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Musculoskeletal manifestations of mucopolysaccharidosis type VI and effects of enzyme replacement therapy

Case Report

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Abstract: The aim of this study was to describe the musculoskeletal manifestations of mucopolysaccharidosis VI and to assess the effectiveness of enzyme replacement therapy (ERT) with recombinant human arylsulfatase B on the bone and joint involvement in a patient with a severe phenotype of the disease. Before the initiation of ERT, the patient presented with significant range of motion (ROM) limitations at multiple joints. Flexion contractures were noticeable in all joints. After 48 weeks of ERT, improvement in active and passive shoulder flexion, as well as passive elbow and wrist flexion, was noticed. ROM improvements were reflected in patient's enhanced self-care.

Keywords: *Mucopolysaccharidosis type V • Maroteaux-Lamy syndrome • Enzyme replacement therapy • Range of motion • Physical therapy • Anthropometric features • Growth retardation*

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Abbreviations

ADL - activities of daily living;
GAG - Glycosaminoglycan;
ERT - Enzyme replacement therapy;
HAQ - Health Assessment Questionnaire;
ARSB - arylsulfatase B;
MPS - Mucopolysaccharidosis;
PT - Physical therapy;
ROM - Range of motion;
SFTR - sagittal, frontal, transverse rotation system.

References to electronic databases

N-acetylgalactosamine 4-sulfatase: EC 3.1.6.12.
Maroteaux-Lamy syndrome: OMIM 253200.

1. Introduction

Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, OMIM 253200) is an autosomal recessive disorder caused by impaired activity of N-acetylgalactosamine 4-sulfatase (arylsulfatase B, ARSB, EC 3.1.6.12) [1]. In the absence of sufficient enzyme activity, the stepwise degradation of the glycosaminoglycan dermatan sulfate is decreased, resulting in intracellular accumulation of the substrate into the lysosomes and leading to a progressive disorder with multiple organ and tissue involvement [1]. The reported birth prevalence of MPS VI is variable, as several studies have documented, ranging from 1 in 43,261 to 1 in 1,505,160 live births [2-4].

Maroteaux-Lamy syndrome is a disorder of the connective tissue, as demonstrated by significant involvement of the bone and cartilage. Bone and joint manifestations are

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prominent among most MPS VI patients because of profound disruption in the normal mechanism of growth and development [1,4,5]. Abnormal bone and cartilage development arises from a lack of skeletal remodeling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis, and infiltration by glycosaminoglycans (GAGs) [6-9]. Other clinical findings may include cardiac valve disease, reduced pulmonary function, hepatosplenomegaly, sinusitis, otitis media, hearing loss, sleep apnea, corneal clouding, carpal tunnel disease, and inguinal or umbilical hernia [4,10,11]. Although intellectual deficit is generally absent in MPS VI, central nervous system findings may include cervical cord compression, communicating hydrocephalus, optic nerve atrophy, and blindness [4].

Clinically, bone and joint involvement can be assessed using anthropometric parameters and joint range of motion (ROM) measurements.

Before enzyme replacement therapy (ERT), clinical management was limited to supportive care and hematopoietic stem cell transplantation. Supportive care has focused on optimizing general health with nutrition counseling, occupational and physical therapy, and management of individual symptom complications, such as respiratory insufficiency, tonsillectomy, adenoidectomy or tracheostomy, cardiac failure requiring medication and/or valve replacement, spinal cord compression or carpal tunnel compression, corneal clouding, or hydrocephalus [4,12]. Since 2005, ERT using galsulfase (recombinant human arylsulfatase B, Naglazyme®) has become available for MPS VI. Galsulfase has been shown to be effective in ameliorating some of the clinical manifestation of MPS disease [13-17]. Prognosis is variable, depending on the age of onset, rate of disease progression, age at initiation of ERT, and on the quality of medical care provided.

The objective of this study was to evaluate the efficacy of 48 weeks of ERT with galsulfase on anthropometric parameters, passive and active joint range of motion, as well as on activities of daily living (ADL) in a patient with a rapidly advancing phenotype of MPS VI.

2. Materials and methods

2.1 Patient

The patient, the second child of unrelated parents, was naïve to galsulfase therapy and presented with a severe phenotype of MPS VI. The pregnancy, delivery, and neonatal period were uneventful. At birth, her Apgar score was 10, birth weight 4250 g (between 90 and 97th percentiles), length 58 cm (> 97 percentile), and head circumference 35 cm (ca 50th percentile). Characteristic phenotypic features such as short stature, increased head circumference, coarse facial features, hepatomegaly, hearing impairment and typical radiological findings led to suspicion of MPS VI at age 3 years. The diagnosis was confirmed by biochemical determination of arylsulfatase B deficiency in leucocytes and molecular analysis. Prior to initiation of ERT (at age 7 years), the patient exhibited a range of clinical problems reflecting the multisystemic and progressive nature of the disease. The spectrum of symptoms included recurrent inguinal hernias, chronic rhinitis, pulmonary disease, joint stiffness, flexion contractures, corneal clouding, *dysostosis multiplex*, and cardiac valve disease (Figure 1-3). The patient underwent active physical rehabilitation while receiving ERT. Currently, she is 8 years old.

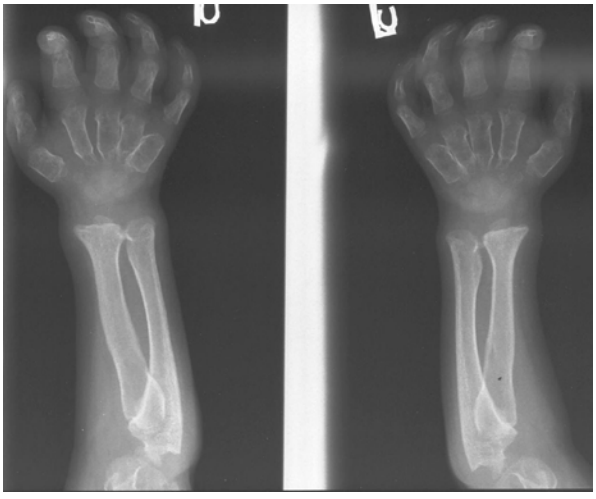

Figure 1. Rapidly progressing 7-year old female MPS VI patient: radiograph of hand. Typical radiological findings of MPS VI include thickened, short metacarpal bones with proximal pointing and thin cortices, carpal bones that are irregular and hypoplastic, V-shaped deformity of ulna and radius.

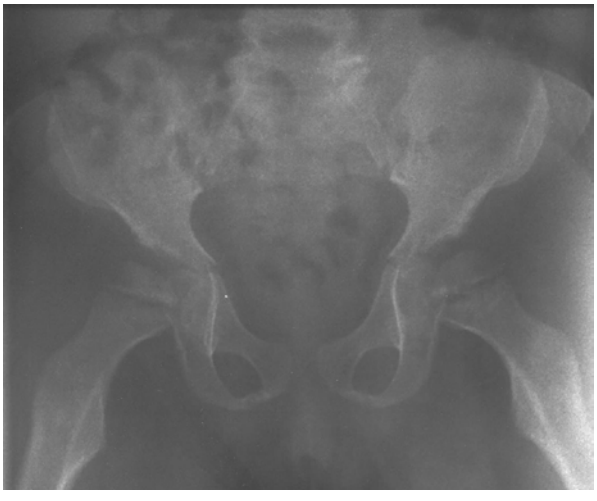

Figure 2. Rapidly progressing 7-year old female MPS VI patient: radiograph of hip showing dysplastic femoral head and hip dysplasia.

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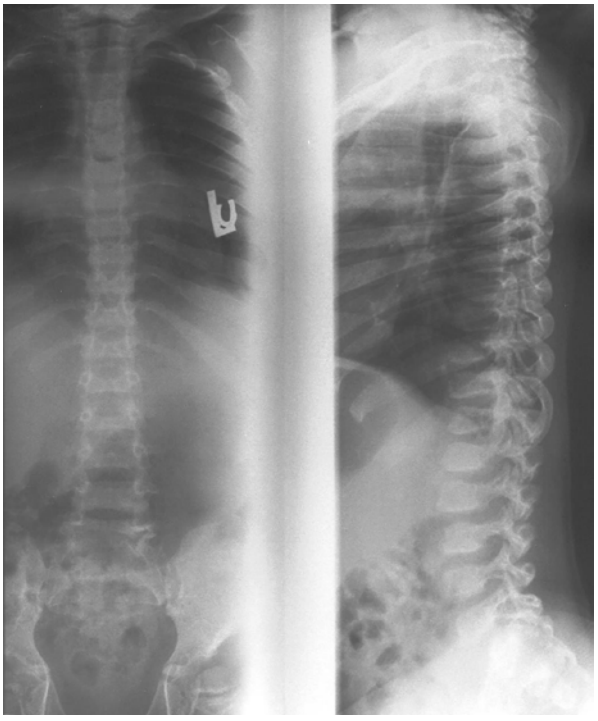

Figure 3. Rapidly progressing 7-year old female MPS VI patient: radiograph of spinal column showing abnormal development of vertebral bodies, paddle-shaped widened ribs, and severe lordosis.

2.2 Ethical consideration

The study was approved by the local medical ethical review board at The Children's Memorial Health Institute. Written informed consent was provided by the patient's parents.

2.3 Galsulfase treatment

Recombinant human ARSB (Naglazyme®, BioMarin Pharmaceutical Inc, Novato, Calif.) was administered at a dose of 1 mg/kg in weekly intravenous infusions.

2.4 Evaluation of efficacy

2.4.1 Measures of skeletal growth

Anthropometric measurements included body height, weight, length of the head and neck, trunk length, lower and upper extremities length, shoulder, chest and hip width, chest depth, chest circumference, head circumference, head length and breadth. All measurements were taken at the Division of Anthropology, Department of Pediatrics, CMHI, according to standard anthropometric techniques. Until the age of 3 years, length was measured in the supine position using a liberometer (accuracy to 1 mm). The same measurements of older children were performed as standing height using a stadiometer (accuracy to 1 mm). Weight was measured using an electronic scale accurate within 0.05 kg. A non-stretchable tape was used to assess head and chest circumference (accuracy to 5 mm). All assessments were performed by the same anthropologist.

2.4.2 Joint range of motion assessment

The passive and active range of motion was measured in degrees with the use of a goniometer (accuracy to 5°). It was assessed by the same physiotherapist using the International Method of Measuring and Recording Joint Motion (SFTR system; sagittal, frontal, transverse, rotation) [18,19].

2.5 Functional status

Functional status was assessed by the age-appropriate Health Assessment Questionnaire (HAQ), which is a comprehensive clinical assessment instrument used to evaluate the functional capabilities and performance in children and adults with MPS developed by doctors and other health care workers for the MPS I Registry. The MPS I Registry is a voluntary multi-centred observational program initiated in October 2003 to track the clinical onset, symptoms, and outcomes of patients with a confirmed diagnosis of MPS I, regardless of disease severity or treatment status. The HAQ Disability Index is an overall summary score for 8 categories: eating/drinking, dressing, bathing, grooming, toothbrushing, toileting, mobility, walking, and stair climbing [20]. The descriptive evaluation was based on a scale as minimal, moderate, complete assistance, or independent [20].

2.6 Statistical analysis

All measured anthropometric parameters were standardized for age and gender using the Polish body growth, weight, head, and chest circumference reference charts [21]. The resulting z-scores were used in all calculations. Descriptive statistics, including means and z-scores were calculated using Statistica 7 PL (Statsoft, Poland).

3. Results

3.1 Measures of skeletal growth

Analysis of anthropometric measurements in our patient allowed us to distinguish the characteristics that deviate from those in the normal population. A significant reduction of body height was observed, and body proportions were different from the proportion observed in the healthy population. At the beginning of treatment, the patient's body height was 94.8 cm (>3rd percentile, z-score value: -4.64) (Figure 4). Both the patient's upper (z-score: -5.72) and lower extremi-

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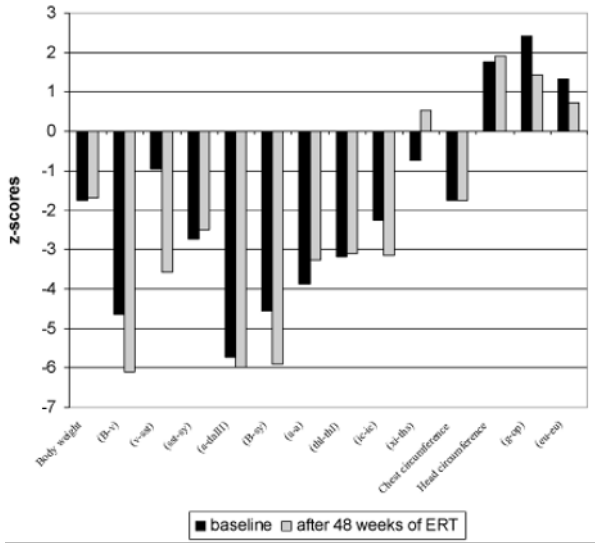

Figure 4. Z-scores values of anthropometric features of the patient with MPS VI.
B-v: body height; v-sst: head and neck length; sst-sy: trunk length; a-dalll: upper extremities length; B-sy: lower extremities length; a-a: shoulders width, thl-thl: chest width; ic-ic: hip width; ths-xi: chest depth; g-op: head length; eu-eu: head breadth.

ties (z-score: -4.55) were shorter than in the healthy population. Narrowing of shoulders (z-score: -3.87), chest and hip was also observed. The value of her head circumference was between 90th and 97th percentile, and the value for head length was greater than in the healthy population.

After 48 weeks of treatment body disproportions increased or remained the same (Figure 4).

3.2 Joint range of motion

Figure 5 presents passive and active ROM in the patient in selected upper and lower limb joints at baseline and after 48 weeks of ERT.

Before the initiation of ERT, the patient presented significant limitations in both upper and lower limb joints (Figure 6a and 7a).

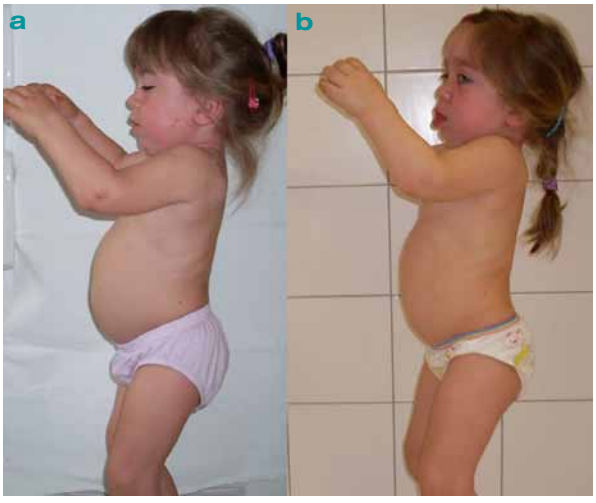

Figure 6. Active shoulder flexion in a patient with MPS VI at baseline and after 48 weeks of ERT with galsulfase. Mean restriction of active shoulder flexion at baseline was 85°. After 48 weeks of ERT, 20° improvement was observed.

Limitations in the upper limb joints included (ERT baseline):

- active shoulder flexion: flexion contracture 85°

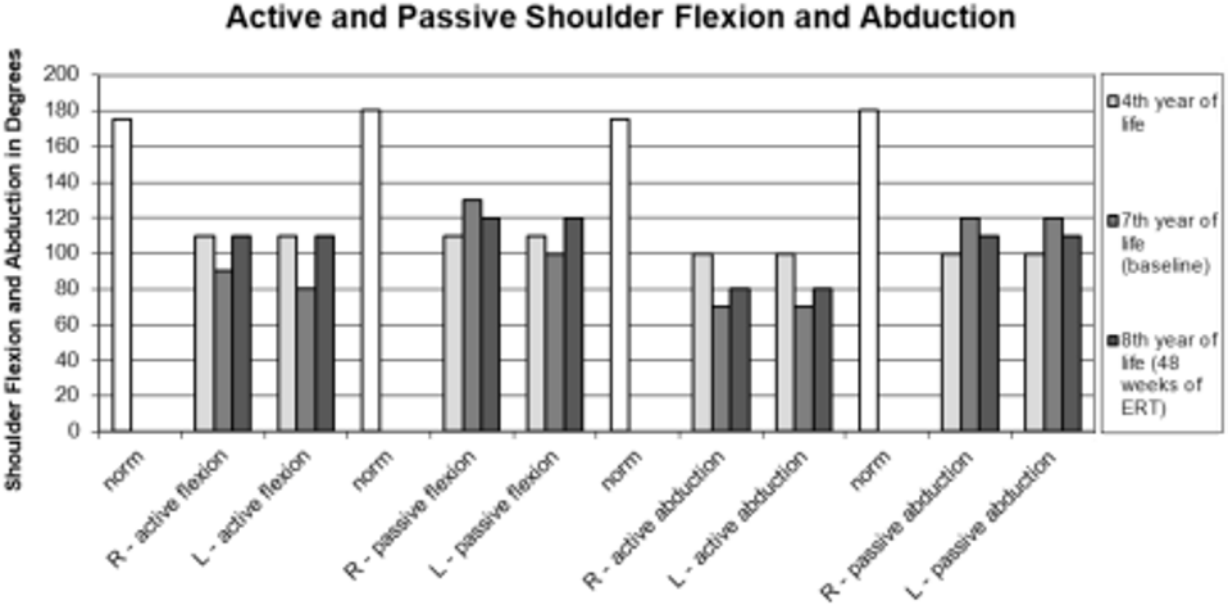

Figure 5. Active/passive shoulder flexion and abduction (in degrees) in MPS VI patient. R: right arm; L: left arm

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(R arm) and 95° (L arm). A difference between right and left side was noticed, which is caused by a right-side scoliosis.

- passive shoulder flexion: flexion contracture 50° (R arm) and 80° (L arm).

The differences between active and passive ROM are caused by muscle atrophy.

- active shoulder abduction: abduction contracture 105° (R and L) - greater restriction than in the case of flexion.
- passive shoulder abduction: abduction contracture 60° (R and L).

Dysfunction of muscle groups responsible for scapula functioning and shoulder girdle was observed in the patient since early age. ROM restrictions in other joints of the upper limbs were predominantly noticeable in elbow extension (extension contracture 20°) and wrist extension (extension contracture 50° for passive and 60° for active ROM).

Limitations in the lower limb joints included:

- active hip extension (extension contracture 15°)
- active knee flexion (flexion contracture 40°), passive knee flexion (flexion contracture 10°) and active and passive knee extension (extension contracture 30°).

After 48 weeks of ERT, we observed improvement (30°) of active shoulder flexion (Figure 6b, 7b, 7c), improvement in passive elbow and wrist flexion (25° and 30°, respectively), and in the lower limbs joints, 10° improvement of passive hip flexion.

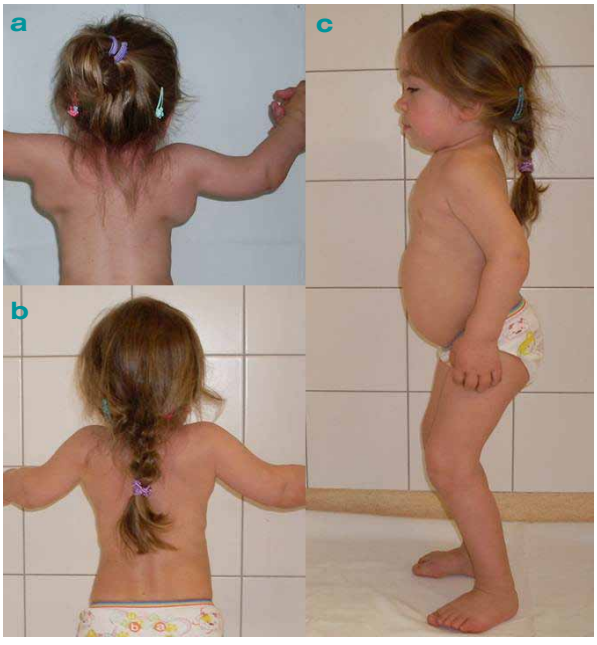

Figure 7. **a** Passive shoulder abduction in a patient with MPS VI at baseline. Dysfunction of muscle groups responsible for scapula functioning can be observed.

b Active shoulder abduction in a patient with MPS VI after 48 weeks of ERT with galsulfase.

c A patient with MPS VI (after 48 weeks of ERT with galsulfase).

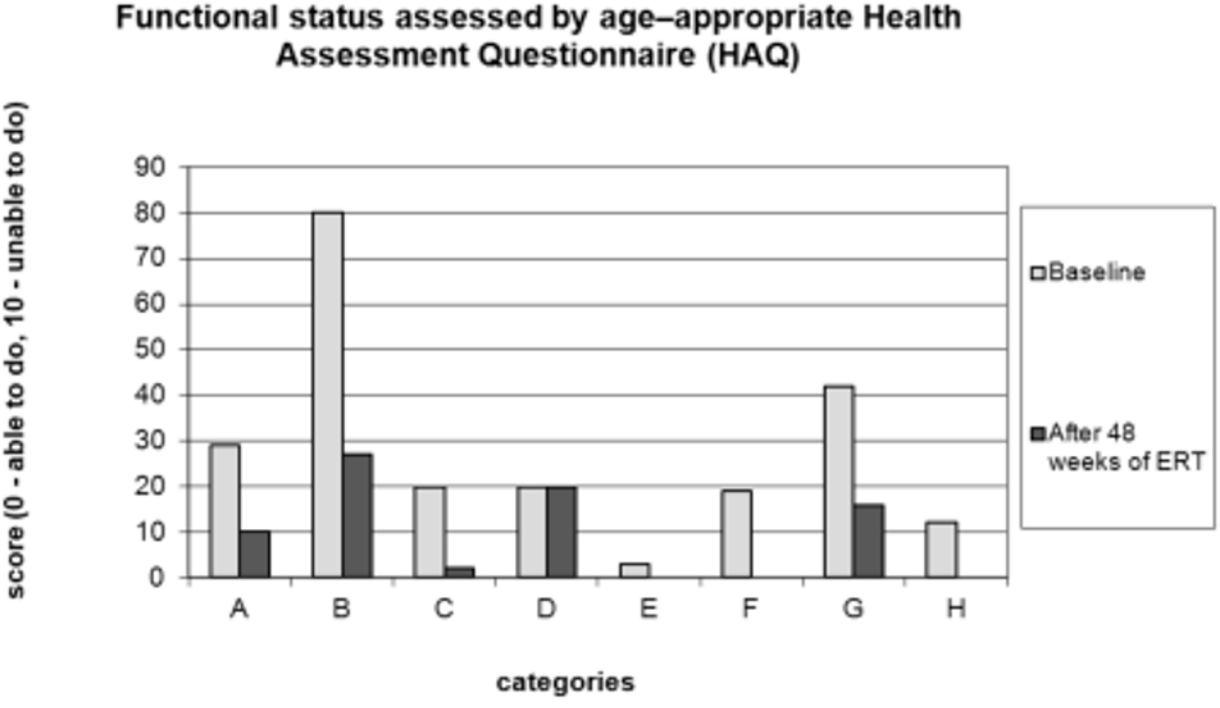

Figure 8. Functional status of the patient assessed by age-appropriate HAQ at baseline and after 48 weeks of ERT.
Categories assessed by HAQ: A: eating/drinking; B: dressing; C: bathing; D: grooming; E: tooth brushing; F: toileting; G: mobility; H: walking and stair climbing.

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3.3 Health Assessment Questionnaire

Improvements in functional status were evidenced by the investigator's observations and responses to the questions on the HAQ (from baseline to 48 weeks, Figure 8). In three assessed categories, the patient achieved full independence, while in other categories improvement was observed.

4. Discussion

Various MPS diseases have overlapping clinical features, such as abnormal cartilage and bone development, leading to short stature, *dysostosis multiplex*, and degenerative joint disease. Analysis of anthropometric measurements in our patient showed differences when compared with those of the normal population, as described previously in the literature for several types of mucopolysaccharidoses (I, II, VI) [5,22,23]. A significant reduction of body height, different body proportions (shortening of the upper and lower extremities, narrowing of the shoulders, chest and hip), and larger head circumference, as well as head length were observed. These irregularities are caused by abnormal cartilage and bone development. Preliminary observations after several months of treatment did not show a clear improvement. Enzyme replacement therapy in MPS diseases represents the most significant recent advance in patient management and the clinical benefits of galsulfase include improvements in respiratory function, joint mobility, walking ability, and quality of life [14,24,25]. However, in the last few years, it has become clear that in patients with LSDs not all organs respond equally to ERT, and some disease manifestations such as bone complications, once established, are difficult to address.

Cartilage is the major site of pathology in mucopolysaccharidoses, leading to painful joints, poor joint mobility, and poor bone growth [8]. The altered mechanical properties of the connective tissue come from the excess amount of collagen fibers, increased and abnormal depositions of GAG in the extracellular matrix, and the reduced amount of elastic fibers caused by their impaired assembly by dermatan sulfate. GAG storage is the primary pathological defect in MPS diseases: it induces a complex sequence of molecular abnormalities leading to inflammation, apoptosis (cartilage), and hyperplasia (synovial membranes), resulting in poorly organized and metabolically abnormal connective tissue matrices. Several recent studies have highlighted the reciprocal relationship between elastogenesis and matrix proteoglycan content of tissues [6,26,27]. In the presence of chondroitin sulfate or dermatan sulfate, tropoelastin is prematurely released from elastin-binding protein, leading to decreased assembly of elastic fibers at the cell surface [6,27]. Accumulation of GAGs within bone, tendon, ligaments, synovial tissue, and skin leads to progressive joint contractures, altered hand function, and loss of fine motor skills. The shoulder joint has the most substantial restriction in MPS patients, with shoulder flexion and abduction being the most compromised movements [28]. This might be explained by the shoulder joints being the first joints to develop in humans, and therefore these are the joints with the longest exposure to GAG accumulation.

The most important aspect of the shoulder joint is the large range of movement that it permits, which is central to many ADL. Scapulas are the most movable parts of the shoulder complex. In the mechanism of shoulder abduction, the first 90° of abduction is performed in the shoulder joint (glenohumeral joint, GH), whereas the scapula does not move in this phase of movement. The next 60° is made possible by scapular rotation. Even with a restricted motion in the shoulder joint, 60° abduction is possible due to scapular rotation. The last 30° of abduction is performed only in the shoulder joint (GH), while the scapulas remains stable [29]. Active shoulder abduction above 90° is performed in sternoclavicular (SC) and acromioclavicular (AC) joints with scapular rotation. Two muscles, the upper trapezius and serratus anterior, are involved in this movement.

The difference between active and passive ROM testing is primarily the difference between the patient's assisting the physical therapist and being fully relaxed. While the passive range of motion focuses on inert tissues, active ROM allows assessment of dysfunction in the movement and determines which muscles are used to make the movement happen.

Analysis of joint ROM in our patient with a severe phenotype of MPS VI showed significant restriction in multiple joints. Flexion contractures were noticeable in all the joints of upper and lower limbs. Dysfunction of muscle groups responsible for scapular functioning and shoulder complex had been observed in the patient since an early age. Shoulder flexion and abduction restriction of passive ROM were greater when compared with active ROM, which may be a result of muscle atrophy. The range of movement in a joint is dependent on two factors: range of motion and muscle length. Flexion contractures cause extensor muscles to stretch and therefore systematically lead to their atrophy [30].

Along with ERT, the patient underwent active physical rehabilitation including mobilization of the nervous system, passive techniques for joint mobility, and active gymnastics for muscle strength. Massage and family training to continue the therapy at home were also provided. After 48 weeks of ERT with galsulfase, we

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observed shoulder mobility improvement (especially in active and passive shoulder flexion), subsequently followed by enhanced self-care. Improvement of shoulder movements enabled the patient to perform daily activities and resulted in a positive impact on both patient and her family. As the patient presents with short stature, improvement of joint mobility impacted ADL, such as the ability to open doors, allowed the patient to be more independent.

ERT, currently approved for patients with MPS I, II, and VI, improves some of the clinical manifestations of MPS disease, such as respiratory function, physical capacity, hepatomegaly, and splenomegaly, as well as joint elasticity, and mitigates the restriction of motion [13-16,31,32]. The long-term impact of ERT on range of motion, and the extent to which treatment may enable achievement and maintenance of full independence in the performance of routine ADL, has been described in a recent study by Tylki-Szymanska *et al* [25]. However, to increase muscle strength, physical exercises and rehabilitation are indispensible. To achieve the holistic benefits of galsulfase therapy, physical therapy should be added and adjusted to the patient's capabilities. Other additional experimental strategies have been suggested to enhance the effects of ERT, such as intra-articular administration of ERT and anti-inflammatory treatment. The results of these studies indicate that by bypassing the synovium using intra-articular ERT, significant reduction in material stored in joint tissues can be achieved [33].

5. Conclusion

Our study illustrates that not all organs respond equally to ERT, and manifestations of the disease in bone cannot be corrected by this therapeutic procedure. Conversely, 48 weeks of ERT combined with enhanced by physical therapy decreased joint restrictions in upper extremities and consequently enhanced self-care in a patient with a severe MPS VI phenotype.

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