

## OSTEOARTHROPATHY IN MUCOPOLYSACCHARIDOSIS TYPE II

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### Abstract

**Introduction.** Mucopolysaccharidosis type II (MPS type II, Hunter syndrome) is a rare (~ 1/1500.000), X-linked inherited disorder (affects boys) due to deficiency of the lysosomal enzyme iduronate sulfatase (Xq.28). The complex clinical picture includes osteoarthropathy with a tendency to flexion stiffness and disability. In our country, the specific diagnosis and enzyme replacement therapy (ERT), are recently available in the Center for Genetic Pathology Cluj.

**Objectives.** Assessment of clinical features, radiological and imaging of osteoarthropathy in MPS type II and their evolution under ERT.

**Material and methods.** The study included 9 male patients with a suggestive clinical picture of MPS type II; the diagnosis was confirmed by enzymatic assay and the patients were treated with ERT. Osteoarthropathy was assessed before treatment: a) clinical tests (joint goniometry, walking test) and b) radiology (X-rays of the hand and wrist, spine and pelvis), bone densitometry in five patients. Clinical tests were repeated after therapy.

**Results.** Chronic osteoarthropathy was present in all patients. Joint mobility was reduced with quasi stationary trend after 12 months of treatment. The walking test was improved after treatment. Radiological assessment revealed: hand bones changes, delayed bone age, vertebral changes, pelvis changes, kipho-scoliosis and aseptic necrosis of the femoral head in 100%, 88%, 88%, 55% and 11% respectively. Bone mineral density was normal in five of the nine patients evaluated.

**Conclusions.** Chronic osteoarthropathy with flexion stiffness is an essential component of the clinical picture of MPS type II. ERT allows an improvement/arrest of evolution (depending on disease severity and time of initiating therapy).

**Keywords:** osteoarthropathy, mucopolysaccharidosis type II, ERT.

### Introduction

Mucopolysaccharidosis type II is an X-linked inherited disorder caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase, owing to a mutation in the I2S gene located on the long arm of the X chromosome. As a result of this deficiency, the glycosaminoglycans that accumulate in lysosomes are dermatan sulfate and keratan

sulfate [1]. The disease occurs exclusively in males, is a multisystemic disease and the clinical presentation is variable from mild to severe forms, although the genetic enzyme deficiency is the same. The clinical phenotype consists of: dysmorphic features (enlarged head, coarsening of facial features, enlarged tongue), hypertrophic tonsils and adenoids, hepato-splenomegaly, abdominal and/or inguinal hernia, cardiovascular and musculoskeletal involvement and variable intellectual delay [2]. The disease is vary rare, the incidence in Europe is 1/140000-156000 neonates [2].

The skeletal involvement “dysostosis multiplex” is

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due to a defect in bone production and its manifestations are: short stature consecutively growth zone involvement of the long bones and bone deformities of the skull, chest and spine (kyphosis, scoliosis), hip dysplasia [3]. The arthropathy is determined by the glycosaminoglycans' storage within the cartilage and connective tissues and inflammation [4]. It is progressive and the clinical manifestations are joint contractures. Enzyme replacement therapy with idursulfase obtained by recombinant DNA (Elaprase), 0.5 mg/kg/dose, i.v., one dose weekly was approved in 2006 [5]. The treatment efficiency is conditioned by the time of the onset. The specific diagnosis of this disease has been possible since 1997, the disease is underdiagnosed and the treatment is started usually late. A better understanding of the clinical manifestations and the arthropathy characteristics could lead to a earlier diagnosis of this disease.

### Objectives

The authors proposed to present the clinical and radiological characteristics of the arthropathy in mucopolysaccharidosis type II and their evolution under enzyme replacement therapy.

### Subjects and methods

Nine males were evaluated by complete clinical examination, iduronate-2-sulfatase blood enzyme test (leukocytes). This enzyme is presented in all types of cells of the body, apart from the mature red blood cells, so its activity can be determined into variable types of cells, plasma and serum. The determination of the enzyme activity by the fluorimetry method was done at Sahlgrenska University of Medicine Sweden and at University of Medicine Mainz, Germany [6].

One patient died, six patients are undergoing enzyme replacement therapy with Elaprase (for one year – 5 patients and for 9 years – one patient who participated in a therapeutic trial before introducing therapy with Elaprase in Europe) and 2 patients newly diagnosed who will initiate the therapy soon.

The arthropathy was evaluated by: a) clinical tests (joint goniometry, 6-minute walking test) and b) radiological and imaging tests (hand and wrist, spine and pelvis) in all patients, osteodensitometry before treatment in 5 patients (DEXA General Electric Lunar Prodigy Advance). Goniometry and walking test are indicated for assessment during treatment. *The mobility of the joints* was assessed in a sagittal plane for the following joints: shoulder (flexion), elbow (flexion, extension) and wrist and digits (flexion, extension) [7,8]. Five patients were assessed before treatment (one who did not undergo treatment and 4 patients who underwent treatment); two patients were not assessed because of their lack of compliance.

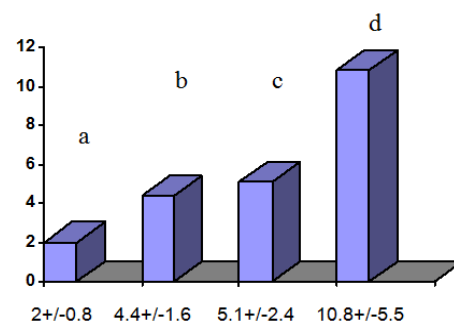
A six-minute walking test measured the distance traveled by the patient back and forth during 6 minutes [9]. The test was done before treatment in 3 of 8 patients: in

2 patients before treatment and after one year of enzyme replacement therapy and in one patient before treatment. The others five patients did not perform the test, 4 patients could not perform the test because of neuromotor delay, immobilization in a wheelchair because of aseptic necrosis of the femoral head and lack of compliance (one, one and 2 patients respectively). A patient who was undergoing the treatment could not be assessed before treatment because he was not under our observation at that time.

The study was conducted with the approval of the ethics committee of the Emergency Hospital for Children Cluj.

### Results

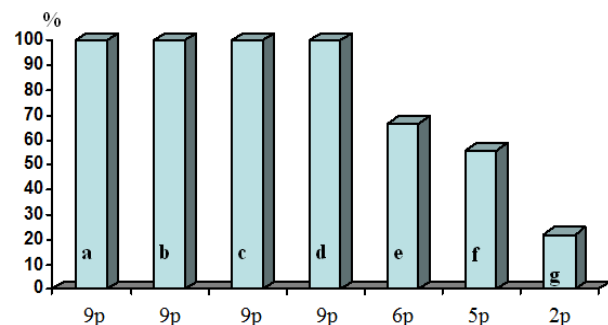
The age at clinical onset, at diagnosis and at starting therapy are presented in figure 1.



a – age at clinical onset  
b – age at nonspecific diagnosis  
c – age at specific diagnosis  
d – age at starting therapy

**Fig. 1.** Age of MPS type II patients.

The clinical characteristics are presented in figure 2.



a – arthropathy  
b – dysmorphic features  
c – hypertrophic cardiomyopathy  
d – respiratory infections (otitis)  
e – intellectual delay  
f – short stature  
g – ear prosthesis

**Fig. 2.** Clinical characteristics in MPS type II patients.

**Table I.** The joint goniometry results.

Patient	Shoulder flexion		Elbow flexion		Elbow extension		Wrist and digits flexion		Wrist and digits extension	
	N - 175 °		N - 150 °		N - 0 °		N - 80°		N - 70°	
	a	b	a	b	a	b	a	b	a	b
R.V. <sup>1)</sup>	110°	110°	120°	120°	20°	15°	40°	40°	10°	20°
A.T. <sup>1)</sup>	110°	110°	130°	130°	30°	25°	40°	45°	20°	25°
V.B. <sup>1)</sup>	100°	100°	120°	120°	30°	30°	40°	40°	10°	10°
S.N. <sup>1)</sup>	80°	80°	125°	125°	30°	30°	40°	40°	10°	10°
A.B. <sup>2)</sup>	120°	-	135°	-	15°	-	50°	-	30°	-

a – before treatment <sup>1)</sup> treated for one year

b – after 12 months of treatment <sup>2)</sup> not treated yet

**Table III.** The radiological changes.

Radiological changes	Hand and wrist radiography		Dorso-lumbar spine radiography		Pelvis radiography		
	Delayed bone age	Short metacarpal, facets metaphysis	Beaked, rounded vertebral body,	Kipphosis, scoliosis	Cup-shaped pelvis	Acetabular cup insufficiently covered	Aseptic femoral head necrosis
Patients	(n) 8	9	8	5	8	8	1
	% 88.8	100	88.8	55.5	88.8	88.8	11.1

The joint goniometry before treatment (in 5 patients) and after one year of treatment (in 3 patients) are presented in table I.

Six-minute walking test results are presented in table II.

**Table II.** Six-minute walking test results.

Patient	Six-minute walking test (m)	
	before treatment	after 12 months of treatment
R.V.	376.2	433.1
A.T.	363.5	461.7
A.B.	351	-

The radiological changes are presented in table III.

The results of osteodensitometry (before treatment) in 5 patients are presented in table IV.

**Table IV.** Z score L2-L4.

Patient	Age (years)	Z score L2-L4
R.V.	11.1	-0.8
A.T.	12.5	-1.1
V.B.	7.9	-0.4
S.N.	9.9	-0.4
A.B.	6	0.3

**Discussions**

The osteoarticular involvement is a very important sign which with dysmorphic features can guide the diagnosis of MPS type II. It is progressive and represents a major cause of disability for these patients.

In our group the median age at clinical onset was 2+/-0.8 years, which is comparable with the age of 1.8 years, reported by Wraith et al. [10]. The median age at specific diagnosis was 5.1 years and at treatment onset was 10.8 years. The difference between the age at diagnosis and the age at starting therapy (5.7 years) is explicable because the enzyme replacement therapy has only been available

in Romania since 2011, 5 years later than when it was approved in Europe.

The arthropathy was accompanied by dysmorphic features and obstructive cardiomyopathy in all patients; 66.6% of patients presented limited/intellectual delay; 55.5% of patients presented short stature and 22.22% of patients had ear prosthesis.

The joint mobility before treatment revealed a reduction in all joints evaluated and after 12 months of treatment showed stationary values, the same as the results reported by other studies [11]. So we can conclude that the enzyme replacement therapy prevents the worsening of the disease but does not improve the already established joint changes.

The distance walked in 6 minutes was 363.5 m, comparable with 362 m, reported by Link et al. [9]. After 12 months of treatment the distance walked in 6 minutes increased with 56.9 m and 98.2 m in 2 patients who were evaluated before and after treatment. Other studies reported a smaller distance (37 m), but because of the large number of patients enrolled (94 patients and 96 patients respectively), a comparison of the results is not permissible [11,12]. The prevalence of the radiological changes (table I): hand bones changes; delayed bone age; aseptic necrosis of the femoral head (100%; 88%; 88%; 55% and 11%) is comparable with that reported by Link et al. [11].

The bone density was normal in 4 patients, because of their age and short duration of disease evolution [13]. The single patient with under normal values was the oldest of the group.

**Conclusions**

Chronic arthropathy with joint stiffness is an essential component of the clinical manifestations of MPS type II and represents a predictive factor for disability and impaired quality of life.

Enzyme replacement therapy can realize an

improvement/stop in arthropathy evolution; the results of the treatment depend on the severity of the clinical form and the age of the treatment onset.

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