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Natural history of Polish patients with mucopolysaccharidosis type VI

Research Article

Agnieszka Jurecka[1,4*], Agnieszka Rozdzynska[2], Jolanta Marucha[1], Barbara Czartoryska[3], Grzegorz Wegrzyn[4], Anna Tylki- Szymanska[1]

[1] *Department of Metabolic Diseases, Endocrinology and Diabetology, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04730 Warsaw, Poland*

[2] *Anthropometry Laboratory, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04730 Warsaw, Poland*

[3] *Department of Genetics, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02957 Warsaw, Poland*

[4] *Department of Molecular Biology, University of Gdansk, Kladki 24, 80822 Gdansk, Poland*

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Abstract: The aim of the study was to describe the natural history, anthropometric features, range of motion (ROM) and molecular characteristics of Polish patients with mucopolysaccharidosis (MPS) VI. Clinical heterogeneity was observed and two major clinical phenotypes of the disease were distinguished, rapidly advancing and relatively attenuated. Two patients developed symptoms early in life presenting with short stature, significant skeletal malformations and other clinical abnormalities. In two other patients, height was only slightly decreased and MPS features developed later in the course of the disease. All patients had similar characteristics at the time of birth but showed significant differences in body proportions when compared with the healthy population. Differences between healthy and affected children increased with age and were reflected in phenotypes. Analysis of ROM showed impairments at multiple joints, although to a various degree in different patients. Restriction in upper extremity ROM was observed since the second year of life, while restriction in lower extremity ROM developed later and influenced stereotype of walking. These limitations intensified with the patients' age, which made self-care more difficult or impossible. The molecular analysis revealed that the milder phenotype may be associated with the R152W mutation, which suggests a specific genotype-phenotype correlation.

Keywords: *Maroteaux-Lamy syndrome • Mucopolysaccharidosis type VI • Anthropometric features • Growth patterns • Growth retardation • Range of motion • Physical therapy*

Abbreviations

ERT - enzyme replacement therapy;
GAG - glycosaminoglycan;
MPS - mucopolysaccharidosis;
ROM - range of motion;
SFTR - sagittal, frontal, transverse rotation system.

1. Introduction

Mucopolysaccharidosis type VI (MPS VI, Maroteaux-Lamy syndrome, OMIM 253200) is an autosomal recessive disorder caused by the deficient activity of the lysosomal enzyme N-acetylgalactosamine 4-sulfatase (arylsulfatase B, ARSB, EC 3.1.6.12), resulting from mutations in the *ARSB* gene [1]. In the absence of this enzyme activity, the stepwise degradation of the glycosaminglycan, dermatan sulfate is blocked, resulting in intracellular accumulation of the substrate into the

* *E-mail: ajurecka@gmail.com*

Table 1. Patient characteristics (demographic and molecular).

Patient No.	Age (y.) diagnosis	Age (y.) current	Gender	GAG in urine (age norm)*	Enzymatic assay**	cDNAmutation	polymorphism
01	3	8	F	1176	13	c.31091insCCTGAAG+delATACT	S384N
				(116 +/- 70)		c.31091insCCTGAAG+delATACT	S384N
02	5	13.5	M	390	***	Y210C	
				(116 +/- 70)		not found	
03	6	17.5	M	579	8.0	Q88X	
				(116 +/- 70)		R152W	
04	37	38	F	624	19.1	R152W	
				(88 +/- 77)		R152W	

** mg/g of creatinine*
*** nmoles/mg of protein/hr; controls 73 ± 38*
**** electrophoresis on polyacrylamide gel (PGE) was performed for discrimination ASB from ASA*

lysosomes and leading to a progressive disorder with multiple tissue and organ involvement [1].

MPS VI is a disorder of the connective tissue, as witnessed by the significant involvement of the bone and cartilage. Bone and joint manifestations are prominent among most patients with MPS disorders due to profound disruption in the normal mechanism of growth and development [2]. Abnormal bone and cartilage development arises from a lack of skeletal remodeling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis and the infiltration by GAGs [3,4]. It has been shown that inflammation, secondary to GAG accumulation, is a critical aspect of MPS disorder and contributes to the bone disease [5]. Clinically, bone and joint involvement can be assessed using anthropometric parameters and joint range of motion (ROM) measurements.

There is a scarcity of literature reporting detailed anthropometric data of untreated children with MPS disease. In studies performed by Tylki-Szymanska et al and Rozdzynska et al, it has been shown that anthropometric features of patients with MPS I and MPS II significantly differ from the healthy population (i.e. children grow considerably slower) and differences increase with age [6,7].

Osteoarticular manifestations of MPS disease are progressive changes that limit movements with some being present from the first years of life onwards [1,8-10]. Both gross and fine motor delays are most evident in patients' locomotor abilities and these abnormalities contribute to a significant inability to perform simple acts of daily living. The shoulder joint has the most substantial restriction of maximum range in MPS patients with shoulder flexion being the movement most compromised, thus leading to considerable limitations in daily activities [8,9].

Since 2005, enzyme replacement therapy (ERT) using galsulfase (recombinant human arylsulfatase B, Naglazyme) became available for MPS VI. ERT has been shown to be effective in ameliorating some of the clinical manifestation of MPS disease [11-13]. The objective of this study was to analyze the natural history, detailed growth patterns and joint range of motion in 4 patients with MPS VI currently living in Poland.

2. Material and Methods

2.1. Study design

The study objectives were as follows:
- to analyze the natural history of patients with MPS VI (patients 1-4, n = 4)
- to evaluate detailed growth patterns in patients with MPS VI before introduction of ERT (patients 1-4, n = 4)
- to evaluate passive and active joint range of motion in patients with MPS VI before introduction of ERT (patients 1-4, n = 4)

All patients were enrolled at The Children's Memorial Health Institute (CMHI) in Poland.

2.2. Patients

All patients enrolled in the study were naive to galsulfase therapy and had to have a diagnosis of MPS VI confirmed by the biochemical determination of arylsulfatase B activity in leukocytes and molecular analysis.
The demographic characteristics of the 4 MPS VI patients are listed in Table 1.

2.3. Ethical Consideration

The protocol was approved by the human-subjects institutional review board at The Children's Memorial Health Institute. Written informed consent had to be provided by the subjects and, if under the age of 18 years, by the parents or legal guardians.

2.4. Methods

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, occipital, forehead, bizygomatic and bigonial breadth. All measurements were taken at the Division of Anthropology, Department of Pediatrics, CMHI according to the 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 the 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) [14-16].

2.4.3. Urinary GAG assays

Biochemical studies included measurements of urinary glycosaminoglycan excretion. Urinary GAG excretion was measured in the first morning void by semi-quantitative method according to Pennock [17]. GAGs were identified by means of electrophoresis on cellulose acetate strips [17].

2.4.4. Measurement of ARSB activity in leukocytes

ASB activity was assayed with p-nitrocatechol as substrate (pH=5.7) in the presence of $AGNO_3$ for ARSA inhibition [18]. In some cases the electrophoresis on polyacrylamide gel (PGE) was performed for discrimination ASB from ASA according to Dubois et al. [19].

2.4.5. Molecular analysis

Molecular analysis was performed commercially by Genomed (Warsaw, Poland).

Table 2. Summary of clinical data of four studied MPS VI patients.

Patient	1	2	3	4
General appearance				
Coarsened facial features	+++	+	+	+/-
Short stature	+++	++	++	+
Head, eyes, nose, throat				
Macrocephaly/scaphocephaly	++	-	+/-	-
Hearing impairement	+		+/-	-
Visual impairment/corneal clouding	+	-	+	+/-
Cardiovascular				
Valve disease	+	+	+	+
Respiratory				
Apnea	+	-	-	-
Gastrointestinal				
Hepato(spelno)megaly	+/-	-	-	-
Umbilical/inquinal hernia	+	-	-	-
Musculoskeletal				
Spinal deformity	+++	+++	++	+
Joint stiffness	++	++	+	+
Joint contractures	+++	+++	++	+
Other	+	+	+	
Neurological				
Carpal tunnel syndrome	-	-	-	-
Spinal cord compression	-	-	-	-

+++ very strong, ++ medium, +slight

2.5. Statistical analysis

All measured anthropometric parameters were standardized for age and gender using the Polish body growth, weight, head and chest circumference reference charts [20,21]. The resulting z-scores were used in all calculations. Descriptive statistics, including means and z-scores were calculated using Statistica 7 PL (Statsoft, Poland).

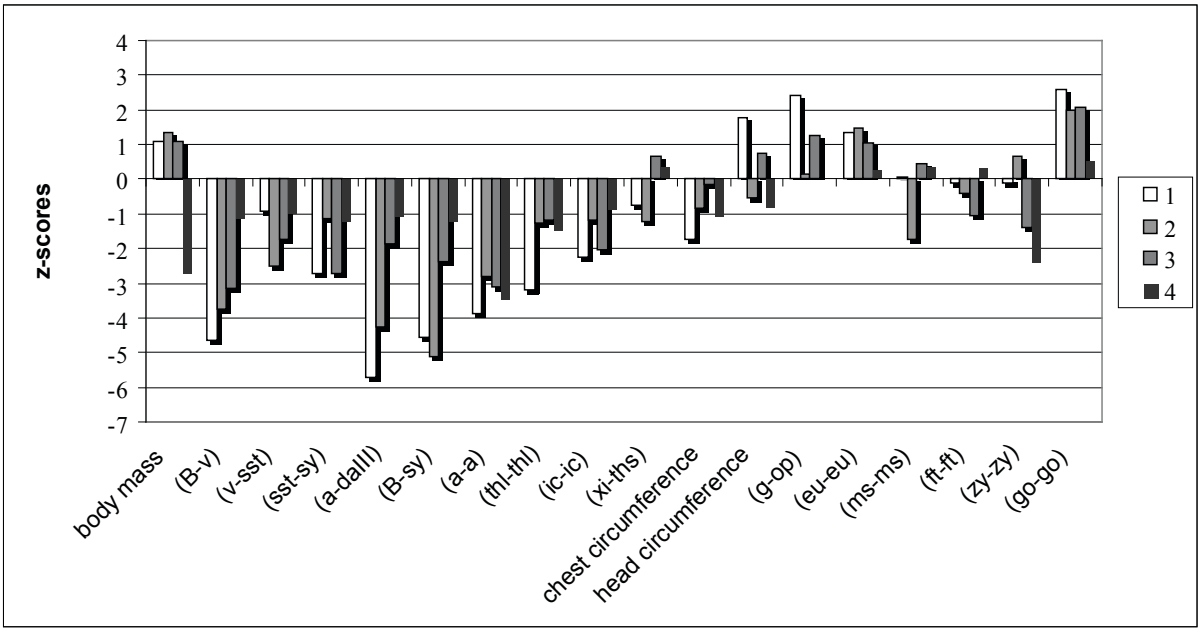
3. Results

Four patients (patients 1-4) were born at term and received a diagnosis of MPS VI at the median age of 5.5 (ranging from 3 to 37 years). All were Caucasian with two being male (50%) and two female (50%) (Table 1).

Clinical evaluation

Table 2 summarizes the clinical data for the studied patients. This section provides more detailed clinical information for the individual cases.

Figure 1. Z-score values of anthropometric features of patients with MPS VI (patients 1-4).



B-v: body height; v-sst: head and neck length; sst-sy: trunk length; a-dalII: upper extremities length; B-sy: lower extremities length; a-a: schoulders width, thl-thl: chest width; ic-ic: hip width; ths-xi: chest depth; g-op: head length; eu-eu: head breadth; ms-ms: occipital breadth; ft-ft: forehead breadth; zy-zy: bizygomatic breadth; go-go: bigonial breadth

3.1. Patient 1

Patient 1, a female, is the second child of unrelated parents. The pregnancy, delivery and neonatal period were uneventful. At birth, her Apgar score was 10, birth weight 4250g (90-97th percentiles), length 58cm (> 97th percentile), and head circumference 35cm (around 50th percentile). At the age of 1, an umbilical hernia was noted and operated on at the age of 2. At that time the other symptoms, such as increased abdomen circumference, recurrent diarrhea and recurrent upper respiratory tract infections, were noted. Due to snoring and sleep apnea, a tonsilectomy was performed at the age of 2.5 years. 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 the age of 3. It was confirmed by elevated urinary GAG with increased dermatan sulphate and the deficiency of ASB i.e. ASB=13 nmoles/mg of protein/hr (normal range 73 ± 38) in leukocytes. At that time physical growth arrest and abnormal gait due to flexional contracture in knee joints became noticeable. Additionally, 1st degree mitral stenosis was noted. Due to joint contractures, the patient started systematic physical therapy. The patient's intelligence is normal.

The found mutation of the *ARSB* gene is c.31091insCCTGAAG+delATACT (homozygous) and polymorphism S384N.

Currently she is 8 years old.

3.2. Patient 2

Patient 2, a male, is the first child of unrelated parents. At birth, his Apgar score was 8, birth weight 4250g (90-97th percentile), birth length 62cm (> 97th percentile) and head circumference 35cm (around 50th percentile). The neonatal period was unremarkable. First symptoms, such as growth arrest and skeletal malformations, were noted at the age of 3 years.

Characteristic radiological features (*dysostosis multiplex*) led to suspicion of MPS VI at the age of 5 years. It was confirmed by elevated urinary GAG with increased dermatan sulphate and by the absence of ARSB band after PGE of arylosulphatases.

Clinically, the patient presented with significant skeletal malformations, abnormal gait and joint contractures. Echocardiography revealed ventricular septum thickening and 4th degree mitral regurgitation.

The mutation of the *ARSB* gene is Y210C/unknown.

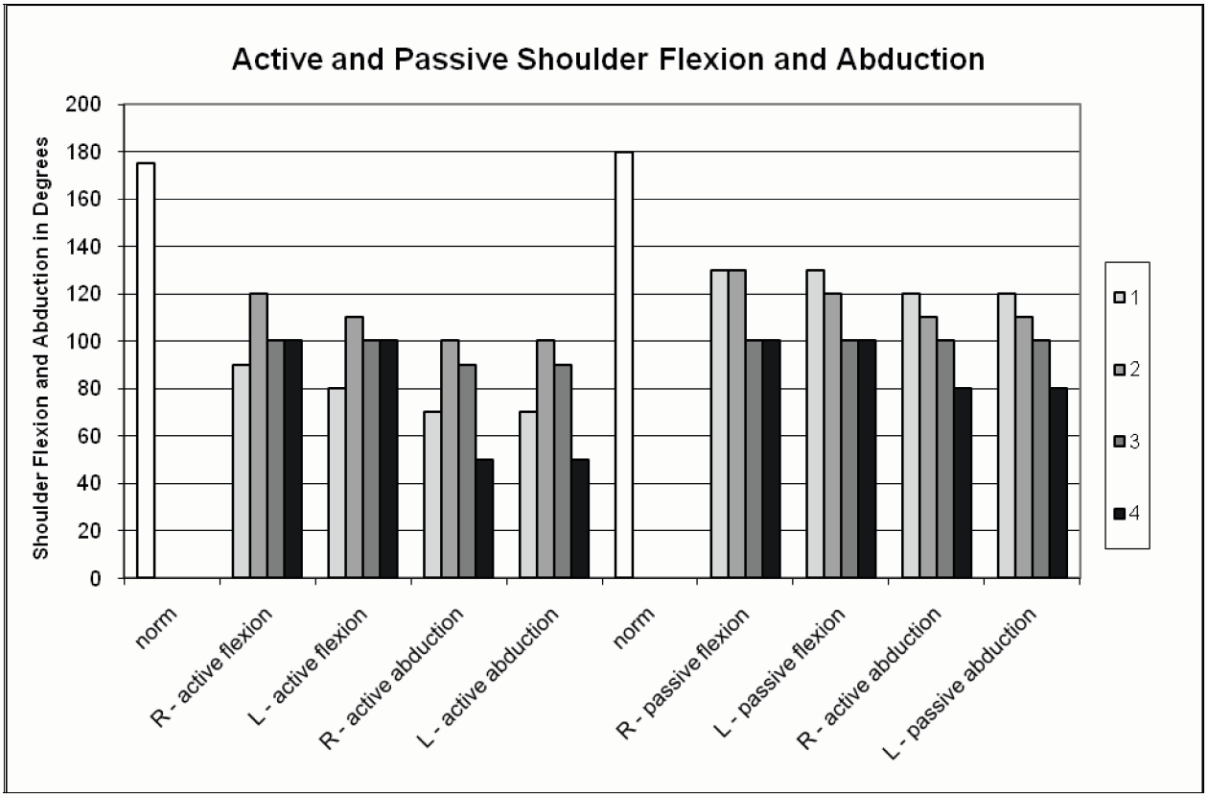
Currently he is almost 14.5 years old.

3.3. Patient 3

Patient 3, a male, is the third child of unrelated parents. At birth, his Apgar score was 8, birth weight 4500g (90-97th percentile) and birth length 61cm (> 97th percentile). The elder sister died at the age of 13 due to cardiac insufficiency in the course of Maroteaux-Lamy syndrome.

At the age of six years a diagnosis of MPS VI was established in a course of a family investigation. The

Figure 2. Active/passive shoulder flexion and abduction (in degrees) in 4 patients with Maroteaux-Lamy syndrome before ERT.



shoulder flexion: upraise of upper extremities troughtout flexor; shoulder abduction: upraise of upper extremities throughtout abduction; R: right arm; L: left arm

main abnormalities at that time were slight skeletal malformations and hearing impairement. At the age of 9 years, thickening of the mitral valve and 2nd degree mitral regurgitation, decreased physical activity tolerance and hearing deterioration were observed. The patient's intelligence is normal, he requires a hearing aid and attends a public school.

It was confirmed by elevated urinary GAG with increased dermatan sulphate and the deficiency of ASB i.e. ASB=8 nmoles/mg of protein/hr (normal range 73 ± 38) in leukocytes.

The mutations of the *ARSB* gene are R152W and Q88X.

Currently he is 17.5 years old.

3.4. Patient 4

Patient 4, a female, is a second child of unrelated parents (from neighbouring villages), birth weight 5200 g (> 97th percentile), birth length 60 cm (> 97th percentile). The neonatal period and subsequent childhood were uneventful. Retrospective analysis of this period by the patient, revealed slightly decreased physical endurance and decreased shoulder joint range of motion when compared with peers. At the age of 21 years, she gave birth. Since then, the patient noticed slight deterioration of her health. She experienced recurrent bone pain. At the age of 37 years, cardiovascular manifestations presented abruptly (significantly decreased physical activity tolerance, dyspnea, generalized fatigue).

A typical result of heart ultrasound examination together with radiologic features (*dysostosis multiplex*) led to the suspicion of MPS disorder. MPS VI was confirmed by elevated urinary GAG with increased dermatan sulphate and the deficiency of ASB i.e. ASB=19.1 nmoles/mg of protein/hr (normal range 73 ± 38) in leukocytes. Very mild corneal clouding was detectable by slit-lamp examination.

The patient's pheonotype is relatively attenuated.

The mutations of the *ARSB* gene are R152W (homozygous).

Currently she is 38 years old.

3.5. Measures of skeletal growth

All measured anthropometric parameters were standardized for age and gender using the Polish reference charts [20,21]. The resulting z-scores were showed in Figure 1. Among three patients (patients 1-4) a significant reduction of body height (z-score values:

from -3.13 to -4.64) was observed. The body height of patient 4 was between the 10 and 25 percentiles, therefore remaining normal. Three patients (1-3) had both upper (z-scores from -1.87 to - 5.72) and lower extremities (z-score value from -2.39 to -5.12) shorter than the healthy population. Among all of the patients narrowing of shoulders (z-score value from -2.80 to -3.87) was observed.

Regarding facial features, it was observed that patients 1-3 had larger values of bigonial breadths than healthy children z-scores from: 1.97 to 2.09), on the other hand, patient 4 had normal value of bigonial breadths, but a larger value of bizygomatic breadth.

The nutrition status, based on BMI, Cole Index and skinfolds measurements, were normal in all of patients. Joint range of motion Figure 2 presents passive and active ROM in 4 patients in selected upper limb joints before introduction of ERT.

Significant limitations in upper limb joints included:

- shoulder flexion: mean restriction of active ROM was 70°. A significant difference may be noticed between right and left side, which is caused by a right-side scoliosis.
- shoulder abduction: mean restriction of active ROM is 95° (greater restriction than in the case of flexion).

Dysfunction of muscle groups responsible for scapula functionining was observed very early.

Other range of motion restrictions in upper limbs are predominantly noticeable in elbow extension, wrist flexion and wrist extension.

Restriction in lower extremity ROM was observed early in life in hip joints (especially in hip extension). In patients 1 and 2 (unlike patients 3 and 4) significant restriction was noticeable in knee extension (mean restriction 30°).

4. Discussion

MPS VI is a a rare lysosomal storage disease with approximately 1,100 patients reported worldwide. During the last 30 years, 7 patients have been recognised in Poland. In this study, we describe the detailed clinical, biochemical and molecular findings of 4 living Polish patients with Maroteaux-Lamy syndrome.

MPS VI disease presents with a broad phenotype spectrum of severity and according to the current concept it is a continuum of phenotypes ranging from severe to mild. Clinical heterogeneity is especially prominent in the less severe end of the spectrum. It is clearly visible in the case of our patients, who represent two major clinical phenotypes: rapidly and relatively attenuated. Two patients (patient 1 and 2) presented with early symptoms and a rapidly advancing phenotype with short stature, coarse facial features and degenerative joint disease. These patients were diagnosed at the age of 3 and 5, respectively. In patients 3 and 4, symptoms appeared later in the course of the disease and these patients were diagnosed significantly later (38th year of life in case of patient 4, patient 3 was recognized through a family history and subsequent screening). Phenotypic features in patient 3 were difficult to notice at an early age as well as at the time of diagnosis, and it is highly probable that the patient would have not been recognized without a family screening until later in life.

In patient 1, clinical symptoms such as growth retardation, skeletal malformations, an inguinal hernia, hearing impairment and corneal opacity were visible already during 2-3 year of life. Similarly, patient 2 presented with joint contractures and skeletal abnormalities since early childhood. Patient 3 was diagnosed through a family screening at the age of 6. At that time, the only symptoms he presented were a slight chest malformation and hearing impairment. In patient 4, diagnosed with MPS VI at the age of 37, cardiac insufficiency (due to a complex mitral valve disease with mitral regurgitation) was a major symptom.

The above comparison shows that despite characteristic MPS VI features (such as short stature, coarse facial features, skeletal abnormalities, joint contractures, corneal opacities, hearing impairment and cardiac manifestations) not all patients presented them with the same intensity and at the same age. Growth retardation and skeletal abnormalities may be visible in the first years of life (patient 1 and 2), in the later childhood (patient 3), but might also remain unnoticed until adulthood (patient 4). Silimarly, corneal opacities, associated with MPS disease, may be present with different intensities in different patients (including no opacities). Cardiac manifestations in our patients included thickening of valves leading to their regurgitation as well as heart hyperthrophy. They were present in all patients although to a different degree.

The molecular analysis revealed that patients with less severe phenotype had the R152W mutation, either in a homozygotic (patient 4) or heteozygotic (R152W/Q88X) state. This was in contrast to the severe phenotype patients which bear different mutations. Therefore, one might speculate that the missense mutation p.R152W may be responsible for a relatively attenuated phenotype of MPS VI as has been suggested in the literature previously [22,23]. On the other hand, this analysis is based on molecular data of only four patients, and the hypothesis on the genotype-phenotype correlation must be tested in a study with a higher number of patients.

An intriguing feature is a lack of correlation between the mutation type, residual enzyme activity and severity of the disease. Nevertheless, this problem has already been addressed in other MPS types, and it was proposed that it is possible to predict (to some extent) severity and the clinical course of MPS patients, only when more parameters are considered simultaneously, like residual enzyme activity and the rate of GAG synthesis [24].

Analysis of anthropometric measurements among patients with MPS VI allowed for distinction of features which deviated from the normal population. Each feature revealed a different individual variability, some irregularities occurred among all patients while others in one of the patients. In three patients (patients 1-3) a significant reduction of body height was observed. In contrast patient 4, with an attenuated form of MPS VI, had a relatively normal body height. The body proportions were different from the proportions observed in the healthy population. Shortening of the upper and lower extremities (patients 1-3), and narrowing of the shoulders (all patients) were observed.

Individuals with MPS VI are described as having large heads which tend to be longer than normal. In our respondents both the head circumference and the head breadth were normal for their age. As for head length, only patient 1 had a longer head in comparison to healthy peers. However increased head size was revealed when head measurements were compared to patients' height age. As for facial features, it was observed that patients 1-3 had larger values of bigonial breadths than healthy children. On the other hand patient 4 had normal value of bigonial breadths but larger value of bizygomatic breadth.

All studied patients with MPS VI were larger then the healthy population at the time of birth. The values of body weight and lenght were above 90 percentile.

Irregularities observed in our patients are characteristic for several other mucopolisaccharidoses (MPS I, II, VI) and are caused by disruption of bone and cartilage development, probably beginning in the fetal phase [2,3,5,10]. Our data shows that anthropometric features of patients with MPS VI significantly differ from the healthy population. Children with MPS VI grew considerably slower, and differences between healthy and affected children increased with age.

Analysis of joint ROM showed impairments at multiple joints in all MPS VI patients. Restriction in upper extremities ROM can be observed since the first year of life. These limitations were particularly visible in the shoulder joint. The shoulder joint can obtain the largest range of motion of all joints in human body. Functionally, it provides sufficient mobility, in synergy, with the elbow and wrist, to allow many different positions and orientations of hand. Voluntary movement control of the elbow, wrist, and finger flexion always occur when shoulder flexion is initiated.

Restriction in lower extremity ROM, especially contractures of hip and knee joints with shortening of Achilles tendon, tend to develop later in life and influence stereotype of walking. These limitations intensified and became more severe with the patients' age, making patients' self-care more difficult or even impossible. MPS VI patients, similarily to patients with other MPS disease, require introduction of a proper rehabilitation program during the ERT [10]. Practical improvement of joint elasticity achieved by ERT must be enhanced by increased muscle strength achieved by active physical rehabilitation [10].

5. Conclusions

1. Polish MPS VI patients presented with clinical phenotypes within a broad spectrum, ranging from severe to relatively mild. Clinical features of MPS VI varied among our patients; however two major clinical phenotypes of the disease can be distinguished: rapidly advancing and relatively attenuated.
2. Anthropometric features of patients with MPS VI significantly differed from the healthy population. Growth patterns were associated significantly with MPS VI at birth. Children with MPS VI grew considerably slower, and differences in body proportions between healthy and affected children increased with age.
3. Analysis of joint ROM showed impairments at multiple joints in all MPS VI patients, although to a various degree in different patients. Restriction in all upper extremity ROM was observed since the second year of life, while restriction in lower extremity ROM developed later in life and influenced stereotype of walking. These limitations intensified and became more severe with the patients' age, making patients' self-care more difficult or even impossible.
4. The R125W mutation may be responsible for a milder phenotype of patients. This hypothesis should be tested in studies on a bigger group of MPS VI patients.

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