CT can assess the entire airway in patients, while MRI of the head and neck can be useful for detecting hydrocephalus or cervical cord compression [15].

Treatment options for MPS VI are limited, and those that exist have limited availability. Treatment is mainly symptomatic and supportive, with close follow-up by cardiology and pulmonology recommended for valve disease and restrictive or obstructive lung disease [16]. Physical therapy can provide improvements in activities of daily life and functionality, while orthopedic surgery can target spinal deformities and kyphoscoliosis if severe enough. Recombinant ERT is a newer treatment option being developed, with clinical trials currently underway [17].

CONCLUSIONS

Mucopolysaccharidoses (MPS) are a group of rare and serious illnesses that require prompt diagnosis and multidisciplinary management to preserve functionality. This case report highlights the importance of using clinical features and radiological findings for targeted genetic testing. Our review of MPS VI and the relevant radiological findings aims to aid in the prompt diagnosis and guide treatment based on the severity and extent of bone deformity. By contributing to the medical literature on this rare disease, we hope to better educate clinicians and researchers to understand and manage MPS VI more effectively.

DECLARATIONS

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Author contributions:
M.H, F.S, F.H.S, M.A.M contributed to the conception and design of the manuscript. M.H, M.A.M, F.H.S supervised the project. M.H, M.K.K, M.A.M provided the materials and contributed to data collection and processing. F.S, M.K.K, M.T.A, F.H.S contributed to the interpretation and analysis of the project. F.S, M.K.K, M.T.A, F.H.S contributed to the literature review and writing of the manuscript respectively. M.H, F.S, M.K.K, M.T.A, M.A.M critically revised the manuscript.

Conflict of Interest:
The authors declare no conflict of interest.

Ethical approval:
The case report was approved for publication by the National Institute of Child Health's Institutional Review Board. The IRB number is NICH/23/0085.

Ethics Statement and Consent to Participate: The manuscript complies with the ethical recommendations of the Declaration of Helsinki of World Medical Association (WMA). An approval from the Ethics Committee was not applicable. The patient gave a written and signed consent with complete understanding of the publication and production of the case.

Consent to publication: The patient gave signed and written consent for the publication of the case report along with the images.

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