Three Adult Siblings with Mucopolysaccharidosis Type II (Hunter Syndrome): A Report on Clinical Heterogeneity and 12 Months of Therapy with Idursulfase

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Abstract Mucopolysaccharidosis type II (MPS II – Hunter syndrome) is a rare X-linked recessive disease of lysosomal glycosaminoglycan metabolism leading to a systemic storage disorder. We report three adult brothers (aged 46–52 years) with attenuated Hunter syndrome after 12 months of enzyme replacement therapy with idursulfase. Before enzyme replacement therapy, each had serious complications of their disease: in addition to all requiring urgent cervical spinal canal decompressions in middle age, one required emergency aortic and mitral valve surgery, another had stage IV airways disease, and the third had acute glaucoma resulting in unilateral blindness. One brother discontinued therapy after 12 months. The other two brothers reported subjective improvements in energy and exercise tolerance.

Keywords Enzyme replacement therapy · Hunter syndrome · Mucopolysaccharidosis type II

Introduction

Mucopolysaccharidosis type II (OMIM #309900) is an X-linked recessive disorder due to deficiency of iduronate-2-sulfatase (*IDS*, EC 3.1.6.13) which is responsible for the cleavage of O-linked sulfates from dermatan sulfate and

heparan sulfate. The incidence is approximately 1.3 per 100,000 live male births (Poorthuis et al. 1999; Baehner et al. 2005), although affected females with skewed X-inactivation have been described (Manara et al. 2010). Hunter syndrome demonstrates a spectrum of disease with severe patients defined by cognitive impairment and progression of somatic disease with death from cardiac, respiratory, or neurological events in the second decade of life. Patients with the attenuated form do not have cognitive involvement and survive to adulthood, but have variable and often severe somatic involvement including cardiac valvular disease, airway compromise, spinal canal stenosis, short stature, joint restriction, dysostosis multiplex, hepatomegaly, and carpal tunnel syndrome (Wraith et al. 2008a, b).

Enzyme replacement therapy with idursulfase for MPS II was made available in Australia in 2008 for patients with the nonneurological form of the disease under the Federal Department of Health Life Saving Drugs Program. Idursulfase (Elaprase – Shire Human Genetic Therapies) is a recombinant human protein produced in HT1080 human fibroblast cultured cells that is posttranslationally modified to form active enzyme (Muenzer et al. 2006, 2007). Clinical trials demonstrated reduction in urinary glycosaminoglycan (GAG) excretion, an increase in the 6-min walk test (6MWT) distance, improvement in forced vital capacity (FVC), and normalization of organomegaly (Muenzer et al. 2006, 2007).

Adult siblings with MPS II have not, to our knowledge, been described in the literature. All these three men had symptoms in early childhood but were not diagnosed until young adulthood. The causative family mutation in *IDS* was determined in 2002 and reported as p.S152G. Two of the brothers have their own children, and one of them has a grandson who was determined to be unaffected by prenatal diagnosis (Fig. 1). Before treatment with idursulfase, at 0.5 mg/kg/week, they all had significant skeletal and connective tissue disease and had required cervical laminectomy for severe symptomatic cervical spinal canal stenosis as well as carpal tunnel releases. Idursulfase was commenced

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Fig. 1 Family pedigree showing GM (III.1), PM (III.3), and DM (III.4)

in early 2009; however, they all lived at significant distances from our hospital, and thus therapy was instituted at our center initially, but transferred to a local hospital after 4–6 weeks. Many of the monitoring investigations were performed at local institutions, and as a consequence, liver and spleen volumes were not calculated. Treatment compliance was 100% at 12 months.

We report here the clinical phenotype of each patient as well as responses to enzyme replacement therapy (Fig. 4 and Table 1).

Patients

DM (III.4)

DM is a 46-year-old man diagnosed at the age of 20 by the finding of elevated urinary glycosaminoglycans (18 g/mol creatinine), and low enzyme activity levels in plasma (0.05, normal = 4.8 pmol/min/mg protein) and blood leukocytes (1.1, normal = 11.8 pmol/min/mg protein) after he presented with long-standing restriction of joint range of motion. His adult height was 162 cm and he had subtle facial features consistent with a storage disorder (Fig. 3a). DM had joint restriction from childhood; he recalled having difficulty in crossing his legs to sit on the floor in kindergarten and being unable to put his hands on his head. Although he played representative sport during school (including soccer, cricket, and rugby league), he was never a fast runner and always had problems throwing a ball.

DM had acute angle closure glaucoma of the right eye at the age of 20 with intraocular pressure documented at over 80 mmHg. On his most recent ophthalmology review, he had an opaque right cornea and an atrophic optic nerve, with no vision in that eye. His left eye intraocular pressure was

maintained at around 14 mmHg with pilocarpine and later latanoprost. He had iridectomy operations performed on both eyes. His left pupil was permanently constricted, presumably from long-standing glaucoma therapy and/or scarring from laser iridectomy, although the effect of GAG storage in the iris sphincter and dilator pupillae muscles may have been contributory. His left eye corrected to 6/7.5 but had severely constricted visual fields. He had no residual night vision and was considered legally blind. Pigmentary retinopathy has not been documented; however, fundoscopy and ERG were not possible due to his right corneal scarring and left miosis.

He presented with parasthesias on neck extension at the age of 30, and MRI demonstrated central spinal canal stenosis in the upper cervical region with abnormal signal intensity at the C2/3 level. The predominant abnormality was described as a greater than 2 mm thickening of a membrane surrounding the dural sac. He underwent surgical decompression at 39 years of age. He underwent left carpal tunnel release at the age of 41 and still has electrophysiological evidence of mild bilateral carpal tunnel syndrome without diminished hand function. DM did not have a history of cardiac symptoms, although echocardiography at the age of 44 showed mild mitral regurgitation and mild aortic sclerosis. The left ventricular and systolic functions were normal and there was mild left ventricular diastolic dysfunction. Respiratory function tests showed a mild obstructive picture [FVC 3.72L (99%), FEV₁ 2.3L (74%)], and he had normal exercise tolerance without shortness of breath. DM had mild bilateral high frequency sensorineural hearing loss but did not wear hearing aids.

His other past medical history included Hashimoto's thyroiditis diagnosed at the age of 34, Poland anomaly of the right pectoralis major, a right inguinal hernia repair, and a tonsillectomy. He had a diagnosis of acne rosacea for which he was treated with minocycline. Minocycline caused a

Fig. 2 (a) DM (aged 6 months, second from left), PM (aged 22 months, first on left), GM (aged 6 years, third from left), and unaffected brother (aged 4 years, far right). GM's hand contractures were clearly present at that age. (b) DM (age 3.5, second from left), GM (age 9 years, third from left), PM (age 5 years, far right) and unaffected brother (age 7 years, far left). Hand contractures are evident in all three affected brothers. (c) Unaffected brother (age 20, far left), PM (age 18, second from left), DM (age 16, third from left) and GM (age 22, far right).

striking blue discoloration of his nails and ears – a known complication of this medication (Eisen and Hakim 1998) – and was ceased without resolution of the discoloration.

DM commenced infusion with idursulfase 30 mg weekly at the age of 44. His baseline measurements and changes during the first 12 months of therapy are documented in Fig. 4 and Table 1. There were no infusion reactions or adverse events. DM reported feeling generally fitter and

that his joints felt looser, although there were no objective significant changes in his joint range of motion. Liver and spleen volumes were unchanged according to the reports of abdominal CT scans, although organ volumes were not formally quantitated. 6MWT was increased at 12 months compared to baseline (802 m c.f. 564 m). Repeat echocardiography and respiratory function testing after 12 months of idursulfase did not reveal significant changes.

Fig. 3 (a) Facial features of DM at the age of 46. (b) Facial features of PM at the age of 48. (c) Facial features of GM at the age of 52

GM (III.1)

GM is a 52-year-old man diagnosed with Hunter syndrome at the age of 26 following the diagnosis being made in his sibling. His adult height was 160 cm and he also had subtle facial features consistent with his storage disorder (Fig. 3c). GM recalled being unable to cross his arms or legs at the commencement of primary school due to joint restriction.

Cardiac valvular disease predated his diagnosis of MPS II with asymptomatic mitral and aortic valve regurgitation detected as a teenager. Cardiac monitoring was sporadic over the following years, and he presented at the age of 50 in extremis with cardiogenic shock and acute pulmonary edema secondary to severe aortic valve stenosis and mitral regurgitation. He underwent aortic valve replacement with a porcine aortic valve and mitral valve annuloplasty. His postoperative course was complicated by pneumonia, pancreatitis, cardiac tamponade, and *Pseudomonas* sepsis; however, he eventually made a full recovery.

A cervical spine MRI performed at the age of 35 demonstrated dural and extradural thickening from the upper clivus

to the C3/4 intervertebral disk level with cord compression and increased signal at the C2 level. Cervical laminectomy was performed at the age of 46 following progression of his chronic neck pain to gait disturbance and bilateral upper limb weakness. Left and right carpal tunnel surgeries were performed at the ages 43 and 47. Baseline respiratory function testing before enzyme replacement therapy at the age of 51 demonstrated mild obstructive and restrictive airways disease [FVC 2.83L (77% predicted), FEV₁ 2.10L (70% predicted)]. He had bilateral hearing loss and had worn hearing aids from the age of 43. His other past medical history included tonsillectomy, bilateral inguinal hernia repairs, umbilical hernia, Hashimoto's thyroiditis, and depression.

GM commenced infusion with idursulfase 36 mg weekly at the age of 51. His baseline measurements and changes during the first 12 months of therapy are documented in Fig. 4 and Table 1. There were no infusion reactions or adverse events. He reported an increase in energy levels and exercise tolerance. PM had a significant weight gain of around 10 kg over the first 12 months of therapy. Examination excluded fluid overload from cardiac failure as the cause; abdominal adiposity was felt to be the predominant cause of weight gain. Ophthalmoplegia with restriction of medial and upward gaze bilaterally was noted after 12 months of therapy. Liver and spleen volumes were unchanged according to the reports of abdominal CT scans, although organ volumes were not formally quantitated. 6MWT was 401 m at baseline, 520 m at 6 months, and 425 m after 12 months. Repeat echocardiography at 9 months documented severe dilated cardiomyopathy with good valvular function.

PM (III.3)

PM is a 48-year-old man diagnosed clinically, but not biochemically or molecularly, at the age of 22 following the diagnosis being made in his siblings. The diagnosis was confirmed many years later when his daughters were shown to carry the family mutation. His adult height was 173 cm and he also had subtle facial features consistent with his storage disorder, although these were somewhat masked by a cushingoid appearance from chronic steroid usage (Fig. 3b). PM recalled joint restriction, and a prominent abdomen being present from early childhood. He was never able to pursue physical activity as well as his peers during adolescence and presented with obstructive airways disease at the age of 23.

PM had progressive airways disease and when seen at the age of 46 he had an FVC 2.27L (51%) and an FEV₁ 0.72L (20%) corresponding to stage IV COPD (GOLD 2009).

Fig. 4 PM (square), GM (circle), and DM (triangle). (a) Urinary GAG excretion; upper limit of normal=8.3 mg/mM creatinine. (b) 6MWT. (c) FVC. (d) FEV₁

He had previously been assessed for combined heart–lung transplantation at the age of 33 but was not considered fit for operation. PM was steroid dependant by the age of 45 and was currently maintained on prednisone 10 mg daily. He had a number of hospitalizations for exacerbations of airways disease, and his exercise tolerance was limited to a few hundred meters on flat ground or ten stairs. He required two rest periods to complete dressing himself each morning. Obstructive sleep apnea was diagnosed at the age of 48 and managed with nocturnal CPAP. High-resolution chest CT demonstrated widespread subtle heterogeneous parenchymal densities with scattered bronchial thickening but no bronchial dilatation. Bands of linear fibrosis were seen in the lower lobes and there was air-trapping present, supportive of the diagnosis of small airways disease. There was no evidence of the paraseptal emphysematous changes we have seen in our adult patients with MPS I (unpublished results). He was a nonsmoker and α_1 -antitrypsin deficiency had been excluded.

PM had complete vertical ophthalmoplegia and severe concentric restriction of visual fields. He did not have

increased intraocular pressure. New retinal pigmentation was noted at his ophthalmology review 12 months after commencing idursulfase. ERG was not performed. Cervical laminectomy was performed at the age of 43 after he presented with pain, parasthesias, and limb weakness on neck extension. MRI at that time demonstrated spinal canal stenosis from C2 to C4 with diffusely increased cord signal secondary to thickening of the dural and extradural tissues. Surgery did not improve these symptoms, although there was no subsequent progression of his pain, parasthesias, or weakness. Bilateral carpal tunnel surgery was performed at the age of 22. PM had significant hearing loss and was deaf in the left ear and wore a hearing aid in the right ear. Echocardiography demonstrated aortic valve stenosis (valve area 1.2 cm²) with normal systolic function and mild diastolic dysfunction.

PM commenced weekly 36 mg idursulfase at the age of 46. His baseline measurements and changes during the first 12 months of therapy are documented in Fig. 4 and Table 1. There were no infusion reactions or adverse events. He traveled an hour each way to his treatment center each

Table 1 Joint range of motion measurements made at baseline and 12 months. Each joint was measured bilaterally and the two results averaged (except for flexion and extension of the neck). Results are presented as the mean degrees $\pm$ standard error of the mean. The *p* values were calculated using a two-tailed Student's *t*-test. There was no significant change in joint range of motion following 12 months of idursulfase

	Baseline					12 months					Change	<i>p</i> Value
	GM	PM	DM	Mean	SE	GM	PM	DM	Mean	SE		
Ankle												
Dorsiflexion	2.5	−12.5	0.0	−3.3	±4.6	4.5	−17.5	5.5	−2.5	±7.5	0.8	0.8125
Plantarflexion	49.5	52.5	43.5	48.5	±2.6	46.0	40.0	45.5	43.8	±1.9	4.7	0.3846
Inversion	4.0	5.5	5.0	4.8	±0.4	8.0	0.0	19.0	9.0	±5.5	4.2	0.5363
Eversion	11.0	24.5	19.5	18.3	±3.9	12.5	0.0	24.5	12.3	±7.1	6.0	0.5851
Knee												
Flexion	122.5	127.5	138.5	129.5	±4.7	122.0	125.0	127.0	124.7	±1.5	4.8	0.2893
Extension	−11.0	2.5	−3.5	−4.0	±3.9	−10.5	0.0	−4.0	−4.8	±3.1	0.8	0.4444
Hip												
Flexion	86.5	100.0	101.0	95.8	±4.7	96.0	110.0	96.0	100.7	±4.7	4.8	0.4294
Extension	−9.5	0.0	−2.0	−3.8	±2.9	−11.0	1.0	−12.0	−7.3	±4.2	3.5	0.4034
Abduction	24.5	20.0	20.5	21.7	±1.4	31.0	20.0	37.5	29.5	±5.1	7.8	0.2545
Adduction	13.0	12.5	21.0	15.5	±2.8	22.0	17.5	19.5	19.7	±1.3	4.2	0.3064
Internal rotation	0.5	−2.0	11.0	3.2	±4.0	0.0	2.5	8.0	3.5	±2.4	0.3	0.8937
External rotation	30.5	35.0	22.0	29.2	±3.8	35.0	27.5	15.0	25.8	±5.8	3.3	0.4846
Wrist												
Flexion	48.0	54.0	76.0	59.3	±8.5	67.5	52.5	46.5	55.5	±6.2	3.8	0.8124
Extension	42.0	51.0	41.0	44.7	±3.2	51.0	40.0	44.0	45.0	±3.2	0.3	0.9603
Ulnar deviation	39.5	36.5	32.5	36.2	±2.0	37.5	27.0	36.5	33.7	±3.3	2.5	0.5876
Radial deviation	11.5	1.5	10.5	7.8	±3.2	12.5	7.0	18.5	12.7	±3.3	4.8	0.1422
Elbow												
Flexion	140.0	137.0	145.0	140.7	±2.3	140.0	134.0	147.5	140.5	±3.9	0.2	0.9261
Extension	−15.0	−35.0	−24.0	−24.7	±5.8	−17.5	−26.0	−26.5	−23.3	±2.9	1.3	0.7612
Shoulder												
Flexion	120.0	116.0	110.0	115.3	±2.9	115.0	105.0	135.0	118.3	±8.8	3.0	0.8129
Extension	58.0	50.0	65.0	57.7	±4.3	43.5	40.0	61.0	48.2	±6.5	9.5	0.0890
Abduction	92.5	69.5	124.0	95.3	±15.8	85.0	98.0	125.0	102.7	±11.8	7.3	0.5692
Internal rotation	26.0	15.5	23.5	21.7	±3.2	55.0	20.0	21.0	32.0	±11.5	10.3	0.3923
External rotation	19.0	54.0	72.5	48.5	±15.7	0.0	72.5	70.0	47.5	±23.8	1.0	0.9350
Neck												
Flexion	39.0	40.0	45.0	41.3	±1.9	45.0	40.0	35.0	40.0	±2.9	1.3	0.8020
Extension	23.0	26.0	54.0	34.3	±9.9	35.0	30.0	70.0	45.0	±12.6	10.7	0.0942
Rotation	41.0	60.0	39.0	46.7	±6.7	37.5	50.0	61.5	49.7	±6.9	3.0	0.7911
Lateral flexion	20.0	26.0	18.5	21.5	±2.3	16.5	20.0	23.5	20.0	±2.0	1.5	0.6964

week and felt exhausted following each infusion, such that he would sleep the rest of the day and be unable to perform general tasks around the home the next day. He felt that treatment had not increased his exercise tolerance and that it had a significantly detrimental effect on his quality of life. He ceased treatment following his 12-month review.

Discussion

These three brothers demonstrate the attenuated spectrum of disease associated with MPS II and the variability that may be present. Each has had similar manifestations with regard to the organ systems affected, but there has been striking variability in the severity of each disease symptom. A response to enzyme replacement therapy was not

demonstrable on objective measurements, although for GM and DM there were subjective improvements in energy and exercise tolerance. For PM, the burden of weekly therapy was more than any perceived benefit.

All three have had serious skeletal and connective tissue manifestations of disease including joint restriction, cervical spine stenosis, and carpal tunnel syndrome. These have all been described as common in published series of attenuated MPS II patients (Young and Harper 1982; Kulkarni et al. 1987; Parsons et al. 1996; Wraith et al. 2008a, b). In contrast to descriptions in the literature in which hip dysplasia is a common complaint, it was not present clinically in these patients, although radiographs were not performed to exclude subclinical involvement.

All three brothers had ocular manifestations. DM presented before diagnosis with an episode of acute angle closure glaucoma that rendered him blind in his right eye.

Despite good subsequent control of intraocular pressure, he had constricted visual fields and night blindness in the contralateral eye. Both PM and GM had partial ophthalmoplegia, and PM also had retinal pigmentation and severely restricted visual fields. Other ocular changes in MPS II, not seen in these brothers, include exophthalmos and disk swelling with optic atrophy (Ashworth et al. 2006a, b).

We believe this is the first description of ophthalmoplegia in MPS II, although a single patient with MPS I has been described with mechanical limitation of superior oblique tendon movement (Bradbury et al. 1989). In that case, it was thought to be due to tendon shortening, and this could also be the mechanism in our patients, although deposition of storage material producing a mass effect in and on the extraocular muscles is also possible.

Ocular hypertension and glaucoma have been documented in the mucopolysaccharidoses and are due to deposition of storage material in the anterior chamber structures and obstruction of outflow through the trabecular network (McDonnell et al. 1985; Ashworth et al. 2006a, b). Chronic closed angle, acute closed angle, and open angle glaucoma have all been documented, although there is only one previously described case of acute closed angle glaucoma in MPS II (Kaiden 1982). A review of 50 patients with MPS documented raised intraocular pressure in nine (seven of whom had MPS VI), although none had acute glaucoma as our patient did (Ashworth et al. 2006a, b).

Pigmentary retinopathy is well documented in the MPS disorders, particularly in MPS III (Ashworth et al. 2006a, b), and in advanced cases causes night blindness and loss of peripheral vision. Five of ten patients in the JET study had retinal degeneration (Okuyama et al. 2009). Although retinal pigmentation had not been documented in PM before the completion of 12 months therapy with idursulfase, the history of restricted visual fields argues that he had pigmentary retinopathy of a long-standing nature. DM also had restricted visual fields and night blindness in the left eye, both suggestive of a pigmentary retinopathy although this has not been demonstrated.

Cardiac valvular disease is a nearly ubiquitous feature in older patients (Young and Harper 1982); even in the younger cohort of the Hunter Outcome Survey, it was present in 57% of patients and manifested at a median age of 6.1 years (Wraith et al. 2008a, b). The variability in severity of this manifestation between these brothers was striking, with GM manifesting an almost fatal degree of aortic stenosis and DM having minimal disease.

PM had severe obstructive airways disease with newly diagnosed obstructive sleep apnea. This is in contrast to the commonly described airways disease of MPS II which is an upper airways crowding secondary to soft tissue enlargement, followed by a restrictive pattern due to thoracic skeletal involvement (Wraith et al. 2008a, b). PM's lung disease

was very severe, and it should be noted that both DM and GM also had mild airways disease.

It is interesting that both GM and DM had Hashimoto's thyroiditis; however, we do not feel that this is likely to represent an association with MPS II, as autoimmune thyroid disease is a common disorder with familial clustering and a complex genetic background, with recent studies implicating numerous susceptibility loci (Tomer 2010).

There was a lack of objectively measurable clinical response to idursulfase in these brothers, although there were clear biochemical responses with normalization of urinary GAG's in the first 6 months. Comparisons between the response to idursulfase in these siblings and those of the clinical trial patients are difficult to make, particularly because of the significant age difference. The oldest phase I/II/III trial patient was 31 years old, and around half were prepubertal at the time of baseline investigations (Muenzer et al. 2006; 2007). A more meaningful comparison can be made with the patients in the JET study; an investigation of ten Japanese adults with MPS II following 12 months therapy with idursulfase in whom the mean age was 31 and the oldest patient was 53 (Okuyama et al. 2009). Patients in the JET study significantly improved their liver and spleen volumes, normalized urinary GAG's, and improved 6MWT and FVC although these last two measurements were not increased to statistically significant levels. Similarly, these brothers normalized their urinary GAG excretion but did not have significant changes in respiratory or cardiac function. The variability in results of the 6MWT demonstrates that patient effort plays a significant role in the reliability and reproducibility of this test, and that as a measure of clinical efficacy its usefulness is limited in individual patients. It is likely that the age of the patients and the correspondingly long-standing nature of their disease made it difficult to reverse measurable symptoms over this initial 12-month period of therapy.

Conclusion

MPS II in these adult siblings has caused significant morbidity, albeit in different ways for each patient: GM had near fatal cardiac valvular dysfunction, PM has severe chronic obstructive airways disease, and DM is legally blind. These siblings demonstrate the multisystem nature of this disorder and its variable effects even within members of the same family.

GM and DM felt they had increased energy and exercise tolerance following 12 months of treatment with idursulfase. In contrast, PM did not feel improved on therapy and felt that the weekly burden of traveling a long distance to receive therapy and the associated fatigue resulted in a decrease in

his quality of life. There were no infusion reactions or adverse events, and over 12 months of therapy the clinical status of the patients remained stable.

In adults with long-standing accumulation of GAG's and a resulting significant burden of disease, it is likely that objectively measurable improvements in clinical outcomes will be slow to achieve; however, achieving clinical stability in these patients is a lifesaving outcome. The importance of early diagnosis, which could have been made at a young age in this family, should be emphasized as enzyme replacement therapy is more likely to be effective in preventing, rather than reversing, the serious sequelae of this multisystem disease.

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Synopsis

Three adult siblings with MPS II demonstrated the striking variability of this disorder; we documented the findings after 12 months of enzyme replacement therapy.

Author Contributions

Michel Tchan wrote the initial draft article and performed examinations and investigations on the patients. Guarantor.

Kerry Devine administered enzyme replacement therapy and provided revision and criticism of the article.

David Sillence revised the draft article and supervised enzyme replacement therapy.

Competing Interest Statement

Dr. Tchan reports having received reimbursement from Genzyme Corporation for travel expenses to attend educational meetings.

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No funding was obtained for this study.

Ethics Approval

No ethics approval was required for this study.

Patient Consent

Consent was obtained from the family, including consent for publication of photographs.

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