Case Report

Delayed Diagnosis of an Attenuated form of Mucopolysaccharidosis Type VI (Maroteaux-Lamy Syndrome) via MRI of the Cervical Spinal Cord

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Abstract

Introduction: We present the unexpected findings of a 59-years-old female patient who was admitted for an imaging investigation after the exclusion of rheumatoid arthritis and recurring carpal tunnel syndrome she was operated on both hands several years earlier.

Case presentation: Magnetic resonance imaging of the cervical spine revealed severe scoliosis in the cervicothoracic junction with biconcave-shaped vertebrae and dural thickening, especially in the craniocervical junction, leading to compression of the cervical spinal cord.

The history of this patient detailed many therapeutic interventions, such as treatment of severe scoliosis during childhood, operations for a bilateral hallux valgus, replacement of the aortic and mitral valves, total hip endoprosthesis on one side and bilateral iridectomy due to glaucoma. She had severe hyperopia and hearing deficits on one side due to recurrent otitis media. Subsequent biochemical tests revealed an increased excretion of urinary glycosaminoglycans, which suggested an attenuated form of mucopolysaccharidosis. Moleculargenetic testing confirmed two combined heterozygous mutations in the ARSB-gene, which is responsible for mucopolysaccharidosis type VI -Maroteaux-Lamy syndrome. The diagnosis was made after the patient retired from working at a challenging full-time job for 41 years.

Discussion: The key to the diagnosis was the finding of dural thickening in the craniocervical junction in the presence of severe cervical scoliosis and multiple ovoid-shaped vertebral bodies. The milder forms of mucopolysaccharidosis remain a challenge to diagnose them in adult patients. The confirmed diagnosis allowed the patient to be treated adequately with decompression by laminectomy and enzyme replacement therapy.

ABBREVIATIONS

MRI: Magnetic Resonance Imaging; MPS: Mucopolysaccharidosis; C: Cervical Vertebral Body; Th: Thoracic Vertebral Body; L: Lumbar Vertebral Body; CTS: Carpal Tunnel Syndrome; GAG: Glycosaminoglycans

INTRODUCTION

Several types of mucopolysaccharidosis can cause cervical myelopathy because of spinal canal stenosis [1-3]. Owing to emerging specific therapies, patient outcomes have improved, which underlines the importance of an early diagnosis [4]. We present a case of mucopolysaccharidosis (MPS) type VI-Maroteaux-Lamy syndrome -in the oldest reported patient with this type of MPS in whom the key to the diagnosis was mild cervical myelopathy.

CASE PRESENTATION

A 59-years-old female Caucasian patient was admitted to the Institute of Radiology for MRI of the cervical spine and the left hand because of progredient vertigo and increasing hypesthesia of the left hand over the past several years. At the ages of 49 respectively 51 years, she suffered from carpal tunnel syndrome (CTS) and underwent surgery on both hands. The first diagnosis was relapse of CTS, but the re-evaluation of the nerve conduction velocity showed no pathology. After the exclusion of rheumatoid...
arthritis, another diagnosis known from earlier clinical history, the patient was referred to the Institute of Radiology for examination of the cervical spine. Spinal deformity was known since early childhood, the time when treatment started with physiotherapeutic interventions and daily exercises.

**Imaging procedures and results**

An MRI examination (MagnetomVerio, 3.0 Tesla, Siemens, Erlangen/Germany) of the cervical spine revealed severe scoliosis of the cervicothoracic junction. All cervical and upper thoracic vertebrae showed a biconcave shape. The most significant finding was a smooth outlined dural thickening with a punctum maximum at the craniocervical junction. The dural thickening caused an absolute stenosis at the craniocervical junction, leading to compression of the spinal cord at the level of the foramen magnum. The spinal cord contained small hyperintense foci at the level of C5 and C6, and an additional lesion was suspected near the foramen magnum. No significant degenerative changes in the cervical spine were observed (Figure 1A-C).

An MRI examination of the left hand revealed a marked synovitis with intraarticular fluid collection at the radio carpal and intercarpal joints. The processus styloideus ulnae was destroyed and subchondral erosions were present on the articular surface of the radius and on the scaphoid. Smaller erosions were also found on the other carpalia. Bone marrow edema of the scaphoid and the proximal and middle phalanges of the fifth digit were noted. The metacarpal bones seemed to be shortened.

The shortening of the metacarpal bones and the Madelung-deformity of the radius and ulna were much easier to perceive on conventional radiography of both hands (Figure 2A,B). An MRI examination of the brain and the thoracic and lumbar spine were performed by using fluid-attenuated recovery inversion (FLAIR) magnetic resonance to observe any additional intracranial and spinal abnormalities. The brain showed enlarged ventricles and mild macrogyri and sulci that were predominantly in the frontal region, but no white matter abnormalities were observed (Figure 3). At the level of the thoracolumbar gibbus, the Th12 vertebra was found to be an anterior hemivertebra with secondary degenerative changes of the neighboring intervertebral discs and a consecutive stenosis of the spinal canal (Figure 4). Similar to the cervical region, small hyperintense foci were also observed in the thoracolumbar spinal cord. No further significant anomalies were revealed. The patient had a mild short stature with a gibbus in the middle spine, a slight cephalomegaly and slightly coarse facial features (Figure 5), but had excellent intellectual abilities. Considering the completely normal intelligence of the patient, radiological findings indicated MPS VI - Maroteaux-Lamy syndrome.
Patients history

After an uneventful pregnancy the patient was born spontaneously. Her body size was large, but a growth delay soon developed. During childhood, the patient underwent tonsillectomy and surgery on the adenoids. Not long after, scoliosis and crossed-legs were noticed, leading to physiotherapeutic interventions over several years and the temporary use of a plaster cast. When she was 19 years old, both halluces were operated on because of a valgus position. Although the patient had always been active in sports, she suffered from unexplained shortness of breath after a cycling trip. The first cardiac investigations revealed heart valve insufficiency. She then underwent aortic and mitral valve replacement at the age of 44 years. After subsequent operations for CTS on both hands, she received a total hip endoprosthesis on the right side at the age of 51 years. She developed glaucoma, necessitating an iridectomy on each eye at the ages of 55 and 56 years. She had severe hyperopia and a hearing deficit in the left ear because of recurring mid-ear infections. Her body size was 148 cm and her weight was 40 kg at the time of her visit at the genetic counselling unit.

Family history

The female patient had two older brothers of whom the eldest had died at the age of 40 years because of lung edema during a stay in high mountains. This brother had similar skeletal abnormalities and slightly reduced body-size, but otherwise felt well, was athletic and was not under any medical observations except for orthopedic treatments. The second older brother was completely healthy. The parents had no similar symptoms, suggesting an autosomal recessive trait.

Biochemical and genetic findings

The patient was admitted to the genetic counselling unit. The patient’s history suggested several differential diagnoses including attenuated forms of MPS or mucolipidosis III α/β (Figure 5). Investigations of urinary glycosaminoglycans (GAGs) showed increased excretion, especially of dermatan sulfate but less of heparin sulfate, which is observed in patients with MPS I - Scheie syndrome and MPS VI - Maroteaux-Lamy syndrome. Molecular investigations of the ARSB and IDUA genes with Sanger sequencing revealed two mutations in the ARSB gene with compound heterozygosity, which were previously known from the literature: c.349T>C (p.Cys117Arg) and c.629A>G (p.Tyr210Cys). The trans-position of these two mutations was confirmed in the 94-year-old mother who was identified as heterozygous carrier for one mutation. These genetic findings finally confirmed the diagnosis of MPS VI - Maroteaux-Lamy syndrome.

Clinical course

The patient underwent a spinal cord decompression operation via dorsal laminectomy of C1 and C2. Three months after the operation, she reported almost unlimited cervical motion and improvement of the left hand hypesthesia. She still has some subjective difficulties when climbing stairs but no paresis. Additionally, enzyme replacement therapy was started with weekly infusions of galsulfase (Naglazyme®). The effect of the enzyme replacement therapy, continuously admitted since
four years, was restricted to motor performance and breathing, without any remarkable effect on joint stiffness, especially in the wrists.

DISCUSSION

The diagnosis of MPS is usually made in early childhood and diagnosis at the age of 9 years is considered a delayed diagnosis [5]. Most MPS VI patients die as young adults at the age of twenty-five to thirty years [6]. Our patient obviously had an attenuated form of the disease with slowly progressing clinical symptoms, but all of the specific signs, such as reduced growth, problems with the ears, nose, throat and eyes, CTS, skeletal deformities, hip-operations and a heart valve substitution, which had never been combined and identified as one disease. This has led to an unusually late diagnosis in the sixth to seventh decade of this female patient.

The time to diagnosis can be rather long even up to 30 years [7]. Often, only one of the most affected organs, such as the heart, might result in the diagnosis of an attenuated form of MPS VI [8]. Some patients with attenuated forms of MPS have a rather normal life and are able to contain an education, establish a profession, start families and have children [8,9].

In our patient, the key to the diagnosis was the MRI finding of the spinal dural thickening, which can be observed in various forms of MPS as well as in Wegener granulomatosis and idiopathic hypertrophic pachymeningitis. In the latter two diseases, the dural thickening has a bumpy appearance, is not smoothly outlined, and uniformly diminishes in a cranio-caudal direction as in MPS. Since the phenotype of dysostosis multiplex in MPS can be variable, this typical form of dural thickening can be considered a pathognomonic radiological sign of the disease [10]. Especially in cases with normal intellectual development, early detection of stenosis of the craniocervical junction is of major importance for furthering the perspective on patients. The total absence of the typical white matter lesions in the brain and the high intellect of this patient supported the previously suspected correlation between the extent of the lesions and the severity of intellectual abnormalities [11].

One of the differential diagnoses often made in attenuated forms of MPS is that of rheumatoid arthritis. Suspicious signs can be summarized by criteria such as “Early joint involvement without classic inflammatory features or erosive bone lesions” [12]. Although rheumatoid arthritis was investigated and disclosed in the patient’s history, the erosive bone changes of the hands simulated such inflammatory changes. This uncommon feature was likely observed because most MPS patients have a relatively short life span with no time to develop the whole spectrum of primary arthropathy caused by lipopolysaccharides (LPSs), leading to chondrocyte apoptosis, synovial hyperplasia and inflammatory joint destruction, which is mediated directly by MPS synoviocytes [13]. Our patient underwent surgery for CTS, a much better known feature of MPS, because of the GAG deposits around the median nerve [14,15].

It is well known, that in addition to the rapidly progressing form of MPS VI, a slowly progressing so-called attenuated form also exists [16]. The oldest patients reported in the literature were 44-and 45-year-old females without impressive visible symptoms of MPS [17,18]. However, joint stiffness was reported by all patients and is also a limiting problem in our patient, especially in her fingers.

Our patient was, at the time of diagnosis, 59 years old. She managed her disease well and seemed, at the time of writing this report, - with the introduction of therapeutic interventions such as decompression and laminecortomy in the craniocervical junction and the enzyme replacement therapy-, to have a normal life expectancy with at a relatively good quality of life. The late initiation of enzyme replacement therapy, as in our patient, has an overall positive effect on the quality of life, but the effect on joints, tendons and skeletal aspects may be limited. An early diagnosis would result in mandatory introduction of this therapy much earlier [19].

SUMMARY

Diagnoses of attenuated forms of MPS remain a challenge. The involvement of many organs should suggest a multisystemic genetic disease, such as a metabolic disorder. X-rays of treated skeletal regions could elucidate much earlier findings of a dysostosis multiplex, which is typical for MPS. The described findings of stenosis at the level of the craniocervical junction owing to spinal dural thickening could be a helpful diagnostic clue in such cases.

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REFERENCES

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