Parental Experience of Enzyme Replacement Therapy for Hunter Syndrome

M Buraczewska, D O’Leary, O Walsh, A Monavari, E Crushell
National Centre for Inherited Metabolic Disorders, Children’s University Hospital, Temple St, Dublin 1

Abstract

We aimed to establish the profile of Irish patients with Hunter Syndrome (Mucopolysaccharidosis type II, MPS II) receiving weekly intravenous Enzyme Replacement Therapy (ERT) with recombinant iduronate-2-sulfatase and to assess the social and educational burden of treatment and parental opinion of ERT through the use of a parental questionnaire. Nine patients aged 3.5-14 years have received a mean of 2 (range 0.5-3.5) years of ERT. Treatment was associated with clinical improvements from baseline in hepatosplenomegaly in 6/7 (85%) respiratory manifestations in 4/6 (67%) and a mean reduction in urinary glycosaminoglycanic excretion of 62%. Changes noted by parents included increased energy 3/9 (33%) and softening of skin, hair and facial features 8/9 (89%). Parents report that seven hours weekly were spent on hospitalizations for ERT. Parental employment was adversely affected in 8 (89%) families. All patients were in school/pre-school (60%) but one was taken out of school/pre-school (22%) every week for 8 (89%) children. All parents believed the benefits of ERT outweigh the difficulties involved. All families were broadly welcoming of the introduction of home based therapy. In conclusion the social and educational burden of hospital-based ERT on these children and their families is significant. The introduction of home-based therapy is likely to improve overall quality of life for MPSII patients and their families.

Introduction

Mucopolysaccharidosis type II (MPS II, Hunter syndrome, OMIM 309900) is a rare (1.3 per 100,000 male births) progressive, multisystem disease caused by an X-linked deficiency of the lysosomal enzyme iduronate-2-sulfatase 1. This enzyme is responsible for the degradation of the glycosaminoglycans (GAGs) dermatan sulphate and heparan sulphate, and its deficiency leads to the progressive intra-lysosomal accumulation of GAGs in tissues and organs throughout the body. The signs and symptoms of MPS II may vary 1-3 and splenomegaly, with a median age of onset at 18 months and typically the diagnosis is delayed, being made at a mean age of 6 years 4. The presentation of MPS II may range from mild to severely affected patients. Manifestations include airway obstruction, skeletal deformities, hepatosplenomegaly, ophthalmological changes, valvular heart disease, seizures, and progressive neurological decline 5. Death usually occurs in early adulthood, with airway obstruction and cardiac failure being the most common causes 3. Until recently, treatment for MPS II has been supportive, focusing on the individual management of the many signs and symptoms however the development of enzyme replacement therapy (ERT) using recombinant iduronate-2-sulfatase (Idursulfase, Elaprase®) now presents the possibility of reducing the burden of GAG storage in patients with MPS II, with the aim of alleviating symptoms of the disease and slowing disease progression. Data from clinical trials show that ERT with Idursulfase is well tolerated and that, in addition to reducing urinary GAG excretion, it has beneficial effects on growth, hepatosplenomegaly, physical function, stamina and respiratory function 4.

There is no evidence to date that intravenous ERT will have effects on the CNS manifestations of MPS II. ERT has been available in the UK since 2007. Treatment is co-ordinated and supervised from the National Centre for Inherited Metabolic Disorders (NCIMD) where patients are seen at least 6-monthly at specialist clinics. The aim of the study was to establish the profile of Irish patients with MPS II who are currently receiving ERT and to assess the social impact and parental opinion of ERT.

Methods

The clinical notes of all patients attending NCIMD for treatment of MPS II were reviewed retrospectively to establish the pre-treatment patient characteristics and progress to date. All patients had multidisciplinary assessments annually (cardiology, psychology, physiotherapy, ophthalmology, ENT, Respiratory assessments, pulmonary function tests (where appropriate), sleep apnoea monitoring and abdominal ultrasound). Parents completed specially designed questionnaires on their experience of ERT either during a hospital admission or by phone with a single interviewer (MS).

Results

Nine cases (8 male, 1 female) from 9 families were identified. Age range at time of study was 3.5-14 years. The mean age at diagnosis was 3.3 years (range 0.5-7).

Pre treatment characteristics

Respiratory complications included recurrent upper respiratory tract infections (n=7, 78%) and obstructive sleep apnoea (n=6, 66%). Five (55%) patients had significant hearing loss and 3 (33%) had mild hearing loss. Cardiac involvement was noted in 4/6 (67%) children. Mitral valve was found to be stenosed in 1 (17%), aortic regurgitation was present in 1 (17%) and mitral regurgitation was noted in 1 (17%) patient respectively. There was minimal involvement of the right ventricle (n=3, 50%) with mild aortic regurgitation in 1 (17%) patient. Seven patients (78%) had an umbilical hernia. Joint contractures were present in 8 (89%) patients. Cardial tunnel syndrome was present on electrophysiological testing in 3 (33%) patients. On psychology assessment 5 (55%) patients had normal intellectual function and speech, 2 (22%) had borderline IQ and 2 (22%) had developmental delay. All patients had some coarsening of facial features with marked hirsutism in 3 (33%). Mean urinary GAG excretion pre-treatment was 58.4 (range 29-89 mg/mmol creatinine).

Treatment

Mean age at commencement of ERT was 4.8 years (range 2-11years). At the time of this study, patients had received on average 2 years of ERT (range 0.5-3.5years). Treatment was given at 6 different paediatric centres throughout the country. The majority of patients spent more than 5 hours on the weekly infusion (n=8, 89%) with a mean length of time of seven hours per week involved, including travel time, infusion time etc. All patients tolerated treatment well. Frequency of infusions was every 2 weeks (n=6, 67%), every 4 weeks (n=1, 11%) and every 6 weeks (n=2, 22%). Five (55%) patients had significant hearing loss and 3 (33%) had mild hearing loss. Cardiac involvement was noted in 5/6 (83%) children. Mitral valve was found to be stenosed in 1 (17%), aortic regurgitation was present in 1 (17%) and mitral regurgitation was noted in 1 (17%) patient respectively. There was minimal involvement of the right ventricle (n=3, 50%) with mild aortic regurgitation in 1 (17%) patient.

Post Treatment Characteristics

Following a mean of 2 years (0.5-3 years) of ERT, there was an improvement in sleep apnoea (4/6, 67%) and respiratory tract infections (2/7, 29%) in treated patients. The mean respiratory function did not improve in any one patient and progression of ventricular hypertrophy was seen in 3 (33%). On follow up psychological testing 2 (22%) patients had normal intelligence, development deterioration, developmental delay, 3 (33%) patients had borderline IQ and 2 (22%) had an IQ in the normal range. There were no changes in ERT assessment. Insufficient clinical data was obtained about joint mobility for inclusion. There was a 62% decrease in urinary GAG excretion (mean 17.8, range 5.8-39 mg/mmol creatinine).

Parental Questionnaire

Results are presented in Table 1. All parents were willing for their children to receive ERT. Six (67%) families agreed to the treatment of MPS II in Ireland since 2007. Treatment plans are co-ordinated and supervised from the National Centre for Inherited Metabolic Disorders (NCIMD) where patients are seen at least 6-monthly at specialist clinics. In conclusion the social and educational burden of hospital-based ERT on these children and their families is significant. The introduction of home-based therapy is likely to improve overall quality of life for MPSII patients and their families.

Discussion

MPS II is a rare, but very challenging progressive multisystem condition. Its management requires long-term multidisciplinary input. Treatment with Idursulfase was well tolerated by our patient group, and was found to reduce GAG excretion and to have positive effects on hepatosplenomegaly and respiratory manifestations in particular. As MPS II is a relentlessly progressive disease, year on year worsening of symptoms is expected. Comparable to other
studies, no effect was seen on central nervous system or cardiac manifestations of MPS II. ERT is currently administered intravenously and does not cross the blood brain barrier. Also, cardiac valves are relatively avascular and GAG accumulation and resultant valve deformation appears to progress despite ERT. It is not yet known whether this progression of valvular disease may be slowed by early and long term ERT.

Of interest is the large social burden on families that comes with weekly in-hospital treatment, including adversely affecting parental employment in all but one family and 20% loss of the schooling week for the child. This is a particular concern considering the educational challenges most of these children already face. The weekly commitment to treatment has resulted in negative psychosocial effects, as seen by some parents, for the child, siblings and parents themselves. Yet on the other hand, all of the parents reported positive effects of treatment on their child and feel the burden involved was outweighed by the benefits of treatment. Home therapy with ERT is well established for other lysosomal storage diseases such as Fabry disease and MPS I. A recent study has shown the beneficial psycho-socio and educational effects in a cohort of patients with Hunter Syndrome. Access to hospital beds on a weekly basis has been problematic for some patients and home therapy should be seen as cost-saving in this regard. Similarly home therapy may be coordinated to fit in with normal family and school life. So far clinical data from United Stated and European centers supported the opinion that home ERT in MPS patients is safe provided it is initially performed under the supervision of experienced medical staff.

Moreover, home ERT has been associated with improved compliance with the weekly treatment regimen. In order to implement a successful home infusion program, appropriate training with clear clinical guidelines should be given to patients, parents and medical staff. Patients and their families should be counseled prior to home ERT about its potential complication. In summary the introduction of home therapy would be welcomed by parents and is likely to improve quality of life for patients and their families.

Correspondence: E Crushell
National Centre for Inherited Metabolic Disorders, Children's University Hospital, Temple St, Dublin 1
Email: ellen.crushell@cuh.ie

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