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REGULAR ARTICLE

Restricted joint range of motion in patients with MPS II: correlation with height, age and functional status

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ABSTRACT

Aim: The aims of the study were to assess shoulder range of motion (ROM) in patients with mucopolysaccharidosis type II (MPS II) and to correlate joint mobility with patients' height, age and functional status.

Methods: Passive ROM and *Z*-score of height were followed in 29 patients with MPS II (mean age 11.5 years, range 2–29 years) between the years 2005 and 2010. Passive ROM was measured by a goniometer, and height, by a stadiometer. Functional status was assessed by an age-appropriate health assessment questionnaire (HAQ).

Results: (i) A strong correlation was observed between patients' age and *Z*-score of patients' height ($R = 0.78$, $p < 0.001$). (ii) A medium correlation was observed between *Z*-score of patients' height and passive shoulder flexion and abduction ($R = 0.697$, $p < 0.001$ and $R = 0.63$, $p < 0.001$, respectively). The progression of restriction was slower in attenuated patients. (iii) Restrictions in shoulder flexion and abduction were already observed before the second year of life. (iv) ROM limitations intensified and became more severe with age. (v) Activities of daily living depended on cognitive impairment of patients with MPS II.

Conclusion: Range of motion limitations in patients with MPS II correlate with patients' height, increase with patients' age and are more pronounced in a severe form of MPS II.

INTRODUCTION

Hunter syndrome, or mucopolysaccharidosis type II (OMIM 309900), is an X-linked, progressive lysosomal storage disease in which patients are deficient in the lysosomal enzyme iduronate-2-sulfatase (IDS, EC 3.1.6.13), which results in cellular accumulation of the glycosaminoglycans (GAGs) dermatan and heparan sulphate (1).

As with all the MPS disorders, Hunter syndrome is clinically heterogeneous in terms of the extent and rate of progression of organ impairment in affected individuals. Patients can be broadly classified as having one of two forms of MPS II: a severe form or an attenuated form. In the severe form of the disease, signs and symptoms (including neurological impairment) develop in early childhood, whereas in the attenuated form, signs and symptoms develop in adolescence or early adulthood, and patients do not experience significant cognitive impairment (1,2).

Various MPS diseases have overlapping clinical features including widespread joint abnormalities (stiffness and contractures), skeletal deformities (*dysostosis multiplex*), obstructive and restrictive airway disease and cardiac disease (1,2). The underlying cause of degenerative joint and

Abbreviations
ADL, Activity of daily living; CNS, Central nervous system; GAG, Glycosaminoglycan; HAQ, Health assessment questionnaire; PT, Physical therapy; ROM, Range of motion; SFTR, Sagittal, frontal, transverse, rotation system.

Key notes
- Restrictions in shoulder flexion and abduction in patients with mucopolysaccharidosis type II (MPS II) are observed already before the second year of life.
- Range of motion (ROM) limitations in patients with MPS II correlate with patients' height.
- Range of motion limitations increase with patients' age and are more pronounced in a severe form of MPS II.

bone disease is a lack of skeletal remodelling, disordered endochondral and intramembranous ossification, disruption of normal elastogenesis and the infiltration by GAGs of the ligaments, tendons, joint capsules and other tissue structures (3–5). GAG storage in MPS 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 (5–8).

The objective of this study was to describe the profile of the joint mobility of shoulder girdle in patients with MPS II and to correlate it with patients' height, age and functional status.

MATERIAL AND METHODS

Study design

The objectives of the study were to assess:

passive shoulder ROM in patients with MPS II (n = 29);
correlation between joint mobility and patients' height (n = 29);
correlation between patients' age and patients' height (n = 29);
correlation between joint mobility and patients' age (n = 29); and
functional status (n = 10, 5 patients with cognitive impairment, 5 patients without cognitive impairment).

All patients with MPS II were enrolled at The Children's Memorial Health Institute (CMHI) and were naïve to ERT at the time of the study.

Patients

All patients with MPS II were to have a diagnosis of MPS II confirmed by the biochemical determination of iduronate-2-sulfatase activity deficiency in leucocytes and by molecular analysis.

The demographic characteristics of the 29 patients with MPS II are listed in Table 1.

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. The study was designed and conducted in compliance with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

Table 1 Patient characteristics (demographic, molecular characteristics and clinical phenotypes)

Patient No.	Age (y.) diagnosis	Age (y.) current	Gender	Change at DNA level	Height (SD)	Disease severity
01	2/12	3	M	c.1568A>G	0.82	Mild
02	1 6/12	2	M	c.950_951delCT	0.76	Severe
03	1 3/12	2	M	c.998C>T	0.60	Severe
04	2	2	M	c.950_951delCT	1.02	Severe
05	3 4/12	4	M	c998C>T	−1.04	Severe
06	2 3/12	4	M	nd	2.13	Severe
07	2 6/12	5	M	c.950_951delCT	−0.26	Severe
08	4 3/12	5	M	c.1001A>C	−1.19	Severe
09	3 7/12	5	M	c.1135_1136insGTA	−0.77	Severe
10	4 10/12	6	F	c.1568A>G	−0.80	Severe
11	4 11/12	9	M	c.1011G>A	−4.56	Severe
12	6 3/12	10	M	c.1011G>A	−2.24	Severe
13	9	11	M	c.1048A>C	−2.18	Mild
14	3 7/12	11	M	c.148G>C	−5.77	Severe
15	4	11	M	c.879G>T	−2.91	Severe
16	8 5/12	12	M	c.181T>C	−3.51	Mild
17	1 7/12	12	M	c.419del1588	−5.29	Severe
18	3 4/12	12	M	nd	−2.26	Severe
19	6 6/12	12	M	c.1030G>A	−2.32	Mild
20	4 10/12	13	M	c.1696delT	−3.98	Severe
21	7 7/12	14	M	c.567A>C	−6.03	Severe
22	5 2/12	14	M	nd	−5.68	Severe
23	4 2/12	14	M	c.475G>A	−1.18	Severe
24	6 6/12	15	M	c.163delG	−7.45	Severe
25	4 4/12	17	M	c.196C>T	−6.17	Severe
26	6 1/12	18 ½	M	nd	−9.26	Severe
27	3	22	M	c.1034G>T	−5.41	Mild
28	1 3/12	24	M	c.1034G>T	−5.71	Mild
29	5	26	M	c.1034G>T	−4.43	Mild

ND = Not determined.

Methods

Passive ROM was measured in degrees with the use of a double-armed goniometer as an objective method (shoulder ROM measurements are taken in a sitting position). It was assessed by the same physiotherapist (JM) using the International Method of Measuring and Recording Joint Motion (SFTR system; sagittal, frontal, transverse, rotation). The SFTR method of recording joint motion and position in the internationally accepted neutral-zero method provides an international system (9–12). Normative values for the ROM of passive shoulder flexion and abduction are 180 degrees (9,10,12,13).

Anthropometric measurements were taken according to the standard technique. Until the age of 3 years, length was measured in the supine position using a liberometer (accuracy to 1 mm). The same measurements in older children were taken for standing height using a stadiometer (accuracy to 1 mm).

Functional status was assessed by an age-appropriate health assessment questionnaire (HAQ). It is a comprehensive clinical assessment instrument used to evaluate the functional capabilities and performance in children and adults with MPS (14).

Statistical analysis

The rank Spearman correlation test was used for statistical analyses. Spearman rank correlation was chosen because this correlation describes monotonic dependence between two variables. The strength of the correlation was based upon the STATISTICA Handbook (StatSoft, Krakow, Poland).

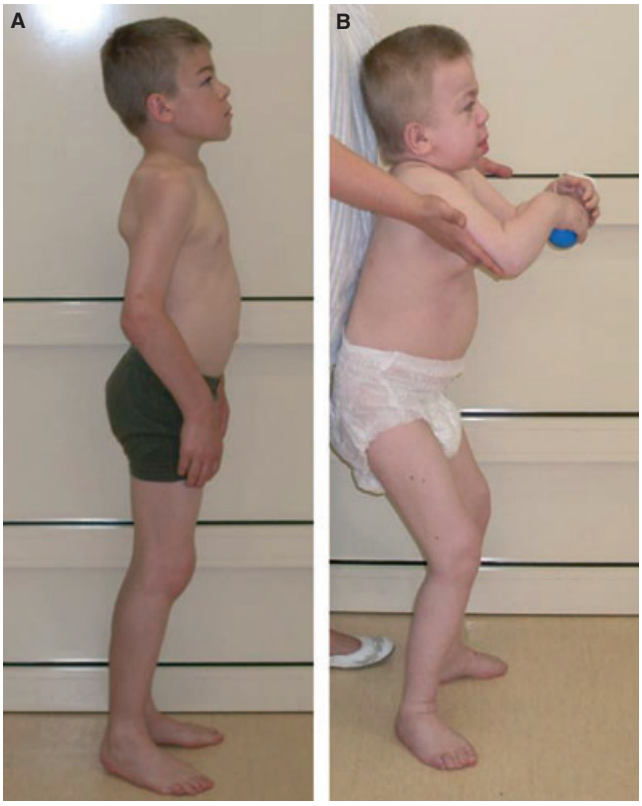

Figure 1 (A) A 12-year-old patient with a mild mucopolysaccharidosis type II (MPS II) phenotype (height 138cm, *Z*-value of height −2.32), visible contractures of upper extremities. (B) A 15-year-old patient with a severe MPS II phenotype (height 116.7cm, *Z*-value of height −7.45), visible contractures of upper and lower extremities.

RESULTS

Patients

Twenty-nine patients (patients 1–29, Table 1) were born at term and received a diagnosis of MPS II at a mean age of 4.1 years (ranging from 2 months to 9 years). They were enrolled in the study at a mean age of 11.5 years (ranging from 2 to 29 years; Table 1). Twenty-three patients were classified as severe with cognitive impairment (78.8%), while 6 patients had the attenuated form with normal mental development (20.2%). All were Caucasian, and one patient was female. All patients were enrolled at the study site in Poland, and all completed the study.

Clinical studies

Passive range of motion in untreated patients with MPS II

Restrictions in shoulder flexion and abduction in patients with MPS II were observed before the second year of life (Figs 1 and 2).

Correlation between joint mobility and patients' height assessed as Z-score

A medium correlation was observed between *Z*-score of patients' height and passive shoulder flexion and abduction ($R = 0.697$, $p < 0.001$ and $R = 0.63$, $p < 0.001$, respectively). In attenuated patients, progress in the restriction of passive shoulder movements was slower (Fig. 3A, B).

Correlation between patients' age and patients' height assessed as Z-score

A strong correlation was observed between patients' age and *Z*-score of patients' height ($R = 0.78$, $p < 0.001$).

Correlation between joint mobility and patients' age

In all patients, ROM limitations intensified and became more severe with age. A medium correlation was observed between patients' age and passive shoulder flexion ($R = 0.563$, $p = 0.001$). In attenuated patients (with normal intelligence), slower progression of restriction of passive shoulder flexion was observed. A medium correlation was observed between patients' passive shoulder abduction and patients' age ($R = 617$, $p = 0{,}0003$) (Fig. 4A, B).

Functional status in patients with cognitive impairment and patients with normal mental development

Patients with an attenuated form of MPS II were generally independent in self-care, mobility and walking, while patients with cognitive impairment needed moderate or complete caregiver assistance in self-care within all

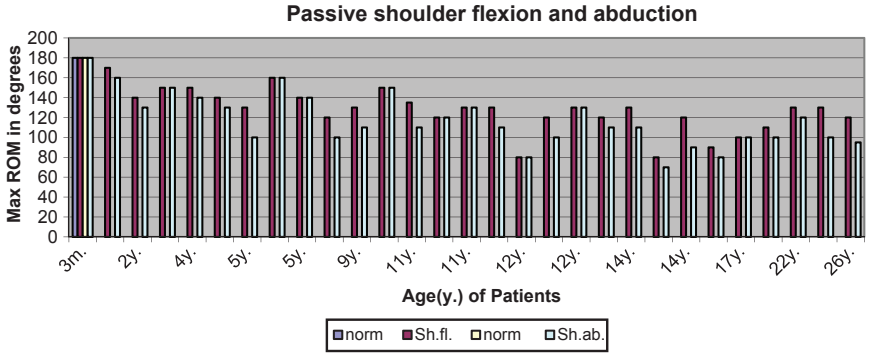

Figure 2 Passive shoulder flexion and abduction in a group of patients with mucopolysaccharidosis type II (n = 29).

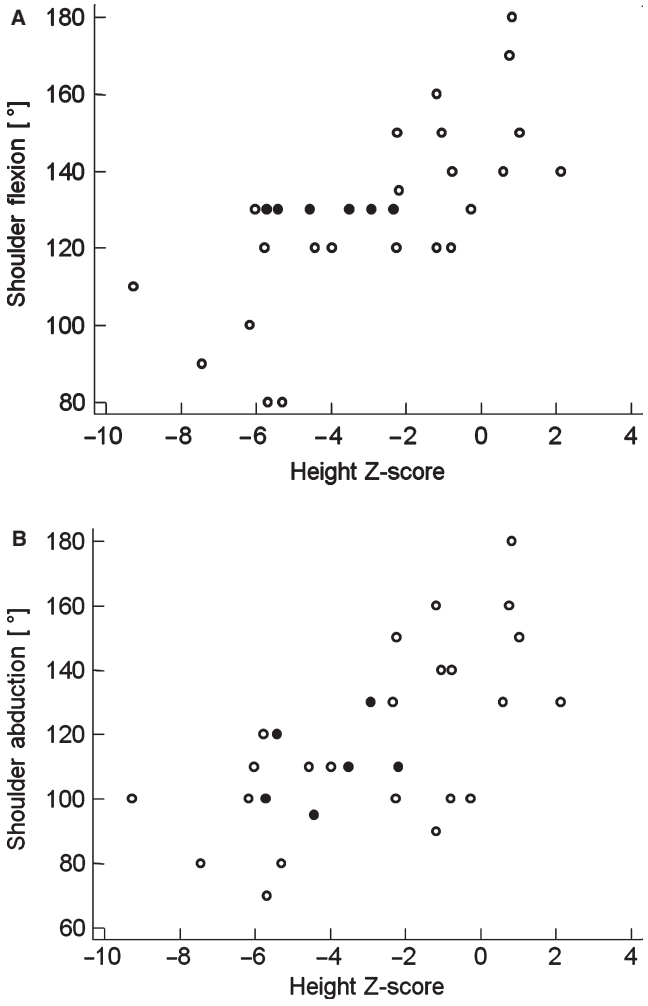

Figure 3 (A) Correlation between passive shoulder flexion and *Z*-score of patients' height in a group of patients with mucopolysaccharidosis type II (MPS II) (n = 29). Black circlets indicate patients with attenuated form. (B) Correlation between passive shoulder abduction and *Z*-score of patients' height in a group of patients with MPS II (n = 29). Black circlets indicate patients with attenuated form.

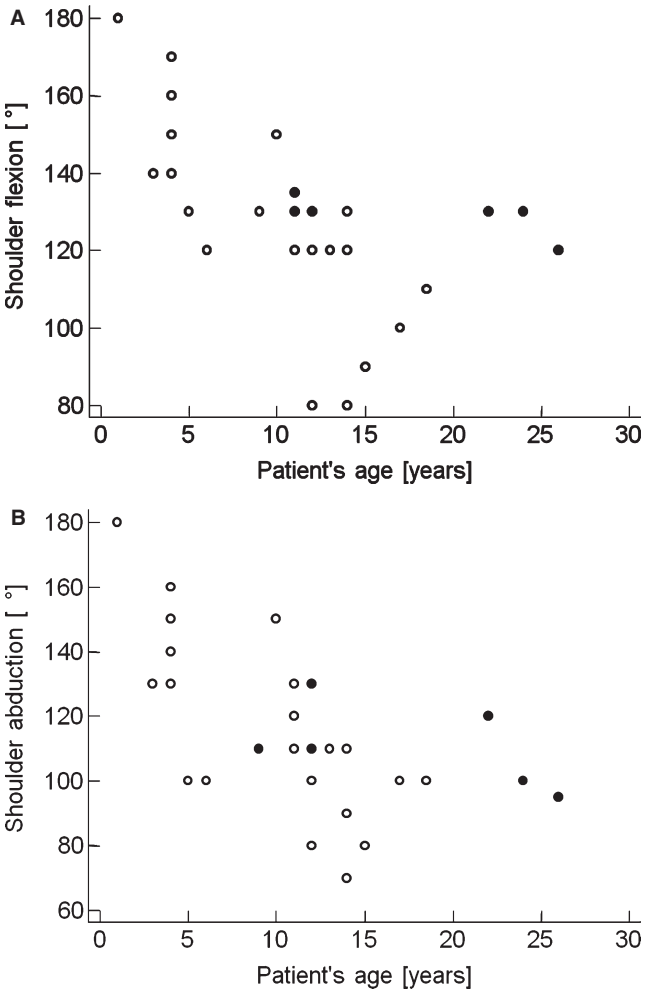

Figure 4 (A) Correlation between passive shoulder flexion and patients' age in a group of patients with mucopolysaccharidosis type II (MPS II) (n = 29). Black circlets indicate patients with attenuated form. (B) Correlation between passive shoulder abduction and patients' age in a group of patients with MPS II (n = 29). Black circlets indicate patients with attenuated form.

categories (data not shown). In the case of attenuated patients, younger boys (11–12 years) already had joint ROM limitations in upper limbs, however, required only minimal help with daily activities. Older attenuated patients were more dependent on external help especially when dressing up and bathing.

DISCUSSION

Mucopolysaccharidosis disorders are characterized by severe skeletal abnormality including growth failure, abnormal bone structure (*dysostosis multiplex*), and severe articular cartilage and joint disease because GAGs are fundamental in connective tissue structure and function. The accumulation of GAGs from foetal life within bone, ligaments, synovial tissue and skin leads to functional deficits including progressive joint contractures, altered hand function and loss of fine motor skills. Cartilage is the major area of pathology in mucopolysaccharidoses, leading to poor bone growth, poor joint mobility and painful joints (5,6,8). The contractures cause significant loss of joint mobility and are one of the earliest noteworthy indicators.

Although the phenotypic expression of MPS II spans a wide spectrum of clinical severity, patients can be divided into two groups: severely affected patients with profound neurologic involvement leading to cognitive impairment and developmental regression and attenuated patients with normal intelligence (1,2). A delay in global milestones is the first clue of brain involvement in children with the CNS form of MPS II. Progression of the CNS disease is inexorable, usually resulting in developmental regression between the ages of 6 and 8 years (15). In a group of studied patients, 70% were above 6 years of age, and only 6 patients had the attenuated form of disease. In patients with the attenuated phenotype, one can assume that higher residual enzyme activity leads to lower levels of toxic dermatan sulphate, which has a detrimental effect on epiphyseal cartilage as well as on bone structure.

In patients with MPS II, widespread joint involvement can cause less or more pronounced loss of function. The most involved joints are the elbows with reduced extension, pronation and supination; the shoulders with limitation of flexion, abduction and lateral rotation; and the wrists with restriction of flexion and extension (16,17). However, studies of the mobility profile of MPS patients are scarce, and those that exist employ these variables as measures of treatment outcomes (18–20).

Our study provides evidence for early ROM impairments in children with MPS II. Restrictions in shoulder joints were the earliest symptoms being observed already before the second year of life. The shoulder joint reaches the largest range of movement in the human body. Functionally, the shoulder provides sufficient mobility, in synergy with elbow and wrist, to allow many different positions and orientations of the hand. The shoulder motion is limited by overlying soft tissue, and shoulder abduction is the first movement that becomes restricted in patients with MPS II. Restrictions of shoulder abduction are more pronounced than those of shoulder flexion, and therefore, they could be a more sensitive marker to measure efficacy of ERT.

A correlation was observed between joint mobility and patients' height. The physical development of children with MPS II significantly differs from standards for healthy children. At the time of birth, patients with MPS II are larger than the healthy population. During the first 3 years of life, they grow faster than normal, slowing down by the end of the third year and in subsequent years reaching increasingly lower values when compared with the reference charts (21). A correlation between joint mobility and patients' age was particularly visible in older patients with cognitive impairment and significantly restricted ROM of shoulder joints. With age, skeletal abnormalities (*dysostosis multiplex)* and joint diseases increase. Flexion contractures in hip and knee joints lead to smaller values of patients' height. In general, shorter patients tend to have greater ROM restrictions, while taller patients have lesser ROM restrictions, especially in lower limbs (knee joints) (18,19). Wolff's law stated that every change in form and function of a bone, or in its function alone, is followed by certain definite changes in its internal architecture and equally definite secondary alteration (11,22). In a shorter version, bone is deposited and resorbed in accordance with the stresses placed upon it. Therefore, if the stress placed upon the bone is higher than its tolerance, it will result in longitudinal bone growth inhibition. The degree of growth inhibition is dependent upon the growth speed, the exertion of the pressure and time of exposure to the pressure. The younger the body, the lesser stresses can lead to growth inhibition (23). Flexion contractures restrict longitudinal bone growth by decreasing the correct pressure on epiphyseal cartilages and their proliferation site where cell proliferation takes place. Additionally, severe changes in the voluntary muscles in MPS II disease have been attributed to a distal motor neuropathy with significant damage to axon terminals and motor end-plates because of GAGs accumulation (24).

In patients with cognitive impairment (78,8% of all investigated patients), ROM limitations intensified with age making patients' self-care more difficult or even impossible.

Greater physical activity supports physiological growth stimulation. It has been suggested that a proper rehabilitation programme is an indispensible part of management of patients with MPS II disease. Physical therapy is designed to preserve and improve physical function and offers a non-surgical approach to the management of joint involvement of Hunter syndrome (20).

CONCLUSION

Range of motion limitations in patients with MPS II correlate with patients' height, increase with the patients' age and are more pronounced in patients with severe form of MPS II.

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CONFLICT OF INTEREST

There was no potential, perceived or real conflict of interest. There were no study sponsors. No honorarium, grant or other form of payment was given to produce the manuscript.

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