

## MUCOPOLYSACCHARIDOSIS TYPE II (HUNTER SYNDROME) IN A BOY FROM THE REPUBLIC OF SERBIA: A CASE REPORT

Jovana M. Tubić Vukajlović<sup>1\*</sup>, Lana P. Bojović<sup>2</sup>, Nevena G. Jevremović<sup>2</sup>,  
Ivan B. Simić<sup>3,4</sup>

<sup>1</sup>University of Kragujevac, Faculty of Science, Department of Biology and Ecology,  
34000 Kragujevac, Serbia

<sup>2</sup>Education Center Kragujevac, 34000 Kragujevac, Serbia

<sup>3</sup>University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine,  
34000 Kragujevac, Serbia

<sup>4</sup>University Clinical Center Kragujevac, Department of Cardiology,  
34000 Kragujevac, Serbia

\*Corresponding author; E-mail: jovana.tubic@pmf.kg.ac.rs

(Received May 04, 2023; Accepted June 12, 2023)

**ABSTRACT.** Mucopolysaccharidosis type II or Hunter syndrome is a hereditary, progressive disease that occurs due to the deposition of acidic glucosaminoglycans in lysosomes, due to hereditary deficits of specific degradation enzymes. A two-year-old boy was hospitalized and diagnosed with macrocephaly, hepatomegaly and at the age of four, an iduronate 2-sulfatase (*IDS*) gene analysis was performed and a mutation on the 3rd exon (c.262C>T, p.R88C) on the X chromosome was determined. Only four years after the diagnosis of Hunter syndrome, the boy begins to receive enzyme therapy - the drug Elaprase. During the period of receiving therapy, the boy's progression of the disease was significantly reduced.

**Keywords:** mucopolysaccharidosis, Hunter syndrome, *IDS* gene, glycosaminoglycan, elaprase.

### INTRODUCTION

Congenital metabolic disorders, primarily enzyme disorders, cause a deficit of the main metabolite and lead to the accumulation of intermediate metabolic precursors. Also, the deficiency of lysosomal enzymes leads to the degradation of complex macromolecules and their accumulation. This accumulation of macromolecules occurs due to a disturbed balance between their synthesis and degradation. It is specific for children with these disorders that they are born healthy, and that the disease develops during life, especially in the first years of their life (TURNPENNY and ELLARD, 2007).

Children with diagnosed mucopolysaccharidosis (MPS) have a progressive disease, with developed vascular and skeletal disorders, as well as problems with the central nervous system. Rough facial features are characteristic of these patients, which is a consequence of

the progressive accumulation of sulfated polysaccharides (glycosaminoglycans, GAG) and impaired breakdown of carbohydrates of the side chain of acidic mucopolysaccharides (TURNPENNY and ELLARD, 2007). The phenotypic similarity causes significant difficulties in identifying types of the disease, which is impossible without modern clinical, biochemical and molecular genetic studies. MPS is a group of genetic disorders with seven types and 13 subgroups characterized by an inherent deficiency of enzymes responsible for GAG (NAGPAL *et al.*, 2022). Mucopolysaccharidoses are hereditary, inherited in an autosomal recessive manner, except for mucopolysaccharidosis type 2 (MPS-II) or Hunter syndrome, which is inherited in an X-linked recessive manner (RAMÍREZ-HERNÁNDEZ *et al.*, 2022).

Hunter syndrome is an ultra-rare, multisystem disease, caused by a variation of the iduronate 2-sulfatase (*IDS*) gene, which contains instructions for the production of a specific enzyme, known as iduronate 2-sulfatase - I2S, which is located on the long arm of the X chromosome (Xq28), which consists of 9 exons and has a length of 28.3 kb (RAMÍREZ-HERNÁNDEZ *et al.*, 2022). This specialized protein is found in the lysosomes of cells, where it helps break down complex sugars - GAG. Genetic variation of the *IDS* gene results in the lack or complete absence of I2S, leading to excessive accumulation of GAGs in body cells (GIUGLIANI *et al.*, 2014). The frequency of MPS II ranges from 0.38 to 1.09 cases per 100,000 live births (D'AVANZO *et al.*, 2020). The syndrome occurs primarily in male children aged between two and five years, while female children are usually not affected, but a case has been reported in a heterozygous female (SEMYACHKINA *et al.*, 2019). The disease can be transmitted through the mother, who is the carrier of the mutated gene, so there is a greater chance that the offspring will get sick, or a *de novo* mutation can occur, where the mother is not the carrier of the mutation, so the risk of a spontaneous mutation in a brother or sister is low. The age at the onset of the disease, the severity of the disease and the rate of progression vary considerably. The clinical picture is manifested by hearing loss, constant infections, diarrhea, macrocephaly and slow growth. In the progressive form of the disease, the central nervous system is affected, respiratory diseases and cardiac anomalies develop, leading to death in the first decade of life. On examination, characteristic rough facial features, enlarged liver and spleen and stiff joints are clearly visible. An X-ray of the spine reveals deformations on the spinal vertebrae. Physical and mental deterioration is progressive, and between the ages of 13 and 19, these children usually die (GIUGLIANI *et al.*, 2014).

Early diagnosis is of great importance for the treatment of Hunter syndrome. The diagnosis is established in the male proband by identifying deficient I2S enzyme activity in leukocytes, fibroblasts, or plasma in the presence of normal activity of another sulfatase. In a female proband with suggestive clinical symptoms, the diagnosis is made by identifying the *IDS* pathogenic variant on molecular genetic testing (SCARPA *et al.*, 2018). Also, the diagnosis is confirmed by the presence of an increased amount of dermatan sulfate and heparan sulfate in the urine (TURNPENNY and ELLARD, 2007). The aim of this study was to point out the specifics of Hunter syndrome through the presentation of the case, in the form of frequent differences between patients, which can be crucial in finding the most adequate therapy.

## MATERIALS AND METHODS

Complete clinical and demographic data were collected from patient's medical records which were recruited from the University Clinical Center Kragujevac, Republic of Serbia. The parents of the examined boy were informed about the aims of the study and they signed informed consent according to the guidelines of the Declaration of Helsinki.

## CASE DETAILS AND DISCUSSION

The study presents a chronological account of the events of a male child who suffered from Hunter syndrome. It is the second child from normal pregnancy and delivery at term. It was born in 2008, with normal weight and growth at birth. Birth weight was 2750 g, length 51 cm, head circumference 33 cm, *Apgar score* 9/10. The liver and spleen were within physiological limits, and the findings on the heart and lungs normal. The boy's speech was developed normally, since when child was 12 months old the first words began. It had an adequate reaction to the environment. He was able to walk on his own.

In April 2010, the child was hospitalized at the University Clinical Center Kragujevac for a clinical examination of rickets and dysmorphia. Upon admission, clinical and laboratory observations were made. An ultrasound examination of the abdominal organs revealed hepatomegaly (the liver was enlarged to 12.5 cm), while an endocranial examination diagnosed macrocephaly. At this time, the disease has not yet been diagnosed. In July, the phenotypic characteristics of mucopolysaccharidosis were observed for the first time at the Institute for Mother and Child Health Care of Serbia "Dr. Vukan Čupić": macrocephalic head and coarse facial features. The liver was mildly enlarged and palpable at 3 cm below the right costal arch, and the spleen was 2 cm below the left costal arch. Blood count and biochemistry analyses were within normal limits. The findings on the lungs and heart were normal. The genealogical analysis established that the marriage was not consanguineous and that the parents were young and healthy. In the same year, enzymatic analyzes were performed in Mainz, Germany, which showed that the I2S level was lower (2.619 nM/ml) than the reference (300-800 nM/ml).

In 2012, a four-year-old boy underwent molecular genetic analysis of the *IDS* gene in Rostock, Germany, and a hemizygous mutation at exon 3 (c.262C>T, p.R88C) of the X chromosome was detected. The confirmed structural aberration, due to the mutation of the *IDS* gene, also led to the formation of the clinical phenotype of Hunter's syndrome. These genetic analyzes were not performed on the parents and sister, so we do not know the family history of this mutation.

In the period from 2011 to 2014, controls were performed every six months, during which no significant changes in the progression of the disease were observed. Biochemical indicators, which show the state of metabolism, were normal. An echocardiographic examination revealed that the boy had moderately significant aortic insufficiency and an enlarged left half of the heart. At the beginning of 2014, the boy started taking Zorkaptil (Angiotensin-converting enzyme (ACE) inhibitors) in the form of 12.5 mg tablets, for hypertension. In addition to heart defects, there are problems with articulation and hearing loss. In August 2014, he started receiving lifelong enzyme replacement therapy - the drug Elaprase (Shire Pharmaceuticals Ireland Limited), which contains the active substance idursulfase. During hospitalization, he received 12 mg of the drug, before which he was given an antihistamine. During the first three treatments, the therapy was given intravenously, drop by drop for 24 hours. The application of the drug went without complications and side effects. Before receiving the therapy, the liver was palpated 4 cm below the right costal arch, with a diameter of 154 mm; and the spleen 3 cm below the left costal arch, 106 mm in diameter. GAG in urine was 59.2 mg/mmol. Skeletal deformities of the dysostosis multiplex type were also determined on the radiographic examination. Active and passive movements were limited to the large and small joints. Two months after receiving the enzyme replacement therapy, an improvement was seen in the form of a decrease in spleen size, which is now palpable 2 cm below the left costal arch. Until the end of 2014, the boy received therapy every week at the Institute for Health Care of Mothers and Children of Serbia, "Dr. Vukan Čupić", in Belgrade.

In February 2015, an abdominal examination was performed. Liver and spleen size continued to decrease, the liver 120 mm, palpable at 3 cm; and the spleen 100 mm, palpable at

2 cm. During 2015, there were no significant changes in the size of organs, nor the amount of GAG in the urine. Audiometry indicated an increase in the perceptual threshold with high frequencies (at 1000 and 2000 Hz at 55 dB) and hearing impairment. Due to hearing impairment and difficulty in speaking, the boy went to the School for Hearing of Impaired Children.

In the year 2016, the child is regularly treated and monitored at the Institute for the Health Care of Mothers and Children of Serbia, "Dr. Vukan Čupić", under the diagnosis of Hunter disease. His vital functions were normal, and no focal neurological outbursts were observed. The liver was palpated 3 cm below the right costal arch, and the spleen was about 1 cm below the left costal arch. While receiving the therapy, the GAG concentration in the urine decreased to 29.9 mg/mmol (reference value < 12 mg/mmol). In addition to the umbilical hernia, an inguinal hernia appears. An electromyoneurography (EMNG) was performed, indicating carpal tunnel syndrome, on both hands. However, due to the difficulty of putting children with Hunter syndrome under anesthesia, the boy was not allowed to operate on either the inguinal hernia or the carpal tunnels. Bilateral sensorineural hearing loss occurs, hearing with a threshold of 1000 and 2000 Hz and around 50 dB, because of which the boy starts wearing hearing aids.

During the 2017 year, the GAG concentration in the urine decreased (23.2 mg/mmol), and the liver and spleen returned to normal. All other findings were in the reference range. A seven-year-old child continues to receive therapy at the University Clinical Center in Kragujevac. Due to frequent insomnia, the boy started taking melatonin every night, at a dose of 1 mg.

During 2018 and 2019 year, a 10-year-old boy's liver and spleen returned to normal, but he developed heart failure with an ejection fraction (EF%) with 52% and the left half of the heart was significantly larger than the right. As a result, the boy was prescribed to drink drugs from the group of diuretics (Lasix and Spironolactone). After prolonged use of the drugs, dehydration occurred, which is why Spironolactone was discontinued, and Lasix was taken every other day.

In the 2020 year, a 12-year-old boy was discontinued from enzyme therapy for unknown reasons. Due to the sudden cessation of receiving the drug Elaprase, there was a rapid progression of the disease. Insomnia occurs more and more often, it was difficult to him to move and could not stand independently, his immunity decreases, loss of body mass was observed, and the ability to swallow decreases. Although the liver and spleen remain within normal limits, deterioration is noted in the form of aortic insufficiency and mental impairment. In the middle of 2020, heart failure occurred with an EF of 45% and the heart muscle weakens even more and more. Table 1 shows the significant parameters of boys with Hunter syndrome that changed over 10 years.

Quantitative and qualitative analysis of urinary GAGs is helpful as a preliminary MPS screening assay. In this case report, the child had extremely low activity of the lysosomal enzyme iduronate sulfatase which indicates the diagnosis of Hunter syndrome. KUMAR *et al.* (2022) in their work report a case of a five-year-old boy in whom molecular genetic testing was not available, but enzymatic analysis showed a very low level of I2S in the serum (5.06 nM/4 hours/ml) and a normal level of total hexosaminidase (1124 nM/ml). Based on this significant laboratory feature, a diagnosis of MPS-II was made.

Molecular genetic testing of the *IDS* gene is sometimes required for confirmation of the diagnosis (SCARPA *et al.*, 2011). At the age of four, the boy underwent a molecular genetic analysis of the *IDS* gene, and a hemizygous mutation was detected on the 3rd exon of the X chromosome (c.262C>T, p.R88C), which leads to the formation of the clinical phenotype of MPS-II and definitively confirms the diagnosis of the syndrome. STEPHAN *et al.* (2022) conducted a study on 17 patients who were relatives diagnosed with MPS-II and found that all of them had a hemizygous variant (p.A77D) in the *IDS* gene. LUALDI *et al.* (2010) found that

two MPS-II patients were hemizygous for a nonsense mutation (c.22C>T; p.R8X) and a frameshift microinsertion (c.10insT; p.P4Sfs) in their genomic DNA. The girl, 4 years old, with Hunter syndrome revealed a hemizygous deletion (c.1436\_1440AGCCG) in exon 9 of the *IDS* gene, inherited from the mother. This mutation leads to a shift of the reading frame and the formation of a premature stop codon at the c.1491\_1493 position of the DNA strand, which corresponds to the codon of the 498 protein strand, indicating the pathogenicity of this mutation (SEMYACHKINA *et al.* 2019).

Table 1. General demographic and clinical characteristics of child with Hunter syndrome over the years.

Characteristics	2010	2014	2015	2016	2017	2018/19	2020
Age (years)	2	6	7	8	9	10/11	12
Body mass (kg)	17	23.9	24.5	25.8	26.2	24.7	21
Body height (cm)	91	110	114	114	116	116	111
GAG (mg/mmol)	/	59.2	/	29.9	23.2	/	/
Liver (palpation - cm)	2	4	3	3	3	2	2
Liver (size - mm)	125	154	120	111	121	104	105
Spleen (palpation - cm)	2	3	2	1	1	/	/
EF (%)	/	/	56	62	56	52	45

Only four years after the diagnosis of the syndrome, the boy was prescribed enzyme replacement therapy. The boy starts with idursulfase therapy and receives Elaprase intravenously. According to the instructions of the drug manufacturer (Shire Pharmaceuticals Ireland Limited), Elaprase (idursulfase) is prescribed to patients who have Hunter syndrome, because it contains a natural enzyme that these patients lack. This drug is available since 2007 in the European Union (MUENZER *et al.*, 2007). Through testing, this therapy has been shown to help improve mobility and reduce spleen volume. It is administered as an intravenous infusion, once a week. The recommended dose is 0.5 mg/kg of the patient's body weight (OKUYAMA *et al.*, 2010).

Cardiovascular diseases in patients with MPS II are frequently present, and cardiac valve disease is present in over half of patients (WRAITH *et al.*, 2008). At the age of six, due to the progression of the disease, the boy was diagnosed with serious cardiovascular problems (aortic insufficiency, degenerative changes of mitral valves, and an enlarged left half of the heart). This finding is similar to the findings of other patients with Hunter syndrome. STEPHAN *et al.* (2022) showed a very rapid progression of heart failure and determined the need for heart transplantation, which was performed for the first time in these patients. However, the surgical procedure did not succeed, because the patient died of primary graft failure on the second postoperative day. The valvular disease may occur in 60% of patients with MPS-II (WRAITH *et al.*, 2008).

In addition to cardiovascular disorders in the boy shown, hearing impairment and difficulty speaking were also noted. Most authors believe that sensorineural hearing loss is progressive and refers to cochlear fragility due to impaired cilia function. These findings indicate the importance of referring these patients to audiological evaluation, as well as monitoring from an auditory perspective (LUALDI *et al.*, 2010; OKUYAMA *et al.*, 2010).

In recent years, treatment of mucopolysaccharidosis with bone marrow transplantation has been attempted, which gives good results, as confirmed by biochemical indicators and clinical pictures. Hematopoietic stem cell transplantation seems to be more effective than

therapy with enzyme replacement therapy for MPS II in a wide range of disease manifestations and is considered a treatment option for this condition in the future. Engrafted leucocytes of donors secrete an enzyme, which takes over the deficient host cells in a process known as a cross correction, forming the basis for the correction of metabolic disorders by transplantation (KUBASKI *et al.*, 2017).

## CONCLUSION

Enzyme replacement therapy cannot cure a patient with Hunter syndrome, but it can significantly slow the progression of the disease. Once started, the therapy must be taken for life because the enzyme idursulfase is very strong, and stopping the treatment can be very harmful to the patient. In boys, the therapy showed remarkable results in liver and spleen parameters, which returned to normal values. During treatment, the ejection fraction managed to remain at the same level and did not cause major complications. However, due to the interruption of the therapy (Eleprase) for unknown reasons, the boy's condition drastically worsened and he died.

## Acknowledgments

This work was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Agreement No. 451-03-47/2023-01/200122).

## References:

- [1] D'AVANZO, F., RIGON, L., ZANETTI, A., TOMANIN, R. (2020): Mucopolysaccharidosis Type II: One hundred years of research, diagnosis, and treatment. *International Journal of Molecular Sciences* **21** (4): 1258. Doi: 10.3390/ijms21041258
- [2] GIUGLIANI, R., VILLARREAL, M.L.S., VALDEZ, A.A.C., HAWILOU, A.M., GUELBERT, N., GARZÓN, L.N.C., MARTINS, A.M., ACOSTA, A., CABELLO, J.F., LEMES, A., SANTOS, M.L.S.F., AMARTINO, H. (2014): Guidelines for diagnosis and treatment of Hunter Syndrome for clinicians in Latin America. *Genetics and Molecular Biology* **37** (2): 315–329. Doi: 10.1590/s1415-47572014000300003
- [3] KUBASKI, F., YABE, H., SUZUKI, Y., SETO, T., HAMAZAKI, T., MASON, R.W., XIE, L., ONSTEN, T.G.H., LEISTNER-SEGAL, S., GIUGLIANI, R., DŨNG, V.C., NGOC, C.T.B., YAMAGUCHI, S., MONTAÑO, A.M., ORII, K.E., FUKAO, T., SHINTAKU, H., ORII, T., TOMATSU, S. (2017): Hematopoietic stem cell transplantation for patients with Mucopolysaccharidosis II. *Biology of Blood and Marrow Transplantation* **23** (10): 1795–1803. doi: 10.1016/j.bbmt.2017.06.020
- [4] KUMAR, P., DAS, P.C., DAS A. (2022): Hunter syndrome. *JAMA Dermatology* **158** (12): 1438. Doi: 10.1001/jamadermatol.2022.4049
- [5] LUALDI, S., TAPPINO, B., DUCA, M.D., DARDIS, A., ANDERSON, C.J., BIASSONI, R., THOMPSON, P.W., CORSOLINI, F., ROCCO, M.D., BEMBI, B., STEFANO REGIS, S., COOPER, D.N., FILOCAMO, M. (2010): Enigmatic *In Vivo* iduronate-2-sulfatase (IDS) mutant transcript correction to wild-type in Hunter syndrome. *Human mutation* **31**: E1261–E1285. Doi: 10.1002/humu.21208

- [6] MUENZER, J., GUCSAVAS-CALIKOGLU, M., MCCANDLESS, S.E., SCHUETZ, T.J., KIMURA, A. (2007): A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). *Molecular Genetics and Metabolism* **90** (3): 329–337. doi: 10.1016/j.ymgme.2006.09.001
- [7] NAGPAL, R., GOYAL, R.B., PRIYADARSHINI, K., KASHYAP, S., SHARMA, M., SINHA, R., SHARMA, N. (2022): Mucopolysaccharidosis: A broad review. *Indian Journal of Ophthalmology* **70** (7): 2249–2261. doi: 10.4103/ijo.IJO\_425\_22
- [8] OKUYAMA, T., TANAKA, A., SUZUKI, Y., IDA, H., TANAKA, T., COX, G.F., ETO, Y., ORII, T. (2010): Japan Elaprased® Treatment (JET) study: Idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II). *Molecular Genetics and Metabolism* **99** (1): 18–25. doi: 10.1016/j.ymgme.2009.08.006
- [9] RAMÍREZ-HERNÁNDEZ, M.A., FIGUERA, L.E., RIZO-DE LA TORRE, L.C., MAGAÑA-TORRES, M.T., MENDOZA-RUVALCABA, S.C., ARNAUD-LÓPEZ, L., GARCÍA-ORTIZ, J.E., ZÚÑIGA-GONZÁLEZ, G.M., PUEBLA-PÉREZ, A.M., GÓMEZ-MEDA, B.C., GALLEGOS-ARREOLA M.P. (2022): Mutational spectrum of the iduronate-2-sulfatase gene in Mexican patients with Hunter syndrome. *European Review for Medical and Pharmacological Sciences* **26** (14): 5115–5127. doi: 10.26355/eurrev\_202207\_29300
- [10] SCARPA, M., ALMÁSSY, Z., BECK, M., BODAMER, O., BRUCE, I.A., DE MEIRLEIR, L., GUFFON, N., GUILLÉN-NAVARRO, E., HENSMAN, P., JONES, S., KAMIN, W., KAMPMANN, C., LAMPE, C., LAVERY, C.A., TELES, E.L., LINK, B., LUND, A.M., MALM, G., PITZ, S., ROTHERA, M., STEWART, C., TYLKI-SZYMAŃSKA, A., PLOEG, A.V.D., WALKER, R., ZEMAN, J., JAMES E WRAITH, J.E. (2011): Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet Journal of Rare Diseases* **6**: 72. doi: 10.1186/1750-1172-6-72
- [11] SCARPA, M. (2018): Mucopolysaccharidosis Type II; *In*: Pagon, R.A., Adam, M.P., Ardinger, H.H., Wallace, S.E., Amemiya, A., Bean, L.J.H., Bird, T.D., Fong, C.T., Mefford, H.C., Smith, R.J.H., *et al.*, (eds) *GeneReviews*. University of Washington: Seattle, WA, USA.
- [12] SEMYACHKINA, A.N., VOSKOBOEVA, E.Y., ZAKHAROVA, E.Y., NIKOLAEVA, E.A., KANIVETS, I.V., KOLOTII, A.D., BAYDAKOVA, G.V., KHARABADZE, M.N., KURAMAGOMEDOVA, R.G, MELNIKOVA N.V. (2019): Case report: a rare case of Hunter syndrome (type II mucopolysaccharidosis) in a girl. *BMC Medical Genetics* **20** (1): 6. doi: 10.1186/s12881-019-0807-x
- [13] STEPHAN, B.O., QUAIO, C.R., SPOLADOR, G.M., PAULA, A.C., CURIATI, M.A., MARTINS, A.M., LEAL, G.N., TENORIO, A., FINZI, S., CHIMELO, F.T., MATAS, C.G., HONJO, R.S., BERTOLA, D.R., KIM, C.A. (2022): Impact of ERT and follow-up of 17 patients from the same family with a mild form of MPS II. *Clinics* **77**: 100082. doi: 10.1016/j.clinsp.2022.100082
- [14] TURNPENNY, P.D., ELLARD, S. (2007): *Emery's elements of medical genetics. Section B, Chapter 11*. Churchill Livingstone, Elsevier. 13<sup>th</sup> edition, pp. 168–169.
- [15] WRAITH, J.E., BECK, M., GIUGLIANI, R., CLARKE, J., MARTIN, R., MUENZER, J. (2008): Initial report from the Hunter Outcome Survey. *Genetics in Medicine* **10** (7): 508–516. doi: 10.1097/gim.0b013e31817701e6

