Hunter syndrome follow-up after 1 year of enzyme-replacement therapy

Maria Puiu,^{1,2} Adela Chiriță-Emandi,^{3,4} Simona Dumitriu,^{1,2} Smaranda Arghirescu^{3,4}

¹Department of Genetics, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

²Department of Genetics, "Louis Turcanu" Emergency Hospital for Children, Timisoara, Romania

³Department of Pediatrics, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

⁴Department of Pediatrics, "Louis Turcanu" Emergency Hospital for Children, Timisoara, Romania

Correspondence to

Maria Puiu,
maria_puiu@umft.ro

SUMMARY

Mucopolysaccharidosis II (Hunter syndrome) is a rare x-linked disorder caused by a deficiency in the lysosomal enzyme iduronate-2-sulphatase, leading to an accumulation of the glycosaminoglycans (GAGs) dermatansulphate and heparan sulphate. The consequence of GAGs accumulation is progressive, multiorgan disease. Enzyme-replacement therapy is hypothesised to result in disease stabilisation and improved prognosis. We present a severe case of Hunter syndrome diagnosed at age 2 years and 4 months, who started enzyme-replacement therapy at the age of 3 years and 3 months. We report his evolution after 1 year of treatment. The treatment response was good and there was significant improvement in the quality of life. Owing to the rarity of Hunter syndrome, the multisystem nature and the heterogeneity of disease progression, patient care implies interdisciplinary consultations with a wide range of specialists. The best management can be provided in reference centres for metabolic diseases.

BACKGROUND

The mucopolysaccharidoses (MPS) are a group of rare genetic disorders included in lysosomal storage diseases. Mucopolysaccharidosis II (MPS II or Hunter syndrome; OMIM 309900) is an x-linked disorder with an incidence of 0.3–0.71 per 100 000 live births.¹ It is caused by a deficiency in the lysosomal enzyme iduronate-2-sulphatase (I2S), leading to an accumulation of glycosaminoglycans (GAGs) dermatansulphate and heparan sulphate.² The consequence of GAG accumulation is progressive, multiorgan disease.³

MPS II is characterised by clinical heterogeneity, ranging from attenuated to severe phenotype. In patients with severe phenotype, clinical signs and symptoms usually are visible between 2 and 4 years of age, whereas in those with the attenuated phenotype, signs and symptoms may not emerge until late childhood or early adolescence.⁴ Patients with severe disease form may also have profound cognitive impairment and developmental regression, which is not seen in the attenuated phenotype.⁵ Life expectancy is also shorter in patients with severe disease, with death typically occurring in the second decade of life.⁶ Patients with the attenuated phenotype may survive into adulthood, although premature mortality does occur.⁶

Historically, treatment for MPS II has been supportive; however, enzyme-replacement therapy with idursulfase, a recombinant human I2S enzyme (Elaprase, Shire Human Genetic Therapies, Inc, Cambridge, Massachusetts, USA), is now available in many countries. Precocious initiation of

enzyme-replacement therapy may offer the greatest benefit;^{7,8} however, this implies a timely diagnosis. This can be achieved through increased awareness of MPS II among paediatricians and family practice physicians.⁸

CASE PRESENTATION

A boy, aged 2 years and 4 months, was referred to the genetics department of Louis Turcanu Emergency Hospital for Children in Timisoara. The boy is the first child of healthy non-consanguineous parents. There was no family history of similar symptoms. He had a history of repeated upper respiratory infections, and four episodes of otitis media; adenoidectomy was performed at the age of 1 year. Tympanostomy with t-tube was inserted at the age of 3 years. On clinical examination, at the age of 2 years and 4 months, he presented with increased height for age (height=100 cm, SDS +3.6), excess weight 14.3% excess (weight=18 kg), macrocephaly, coarse facial features, including thickening of the lips, tongue and nostrils, a broad nose and flared nostrils, palpebral oedema, hypertelorism, thick hair, pale skin and oral respiration (figure 1). The child presented a short neck, a wide thoracic base, pectus excavatum, dextroconcave scoliosis, kiphosis and tendency for flexion contractures of knees, elbows and shoulders. The abdomen was enlarged.

LAB WORK

The usual laboratory investigations (complete blood count, liver and renal function tests and electrolytes) investigations were unremarkable.

CONSULTATIONS

Psychological evaluation revealed mild mental retardation (IQ=65 on Wechsler Intelligence Scale for Children), hyperactivity and aggressive behaviour.

We investigated the patient's quality of life using the Paediatric Quality of Life inventory-report for toddlers parents' perspective, at the beginning of treatment and after 1 year. The parents reported improvements in health-related quality of life, with the general score rising from 25 to 66 after 1 year of treatment. Most notable advancements were observed in physical and social functioning. The Family Functioning summary score after 1 year was 48 in the mother and 55 in the father.

The cardiology consultation concluded that the child presents nonobstructive hypertrophic cardiomyopathy and thickening of mitral valve.

The otolaryngology consultation indicated serous otitis and chronic adenoiditis. The audiogram at 3 years revealed severe mixed bilateral hypoacusis

To cite: Puiu M, Chiriță-Emandi A, Dumitriu S, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-007644

Figure 1 Facial aspect at the age of 2 years and 4 months (A) and at 4 years (B).

(right ear 100 dB, left ear 86 dB). Sleep test studies could not be performed owing to lack of collaboration.

IMAGING

Hand x-ray showed bone age of 2 years, short metaphyseal bones. Thoracic x-ray revealed short wide ribs. Spine x-ray showed dextroconcave lumbar scoliosis centred on L3, kyphosis on L1. Pelvis x-ray was normal. Abdominal ultrasound showed hepatosplenomegaly (liver volume=600 ml, enlarged 1.33-fold, spleen volume 130 ml—enlarged 3.61-fold).

At age 4, chest CT revealed the following: minimum fibrotic pleuropulmonary lesions located in the medial segment of the right lung; left lung parenchyma with no pathological changes; no intraperitoneal or retroperitoneal lymph nodes; pectus excavatum causing a compressive effect on the right atrium; thoracic scoliosis with double curvature (figure 2).

At age 4, skull CT showed the following: macrocrania (figure 3); fluid space enlargement predominantly intracerebral (third ventricle dimensions of 1.24 cm) and bilateral sylvian the valleys; arachnoidian cyst of maximum thickness 1.17 cm, located in the left

temporal pole; bilateral, symmetrical and diffuse hypodense alterations in the white matter in frontal, parietal, temporal and occipital lobes; dilated perivascular spaces in the paraventricular bilateral white matter and in the frontoparietal semioval centres.

DIAGNOSIS

The clinical features indicated a lysosomal storage disease, thus MPS syndrome was suspected. Lyposomal enzyme assay made at Universitas Klinikum Heidelberg showed plasma iduronat sulphatase=10.01 mU/ml (normal range 1.05–5.58), iduronate 2 sulphatase in leucocytes= 0 mU/mg (normal range 0.07–0.41). No other enzyme deficiencies were found, thus confirming the diagnosis of MPS II (Hunter syndrome). Determination of the activity of a second sulphatase was normal, which ruled out multiple sulphatase deficiency.

TREATMENT

This child became the seventh known case of Hunter syndrome in Romania and he remained, in management, in the genetic department of Louis Turcanu Emergency Hospital for Children

Figure 2 Chest CT: thoracic scoliosis with double curvature, right fibrotic pleuropulmonary lesions.

Figure 3 Head CT: macrocrania, enlarged lateral ventricles.

in Timisoara. Since 2011, Hunter syndrome has been included in the Rare Disease Program funded by the Ministry of Health in Romania, thus supporting the cost of enzyme-replacement therapy with Elaprase (0.5 mg/bodyweight/week). He started treatment at the age of 3 years and 3 months. He is now, 1 year into the treatment, with good compliance. He comes weekly to the hospital for his scheduled enzyme-replacement treatment; delays of maximum 4 days have occurred because of upper respiratory infections.

He joined a kindergarten programme and started physiotherapy. He remains in follow-up in paediatric, cardiology, orthopaedic, otolaryngology, neurology and psychiatric services.

OUTCOME AND FOLLOW-UP

In evolution, palpebral oedema disappeared, his abdomen decreased in size, with amelioration of hepatosplenomegaly. His flexibility of knees and elbows has improved; however, no improvement was seen for shoulder movement ability. He presented improved walking distance and higher vivacity.

He is more interested in motoric activities, which he initiates and manages to finish without requiring help. The hand-eye coordination and fine motor skills are still poor; he engages in these types of activities only after insistent requests.

His sleep pattern has evolved with longer continuous periods without awakening (parent reported). His hyperactivity and aggressive behaviour have also improved. Parents managed to engage him in all daily activities and routines. He presents improved interaction with personnel from hospital care and kindergarten. His vocabulary and pronunciation have developed and the child makes efforts to pronounce clear sentences.

Surprisingly, he continued to present recurrent upper respiratory infections, probably due to contact with the highly crowded area of the kindergarten, with great congregation of children (and viruses), that led to repeated viral respiratory infections.

DISCUSSION

Quantitative and qualitative analysis of urinary GAGs is useful as a preliminary screening test to help establish that an individual has a form of MPS; however, this does not confirm a specific diagnosis of MPS II. The 'gold standard' for the diagnosis of MPS II in a male proband is demonstration of deficiency of I2S enzyme activity in leucocytes, fibroblasts or plasma. This was used to certify the diagnosis in our case.

The multisystem nature of MPS II and the heterogeneity of disease progression implies that patients may present with many different signs and symptoms and thus, referral to a wide range of specialists: genetician, neurologist, cardiologist, pneumologist,

otolaryngologist, physical therapist, physiotherapist, surgeon, orthopaedist and anesthesiologist.⁸ This becomes very difficult considering that it is a very rare disease, and experience with these patients is hard to obtain. Nevertheless, owing to the multitude of specialists involved, the syndrome is difficult to manage. The best management can be provided in reference centres for metabolic diseases that would get referrals from a vast territory.

The treatment response was good and there was significant improvement in the quality of life. His neurological status has improved, with amelioration in hyperactivity and less-aggressive behaviour. Nevertheless, it is well known that enzyme-replacement therapy does not cross the blood-brain barrier; thus, it does not directly influence neurological involvement of the syndrome. This apparent improvement in the neurological state has been reported before. However, in other diseases, like rheumatoid arthritis and fibromyalgia, where chronic pain and altered quality of life is coupled with neurological involvement, low ability to learn and concentrate, irritability and other behavioural disturbances.^{9–12} Without a doubt, improvement in the quality of life leads to enhanced mental capacity.¹¹ On the other hand, the fact that the patient has joined a kindergarten programme and he received high-quality intensive medical care can be other factors to influence his neurological state.

However, despite the intensive medical care involved in this case and the enzyme-replacement therapy, the prognosis of this case remains reserved, owing to the severe progressive nature of the disorder.

Learning points

- ▶ The involvement and awareness of paediatricians, family practice physicians, and paediatric specialists is critical for early identification, diagnosis and referral of patients with mucopolysaccharidoses (MPS), in order to help optimise patient outcomes.
- ▶ The preservation of functionality is an increasing challenge in the treatment of MPS patients.
- ▶ Early enzyme-replacement therapy results in disease stabilisation and improved prognosis.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Martin R, Beck M, Eng C, *et al.* Recognition and diagnosis of mucopolysaccharidosis II (Hunter syndrome). *Pediatrics* 2008;121:e377–86.
- 2 Bach G, Eisenberg F Jr, Cantz M, *et al.* The defect in the Hunter syndrome: deficiency of sulfiduronate sulfatase. *Proc Natl Acad Sci USA* 1973;70:2134–8.
- 3 Burton BK, Giugliani R. Diagnosing Hunter syndrome in pediatric practice: practical considerations and common pitfalls. *Eur J Pediatr* 2012;171:631–9.
- 4 Wraith JE, Beck M, Giugliani R, *et al.* Initial report from the Hunter Outcome Survey. *Genet Med* 2008;10:508–16.
- 5 Young ID, Harper PS, Newcombe RG, *et al.* A clinical and genetic study of Hunter's syndrome. 2. Differences between the mild and severe forms. *J Med Genet* 1982;19:408–11.
- 6 Jones SA, Almássy Z, Beck M, *et al.* Mortality and cause of death in mucopolysaccharidosis type II—a historical review based on data from the Hunter Outcome Survey (HOS). *J Inher Metab Dis* 2009;32:534–43.
- 7 Muenzer J, Beck M, Eng CM, *et al.* Multidisciplinary management of Hunter syndrome. *Pediatrics* 2009;124:e1228–39.
- 8 Scarpa M, Almássy Z, Beck M, *et al.* Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis* 2011;6:72.
- 9 Pulles WLJA, Oosterman JM. The role of neuropsychological performance in the relationship between chronic pain and functional physical impairment. *Pain Med* 2011;12:1769–76.
- 10 Reyes Del Paso GA, Pulgar A, Duschek S, *et al.* Cognitive impairment in fibromyalgia syndrome: the impact of cardiovascular regulation, pain, emotional disorders and medication. *Eur J Pain* 2012;16:421–9.
- 11 Groß M, Warschburger P. Evaluation of a cognitive-behavioral pain management program for children with chronic abdominal pain: a randomized controlled study. *Int J Behav Med* Published Online First: 12 Feb 2012. doi:10.1007/s12529-012-9228-3
- 12 Norton S, Sacker A, Young A, *et al.* Distinct psychological distress trajectories in rheumatoid arthritis: findings from an inception cohort. *J Psychosom Res* 2011;71:290–5.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow