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Modern approaches to therapy of mucopolysaccharidoses in children

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Mucopolysaccharidoses are a group of hereditary metabolic disorders characterized by accumulation of glycosaminoglycans caused by the deficiency of lysosomal enzymes. ***The study was aimed at*** *analyzing effect of enzyme replacement therapy on somatic condition and psychomotor development of children with types I and II mucopolysaccharidosis of varying severity over time and appraising efficacy thereof.* ***Patients and methods:*** *the study used data of a 5-year-long observation of 13 patients with types I and II mucopolysaccharidosis. The study involved analysis of the therapy efficacy using the following criteria: data on physical examinations, ultrasonography of liver, spleen and heart, quantitative determination of urine glycosaminoglycan excretion, assessment of articular and extra articular affection (JADI scale), assessment of social age and social coefficient (Doll's scale).* ***Results:*** *significant differences of urine glycosaminoglycan concentration, results of objective appraisal of liver and spleen dimensions and ultrasonography over the entire spleen area after 6 and 12 months of treatment in comparison with the initial data. A significant reduction in social coefficient had been registered at the first therapy stage; after that, all differences were insignificant. Significant dynamics of the articular syndrome in the setting of the therapy was not observed due to stabilization of the process. Significant proofs of neither positive nor negative dynamics of myocardial involvement or ultrasonic properties of hepatic lobe sizes were observed.* ***Conclusions:*** *enzyme replacement therapy is an efficient method of treating somatic manifestations of various types of mucopolysaccharidoses.*
Keywords: *mucopolysaccharidosis, enzyme replacement therapy, implantable venous access port systems.*

Introduction

Mucopolysaccharidoses (MPSs) are a group of hereditary metabolic disorders characterized by excessive accumulation of glycosaminoglycans (GAGs) caused by the deficiency of specific lysosomal enzymes. Each MPS type is characterized by a particular enzyme defect; this allows classifying patients with MPSs into different categories (tb. 1).
MPSs are characterized by involvement of all organs and systems in the pathological process, including central nervous, musculoskeletal and cardiovascular systems. The disease is often accompanied by psychomotor retardation. The key point defining fate of an MPS patient is early diagnosis; it allows starting enzyme replacement therapy (ERT) on time and determining whether bone marrow transplantation is possible without waiting for complete development of the clinical pattern. Early therapeutic intervention allows delaying and reducing the degree of irreversible affection of organs and systems and the degree of functional disorders, improving quality of life of the child and his/her family in whole and increasing the patient's life expectancy up to 11-21 years of age at severe MPS forms [1], whereas the average life expectancy at the untreated Hurler syndrome is 6.8 years [2].

There is a wide range of non-specific methods of treating patients with lysosomal storage diseases at the moment, including symptomatic and substrate reduction therapy, surgical and non-surgical correction of deformities, chronic ENT-pathology treatment and methods of specific therapy associated with enzyme replacement or not. Substrate reduction therapy is based on the GAG synthesis suppression and prevention of GAG accumulation in cells. The results obtained in the animal studies modeling Tay-Sachs [3] and Sandhoff diseases [4, 5] served as the background for use of substrate reduction therapy. Use of this type of treatment resulted in lower substrate accumulation in the central nervous system and, therefore, lower intensity of the disease symptoms. After that, similar studies were conducted with regard to type I Gaucher's disease (positive effect was attained) [6]. Substrate reduction therapy of MPSs is conducted using genistein, which may be used to treat neurological forms of types I and II MPS, although it is more often used for treating patients with type III MPS. Genistein (4',5,7-trihydroxyisoflavone or 5,7-dihydroxy-3(4-hydroxyphenyl)-4H-1-benzopyrone) is a plant estrogen. The drug inhibits tyrosine kinase of the epidermal growth factor, which reduces GAG generation. Efficacy of this treatment method was demonstrated in studies of fibroblast cell cultures of MPS patients. Fibroblasts of the MPS patients undergoing ERT with α-L-iduronidase were used as the control group. The results were similar: GAG concentration decreased in both cases [7]. It was also established that genistein does not reduce GAG concentration below the normal values due to the feedback mechanism, which determines GAG concentration and is responsible for degradation of the excess of such compounds only. The main side effect is associated with reduction in fertility in male patients. Some patients mention pronounced weight gains in the setting of the drug intake. Due to the known side effects, substrate synthesis suppression method is mostly used for treatment in the event of high residual enzyme activity, especially characteristic of late and more benign disease forms. Unfortunately, genistein does not sufficiently affect GAG synthesis in chondrocytes and fibroblasts despite tyrosine kinase activity inhibition [8]. It is also known that the drug does not feature a dose-dependent effect. Thus, use of high doses (150 mg/kg) in 22 children with MPSs for 12 months did not result in a significant GAG level reduction in comparison with the use of average therapeutic doses (5-15 mg/kg) despite the pronounced reducing effect observed in studies of the mice, which were administered 160 mg/kg of the drug. The drug's estrogen effect resulted in development of gynecomastia corresponding to the 2nd Tanner stage in 2 boys in the setting of the therapy. GAG concentration varied, whereas cognitive development of the patients remained the same or slightly deteriorated (in 2 patients). No significant adverse events associated with the use of high doses of the drug were observed [9].

The therapy associated with enzyme replacement is represented by two variants: ERT proper and bone marrow transplantation (BMT). ERT is based on the use of exogenous enzymes resulting in excretion of the accumulated undegraded products [10], whereas BMT is based on endogenous replacement of the enzymes generated by donor cells. A series of experiments on cell cultures demonstrated the possibility of cross correlation of enzyme deficiency between different lines of cell cultures, i.e. enzyme synthesis in one cell line may affect another group of cells and degrade the substrate [11-13].

BMT efficacy significantly depends on the MPS type an age at the procedure. The best results have been registered in type I MPS patients at the age of 0-2 years, when affection of the central nervous system has not become severe yet. In general, use of BMT in type I MPS patients is more efficient than in patients with other MPS types. Recovery of the enzyme's proper activity up to the normal values and decrease in the formerly excessive GAG excretion level down to the upper normal level for that age was registered in the post-transplantation period. The resulting biochemical shifts (enzyme activity and GAG excretion level) remain stable for a long period of time due to donor chimerism [14-17].

Use of BMT in type II MPS patients did not result in a sufficient increase in the proper enzyme's activity and was unsafe due to high rates of mortality associated with the complications, which may be induced by the BMT procedure itself [18].

Discovery of mechanisms of posttranslational modification and transport of lysosomal enzymes served as the background for ERT development [19]. It was established in 1970s that surfaces of cell membranes contain mannose 6-phosphate receptors, which bind and transport enzyme inside the cell. Experiments on a cell culture with low activity of lysosomal enzymes demonstrated that the exogenous enzyme administered in the cultural environment is capable of penetrating the cell and successfully catabolizing the intracellularly accumulated substrate. The ERT effect was first demonstrated on the example of a fibroblast culture with administration of an exogenous enzyme [20]. Genetically engineered enzymes are the drugs used for therapy of these diseases [21].

The main factor limiting ERT efficacy is impenetrability of the hematoencephalic barrier for the enzyme due to large molecular weight of the protein molecule. That is why the therapy has almost no effect on neurological manifestations of the disease. Intrathecal introduction of enzyme drugs is one of the alternative methods of delivering the drug to the central nervous system. We analyzed cerebrospinal fluid of 10 patients with severe or mild type I MPSs intrathecally receiving laronidase with 30-90-day-long intervals for a period of 1 year in clinical studies. We revealed a transitory increase in the titer of class G antibodies to laronidase and increase in the concentration of interleukin 5, protein and leukocytes. Headache was the most widespread side effect. All the side effects were resolved by oral intake of non-steroidal anti-inflammatory drugs. No immediate or delayed allergic reactions were registered [22]. We continued the observation of 5 patients in order to appraise safety of this mode of administration. The therapy was considered efficient and safe for treating spinal cord compressions [22]. Clinical testing of intrathecal idursulfatase administration aimed at appraising safety (phase I/II completed) and efficacy (in progress) of the therapy is in progress.

Experimental and clinical studies demonstrated that substrate accumulation results in immunological response of the body. We observed correlation of substrate accumulation with inflammatory response of the body in the context of Farber disease. Thus, e.g., it is known that ceramide accumulation in synovial membrane cells leads to activation of CD95+-lymphocytes, which express apoptosis induction signal receptors – antigens Fas [23]. Immunological and immunoinflammatory mechanisms underlie both Farber disease and almost all lysosomal storage diseases. Use of anti-inflammatory drugs in combination with ERT in order to terminate articular syndrome is a new approach to MPS treatment. A range of works proved safety and efficacy of pentosan polysulfate not only in animal studies, but also in patients with MPSs. The drug is a heparinoid featuring fibrinolytic, anticoagulant and chondroprotective activity. In the setting of anti-inflammatory PPS therapy in rats, motion range of joints increases, nasal secretion amount decreases, trabecular structure and mineral bone density improve in the event of early beginning of the therapy. The drug does not affect the accumulated amount of GAGs [24].

Genetic therapy using viral vectors, BMT, BMT-based therapy and pharmacological chaperones constitute the future strategies of MPS treatment, especially of severe MPS forms involving the central nervous system [25].

Moreover, we developed strategies of introducing genetic therapy using adeno- and lentiviruses to treat MPSs [26]. There is a practice of intracerebral introduction of the viral vector containing human lysosomal enzyme, the deficiency whereof causes type IIIA MPS. Efficacy of a 6-month-long such therapy of 4 patients has been confirmed. As a result, health condition improved in 100% of the patients (in the form of stabilization [50%] or lower cortical atrophy [50%]). Moreover, moderate improvement of behavior, attention and sleep in 3 patients and the youngest patient (2 years 8 months of age) and cognitive development progress were observed [27].

The study was aimed at analyzing effect of enzyme replacement therapy on somatic condition and psychomotor development of children with types I and II mucopolysaccharidosis of varying severity over time and appraising efficacy thereof.

Patients and methods

STUDY SUBJECTS

13 patients with types I and II MPS have been observed and undergone ERT at the SPbSPMU 3rd pediatric unit within the last 5 years. The study involved 8 boys and 5 girls: 8 patients with type I MPS (3 boys and 5 girls) and 5 patients with type II MPS (5 boys). Out of the children with type I MPS, 2 girls developed Hurler-Scheie syndrome, the other 6 children – a severe form of the disease (Hurler syndrome). Out of the children with type II MPS, 1 patient developed a mild form of the disease, the other patients – a severe form of the disease. Brief description of the children undergoing therapy is given in tb. 2.

STUDY METHODS

We analyzed the therapy efficacy using several criteria: data on physical examinations (liver and spleen dimensions), ultrasonography of liver, spleen and heart, EchoCG involving appraisal of myocardial thickness of the intraventricular septum and the left ventricle's posterior wall, quantitative determination of urine GAG excretion, assessment of articular and extraarticular affection (JADI scale), assessment of social age and social coefficient (Doll's scale).

STATISTICAL DATA MANIPULATION

The results were statistically analyzed using software package Microsoft Excel and calculation of Friedman and Wilcoxon tests. The data were presented as the median and the interquartile range (25-75%). The differences were considered statistically significant $p < 0.05$.The results are given in tb. 3.

Results

It is known that the enzyme's proper activity is one of the criteria used for establishing diagnosis. The enzyme's normalized activity median in the group of children under study was 0.4% (0.02-1.0%) from the upper normal limit. The ERT beginning median was 6.0 (1.3-6.8) years of age. Therapy efficacy was assessed in 2 points: after 6 and 12 months of the therapy. The obtained results were compared with the initial parameters (before the therapy). We revealed significant differences in the urine GAG level and results of physical assessment of liver and spleen dimensions after 6 and 12 months of the treatment in comparison with the initial parameters (pic. 1). Use of ultrasonography allowed revealing significant positive dynamics only for the spleen area (pic. 2). We revealed significant decrease in the social coefficient at the first therapy stage (the first 6 months); after that, differences are not significant (pic. 3). We revealed no significant dynamics of the articular status (joint stiffness and contractures) in the setting of the therapy due to, apparently, joint alteration process stabilization in the MPS structure. We received significant proofs of neither positive nor negative dynamics of myocardial involvement (hypertrophic cardiomyopathy) or ultrasonic properties of hepatic lobe sizes.

Discussion

ERT has been available for treating type I MPS since 2003, type VI MPS – since 2005, type II MPS – since 2007. In Russia ERT has been available for treating type I MPS since 2007, type II MPS – since 2008, type VI MPS – sine 2009. A drug for treating type IV MPS – recombinant form of N-acetylgalactosamine-6-sulfatase – was developed and registered in 2014; it is not available in Russia at the moment [28].

ERT is especially efficient at mild and moderate forms of types I and II MPS and at type VI MPS. The age at diagnosis establishment and ERT beginning is of crucial importance, as the sooner the treatment has begun, the higher its efficacy and lower the risk of irreversible alterations [19, 29]. The following parameters were selected as ERT efficacy criteria: motion range in shoulder joints, respiratory function and urine GAG excretion level [30]. There are data on generation of antibodies to the drugs used for ERT at MPSs. Antibodies are class G immunoglobulins; according to some researchers, they do not cause anaphylactic reactions or any other severe infusion reactions [31]. Other studies have demonstrated that patients with antibodies against the exogenously introduced enzyme are susceptible to the higher risk of side infusion reactions [32]. These immunoglobulins are not neutralizing, unlike the antibodies generated for the drug, which is used to treat Pompe disease [19]. It was demonstrated in the context of generation of antibodies to the enzyme drug for treating type VI MPS that the average seroconversion duration is 26 weeks (from the beginning of the therapy). The antibody titer was analyzed using semi-quantitative ELISA: 1:1,250-1:6,250 on the average. It was established that the titer increases throughout the first year of the therapy and subsequently stabilizes. No clinical symptoms of the pronounced effect of antibody generation on ERT results were revealed [30]. The other study appraised antibody generation effect at the treatment of type II MPS with iduronate sulfatase. Results of the 2-year-long ERT in 63 patients were summarized. Antibody generation was registered in 37% of the children; it was also observed that synthesis of the antibodies to the drug did not lead to reduction in the forced expiratory volume, six minute walk test or alteration of liver or spleen dimensions.

Our observational data on a group of MPS patients correlates with the experience of our European colleagues and the data given in the foreign literature. The therapy appeared efficient and safe. No severe side effects were registered. Unfortunately, there are no laboratories capable of detecting antibodies to enzyme drugs in the Russian Federation, which is why we are unable to monitor antibody generation processes of our patients.

Approaches to the quality of medical care are changing in the modern conditions, especially in pediatric practice. Medical care of children should first of all meet safety criteria and have the highest possible compliance level. Implantable port systems have been introduced in the countries of Europe and America to perform frequent and prolonged infusions. Such systems were introduced into medical practice in Russia in 1993. The main idea of setting a port system is to transform any (venous, arterial, peritoneal, pleural, spinal) infusion into a simple subcutaneous injection, which would be less painful and easier to perform. In order to reduce the degree of children's discomfort during the visit to an inpatient hospital in order to receive an infusion, as well as to facilitate work of the medical personnel, implantable venous access port systems were implanted to several children with MPSs in Saint Petersburg. Port is a small container with a titanium camera in the bottom part and a silicone membrane in the top part; a special needle is used to penetrate the silicone membrane in order to perform blood sampling punctures, administer drugs and wash the device (pic. 4). A catheter is connected to the lateral part of the port; its other end is put into the superior vena cava over the point of entry to the right atrium (pic. 5). Port is a radiopaque device, which is why it is easy to control position of the system and possible to use magnetic resonance study methods. These systems have come into practice from pediatric oncology, where they are widely used for long-term and frequent infusions of various drugs. They are not exposed to various stimuli between infusions and provide maximum comfort and quality of life. At the Saint Petersburg State Pediatric Medical University (SPbSPMU), port systems are implanted in 5 children with MPSs. Model Celsite Baby port 4.5 French (pic. 6) was implanted to younger children with body weight up to 15 kg, model Celsite port 6.5 French – to older children with body weight of 20-35 kg. The devices are easy to use and do not restrict children's everyday activity. We observed no cases of thrombosis or infection within 2 years of using port systems. A local anesthetic is applied to the skin puncture site in order to minimize painful sensations associated with port puncture. Another

important advantage is a relative freedom of child's movement during the infusion, as the needle is reliably fixed on the skin over the port (pic. 7).

Conclusion

ERT is an efficient method of treating somatic alterations of organs in systems in the MPS structure. In the process of the study, we determined clinical biochemical parameters – efficacy markers of the ERT effect on somatic condition of children: urine GAG excretion reduction, reduction in liver and spleen dimensions. Process stabilization was observed in the setting of the treatment: we registered neither signs of increase in the degree of cardiac affection (hypertrophic cardiomyopathy) nor significant positive and/or negative dynamics. Similar data were obtained on the musculoskeletal system's (joints) affection. ERT does not affect dynamics of psychomotor development parameters. The disease progresses; this is indicated by reduction in the social coefficient in the first 6 months of treatment. The obtained data may be explained by impenetrability of the hematoencephalic barrier for enzyme drugs. However, according to the subjective opinion of parents (poll), children's well-being, behavior and respiratory function improved and nocturnal apneas stopped to occur in the setting of the therapy.

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Table 1. Classification of mucopolysaccharidoses

Type of mucopolysaccharidosis	OMIM	Gene localization	Enzyme	Accumulated glycosaminoglycans	Rate of occurrence
Type I mucopolysaccharidosis: Hurler syndrome Hurler-Scheie syndrome Scheie syndrome	607014 607015 607016	4p16.3	α-L-iduronidase	Dermatan sulfate, heparan sulfate	1:100,000
Type II mucopolysaccharidosis (Hunter syndrome)	309900	Xq27-28	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate	1:110,000-1:1,325,000
Type III mucopolysaccharidosis (Sanfilippo syndrome)				Heparan sulfate	1:100,000-1:200,000
A	252900	17q25.3	Heparin sulfate N-sulfatase		
B	252920	17q21.2	α-N-acetylglucosaminidase		
C	252930	8p11.21	Acetyl CoA:α-glucosamine N-acetyltransferase		
D	252940	12q14	N-acetylglucosaminidase 6-sulfatase		
Type IV mucopolysaccharidosis (Morquio syndrome)	253000	16q24.3 (A)	N-acetylgalactosamine-6-sulfatase	Keratan sulfate, chondroitin sulfate	1:76,000-1:216,400
	253010	3p22.33 (B)	β-galactosidase	Keratan sulfate	Very rare
Type VI mucopolysaccharidosis (Maroteaux-Lamy syndrome)	253200	5q14.1	Arylsulfatase B	Dermatan sulfate	1:43,261-1:1,105,160
Type VII mucopolysaccharidosis (Sly syndrome)	253220	7q11.21-11.22	β-glucuronidase	Dermatan sulfate, chondroitin sulfate, heparan sulfate	Very rare
Type IX mucopolysaccharidosis	601492	3p21.3	Hyaluronidase	Hyaluronic acid	Very rare

Table 2. Description of the children undergoing enzyme replacement therapy

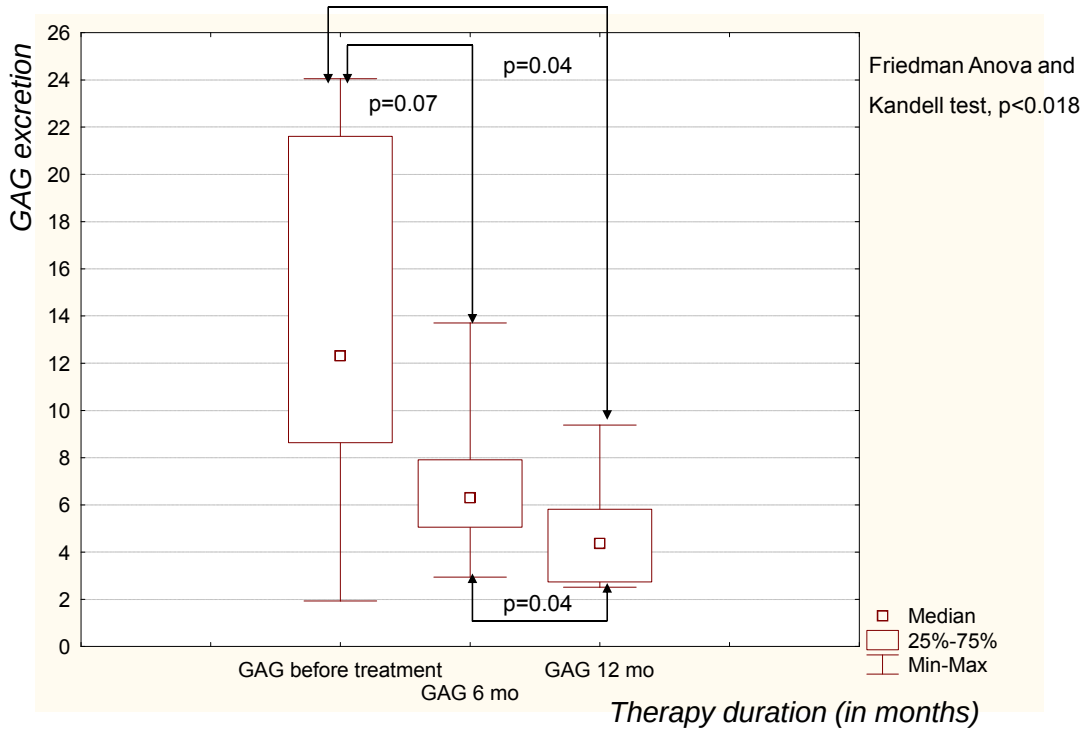
Patient	Diagnosis	Age at diagnosis establishment (in years)	Mutation
Boy V.	Severe type II MPS	4.08	*G374G*
Boy P.V.	Severe type II MPS	1.61	Unknown
Boy K.	Severe type II MPS	1.3	*Gly336Arg*
Boy T.	Mild type II MPS	6.03	Unknown
Girl S.A.	Hurler syndrome (type I MPS)	1.27	*Q70X/Q70X*
Girl S.L.	Hurler syndrome (type I MPS)	1.27	*Q70X / Q70X*
Boy C.	Hurler syndrome (type I MPS)	1.26	*Q70X / Q70X*
Boy I.	Hurler syndrome (type I MPS)	3.67	Unknown
Boy P.D.	Hurler syndrome (type I MPS)	0.86	*Q70X / W47X*
Girl T.	Hurler-Scheie syndrome (type I MPS)	1.22	Unknown/*Q70X*
Girl L.	Hurler-Scheie syndrome (type I MPS)	0.31	*Q70X / delC683*
Girl U.	Hurler syndrome (type I MPS)	1.32	*Q70X / Q70X*

Table 3. Comparative description of symptoms and laboratory alterations in mucopolysaccharidosis patients before and in the setting (after 6 and 12 months) of the enzyme replacement therapy

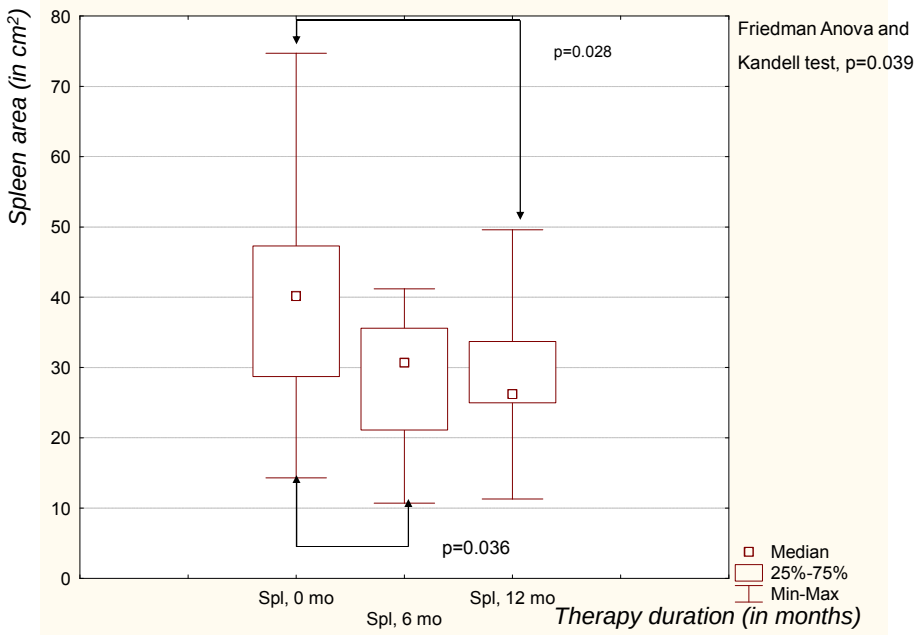
Parameter	Before ERT (Me, IQR)	After 6 months of ERT (Me, IQR)	After 12 and more months of ERT (Me, IQR)	Friedman ANOVA and Kendall's W	Wilcoxon test, *p*
Age at ERT beginning	5.94 (1.3-6.8)	–	–	–	–
Enzyme activity	1.14 (0.07-3.5)	–	–	–	–
Normal enzyme activity	0.004 (0.0002-0.01)	–	–	–	–
GAG exceedance of the upper normal limit (n)	12.3 (8.6-21.6)	6.3 (5.1-7.9)	4.4 (2.7-5.8)	< 0.018	0.07* 0.04** 0.04***
Liver dimensions (in the cm below the costal margin)	3.75 (1.0-8.0)	1.50 (0-3.5)	0.50 (0-2.0)	< 0.0002	0.008* 0.005** 0.003***
Right hepatic lobe size according to ultrasonography (in cm)	10.64 (7.6-12.5)	10.75 (10.0-11.8)	11.88 (9.4-12.0)	0.49	0.44* 0.91** 0.47***
Left hepatic lobe size according to ultrasonography (in cm)	6.2 (5.3-7.6)	5.29 (4.0-6.3)	5.0 (4.5-5.4)	0.55	0.31* 0.17** 0.13***
Spleen dimensions (in the cm below the costal margin)	1.0 (0.0-2.0)	0 (0-0.5)	0 (0-0.5)	< 0.0037	0.027* 0.027**
Spleen area (in cm^2)	40.2 (28.7-47.3)	30.7 (21.1-35.6)	26.2 (25.0-33.7)	0.039	0.036* 0.028** 0.08***
Interventricular septum thickness according to ultrasonography (in cm)	7.9 (6.6-8.4)	8.2 (7.3-10.65)	8.8 (8.0-9.8)	0.42	0.75* 0.046** 0.46***
Left ventricle's posterior wall thickness according to ultrasonography (in cm)	6.9 (6.5-9.4)	9.4 (7.1-10.6)	8.7 (8.0-9.8)	0.57	0.46* 0.75** 0.92***
Cholesterol (in mmol/l)	4.1 (3.4-5.3)	4.4 (4.1-5.0)	4.7 (4.0-6.1)	0.76	0.46* 0.75** 0.29***
Total Ca (in mmol/l)	2.39 (2.3-2.5)	2.33 (2.3-2.4)	2.28 (2.2-2.3)	0.74	0.89* 0.4** 0.75***
Social coefficient (in points)	51.4 (15.7-73.5)	28.6 (14.3-82.3)	12.5 (9.6-70.0)	< 0.001	0.85* 0.018** 0.12***
Articular affection (JADI) (in points)	18.0 (3.0-33.0)	20.0 (4.0-33.0)	20.0 (16.0-33.0)	0.76	1.0* 0.86** 0.42***
Extraarticular affection (JADI) (in points)	3.5 (2.5-4.0)	3.0 (3.0-4.0)	3.0 (2.0-4.0)	0.47	0.59* 1.0**

Note. * - comparison of results after 0 and 6 months; ** - comparison of results after 0 and 12 months; *** - comparison of results after 6 and 12 months. ERT – enzyme replacement therapy, GAG – glycosaminoglycans

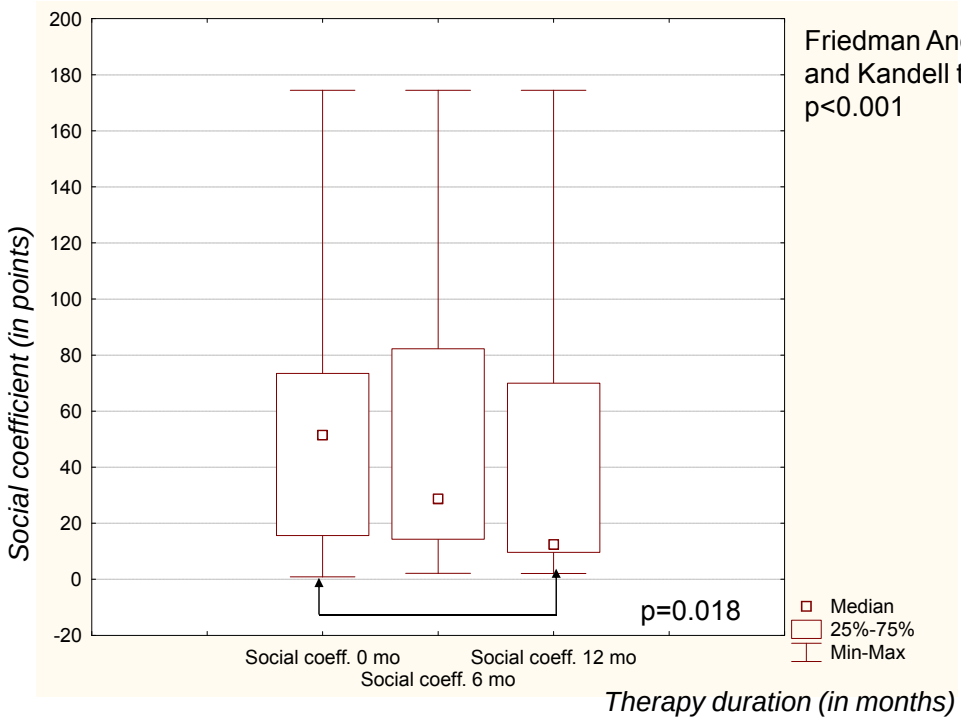
Pic. 1. Dynamics of glycosaminoglycan excretion after 6 and 12 months of the therapy



Pic. 2. Dynamics of spleen area after 6 and 12 months of the therapy (according to ultrasonography)

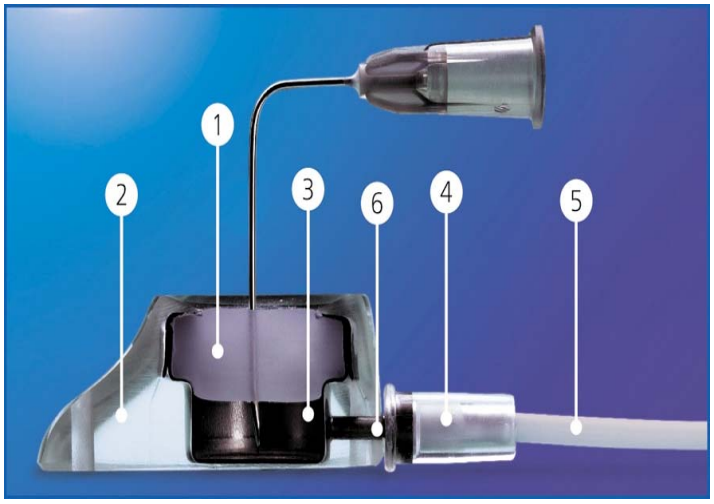


Pic. 3. Dynamics of social coefficient (in points) after 6 and 12 months of the therapy



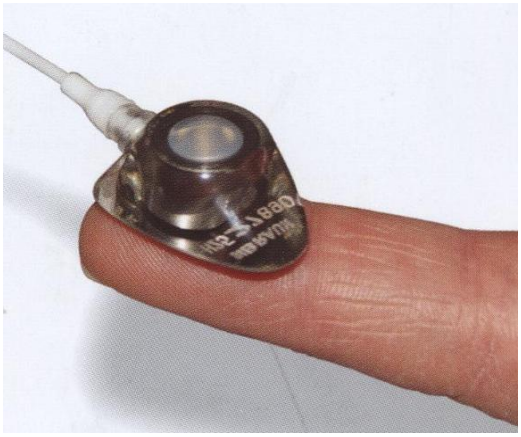
Pic. 4. Venous port system.

Notes. 1 — silicone membrane, 2 — outside casing, 3 — titanium camera, 4 — coupling, 5 - catheter, 6 – port' cannula



Pic.. 5. Implantation versions of venous port system in the thorax.

Pic.. 6. Celsite Babyport.



Pic.. 7. Girl with mucopolysaccharidosis enzyme replacement therapy is carried out through an implantanted venous port.