INTRODUCTION

Mucopolysaccharidoses (MPS), a sub-group of lysosomal storage disorders, are caused by the deficiency of specific lysosomal enzyme involved in catabolism of glycosaminoglycans (GAG). There are two type of known mucopolysaccharidosis (MPS I and II). MPS II, also known as Hunter syndrome (Mucopolysaccharidosis II, MPS II) is a severe genetic disease (X-linked recessive). Its incidence is about 0.3-0.71 per 100 000 live births. It is caused by the deficiency in the lysosomal enzyme iduronate-2-sulphatase (I2S), which catalysts the degradation of the glycosaminoglycans (GAG). This leads to a widespread accumulation of the GAG dermatan and heparan sulphate in many organs with a final progressive multi-system disease. The enzyme-replacement therapy (ERT) with idursulfase, a recombinant human I2S enzyme, is now available (since 2006) in many countries. We described the first case treated in Italy with this method. A 13-month-old male arrived to our Clinic and was diagnosed with MPS II. He was treated with ELAPRASE (0.5 mg/kg intravenously administered every week) since 32 months of age. We monitored the urinary GAG content, the patient’s detailed anthropometric (growth, weight, phenotypic aspects of the face, as well as chest, limbs and whole body), joint range of motion and skeletal radiographs, ultrasound studies of liver and spleen volumes, the distance covered in the 6-minute walk test and respiratory symptoms, echocardiography and heart valvulopathies, otorinolaryngological symptoms, audiological examinations, pain, neurological involvement and psychological tests. The patient was treated for 10 years and he is still in treatment. He now presents i) significant reduction in GAG levels in the biological fluids, ii) important improvements in lung function, in the ability of walking, in other visceral organs function and iii) a significant reduction of the liver and spleen volumes. We can conclude that an early diagnosis is fundamental for an efficient therapy of the Hunter syndrome disease. Indeed the treatment of patients with MPS II before the onset of clinical symptoms may significantly improve the quality of life and the survival. The ELAPRASE treatment is a good option for these patients, but not all patients with MPS II may be elected for this type of treatment. An accurate selection is fundamental also based on high cost of medication.

Key words: Hunter syndrome, enzyme iduronate-2-sulphatase.

CASE REPORT

A 13 months-old boy was referred to our clinic for a delay of speech and deambulation. The MPS II has been suspected based on his phenotype associated with an impaired neurological development. The child had a typical gargoylic aspect (Figure 1) with disproportion between splancno and neurocranium, macrocephaly, thickening of the lips, tongue and nostrils, uneven tooth eruption, thick eyelashes and hair, widened nasal bridge, low hairline, large ears, pale skin and oral respiration. He had also a short neck, joint laxity, joint stiffness, a wide thoracic base, pectus excavatum, dextroconcave scoliosis, kyphosis and contractures deforming limbs with tendency for contracted flexion of knees, elbows and shoulders, with valgus hindfoot and knee, enlarged abdomen. Parents was no consanguineous and his brother was normal. They reported an history of recurrent otitis, rhinitis and fever
since the birth. Blood exams (blood count, liver and renal function tests and electrolytes), electrocardiogram, echocardiogram, ocular fundus, abdominal ultrasound were normal. Skeleton X ray showed an alteration on the spine about L1 and L2 and on the legs, with an hypoplasia of the cephalic femoral nuclei, irregularities of the acetabular cavity and the quadrangular aspect of the iliac wings.

A cerebral MRI that was performed at 18 months showed many features compatible an accumulation of mucopolysaccharides (Figure 2). Skin biopsy confirmed a lysosomal storage disease. Elevated urinary levels of mucopolysaccharides (uGAG) were found. Genetic tests confirmed the diagnosis of MPS II. The patient was hemizygous for the p.H229P mutation, which was also present in the mother. The patient was treated with replacement therapy with ELAPRASE-SHIRE. Based on AIFA protocol the drug was infused at a dose of 0.5 mg/kg-weekly, with a rate of infusion from 8 mL/h to 40 mL/h for a total of three hours period. Every increase in the infusion rate is preceded by the revelation and monitoring of several vital signs (blood pressure, heart rate, respiratory rate, body temperature, O2 saturation). Up to now, alterations of these vital signs has been never detected. During the 4th infusion was observed a fleeting skin rash. From the 7th infusion to the 25th week of infusion, a pre-medication with hydrocortisone and antihistamine was introduced. The actual follow up is 10 years. He is still in treatment. He now presents i) significant reduction in GAG levels in the biological fluids, ii) important improvements in lung function, in the ability of walking, in other visceral organs function and iii) a significant reduction of the liver and spleen volumes. Based these aspects, clinical outcome can be considered satisfactory in term of quality of life for patient and parents.

Figure 1. Clinical phenotype of child: flat feet, short and wide pectus excavatum. Hips flexed and knees together. Typical faces. Stubby hands with short fingers and broad.
DISCUSSION

MPS II is a rare disease with an incidence of 0.3-0.7 per 100,000 live births [1,2]. To date, more than 370 different mutations of the I2S gene and they are related to different clinical disorders. Due to this heterogeneity the choice of therapeutic management is an arduous challenge for paediatricians [3].

The enzyme-replacement therapy (ERT) with idursulfase, a recombinant human I2S enzyme, is available since 2006 in many countries and it changed the treatment of this disease [5-7]. In the same year, the ELAPRASE-SHIRE, in Italy, was introduced as medicine of National Health Service (SSN).

We present this case because he is the first child who underwent this therapy in Italy.

The clinical history of our child shows that the ERT treatment has many advantages for patients with MPS II in term of let-up of disease, survival and quality of life for child and his family.

It is known that it can’t stop the neurological progression of disease, because the enzyme is no able to cross the blood-brain barrier and that all phenotypic manifestations of disease are irreversible, because all of them are the results of GAG accumulation. Its main role, so, is to slow down the disease’s progression and stabilize the patient in the clinical situation of the beginning of therapy. As it is reported in literature, this is an important aspect not only for patients but also for parents. For this reason, an early diagnosis is fundamental, because starting the treatment before of the onset of clinically apparent diseases, especially in its irreversible manifestations, may significantly improve the quality of life and the survival of these patients. Based on our experience, furthermore, we want stress the concept that a multidisciplinary team to support these patients is really important. The treatment of metabolic diseases, indeed, should be done only in specialist centres, to ensure to these families every clinical support.

CONCLUSIONS

In conclusion, we believe that an ERT therapy is a good chance for patients with MPS II. However, it is an expensive treatment that gives good results but it is no a good choice for all patients with MPS II. For this reason, standardized guidelines should be created to select patients who can benefit from this treatment. The use of biomarkers, for example, could help in these terms and they could be used to monitor patients and test the real efficacy of therapy.

An accurate selection is fundamental also based on high cost of medication. Finally, we are aware that future research is necessary to improve the use and the action of ERT.

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