Successful Noninvasive Ventilation and Enzyme Replacement Therapy in an Adult Patient with Morbus Hunter

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Received: 19 July 2011 / Revised: 09 September 2011 / Accepted: 04 October 2011 / Published online: 16 December 2011
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Abstract M. Hunter is characterized by an accumulation of mucopolysaccharides in cells, blood, and connective tissue as a consequence of a deficiency of the enzyme iduronate-2-sulfatase. Unlike enzyme replacement therapy with idursulfase in children, there is limited long-term experience in adult patients with Morbus Hunter.

The case presented here describes the development of a man born in 1971 who was admitted to Hemer Lung Clinic in 2005 with severe obstructive sleep apnea, pulmonary functional impairment, and ventilatory failure (FEV₁: 0.8 L, VC: 1.0 L; pO₂: 52 mmHg; pCO₂: 81 mmHg, 6 MWT: 100 m). Initially, the patient received symptomatic treatment with noninvasive ventilation, which achieved a considerable improvement in pulmonary function and a normalization of blood gasses. Since February 2008, the patient received additional enzyme replacement therapy with idursulfase, which resulted in a further significant functional improvement (FEV₁: 1.6; VC: 2.3 L; VO₂max: 1,350 mL or 28.1 mL/kg body weight), in a normalization of prior elevated pulmonary artery pressures and also in impressive changes in the physiognomy and joint mobility. In November 2010, the polysomnography and nocturnal blood gas analysis without NIV showed only a mild

obstructive sleep-related breathing disorder with no sign of hypoventilation. Therapy was changed to nocturnal CPAP therapy with a constant pressure of 6 cm H₂O. Additional administration of oxygen was not required. With this therapy, the patient has been asymptomatic up to September 2011.

Adult Hunter patients also benefit from enzyme replacement therapy and, in restrictive ventilatory defects with hypoventilation, from symptomatic therapy with noninvasive ventilation.

Abbreviations

6-MWT	Six-minute walk test
AHI	Apnea/hypopnea index
BGA	Blood gas analysis
CPAP	Continuous positive airway pressure
DLCO	Diffusing capacity of the lung for carbon monoxide
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GAG	Glycosaminoglycan
IVS	Inter ventricular septum
MPS	Mucopolysaccharidosis
NIV	Noninvasive ventilation
P01	Negative airway pressure
PA syst.	Pulmonary artery systolic pressure
pCO ₂	Partial pressure of carbon dioxide
Pimax	Maximal inspiration pressure
pO ₂	Partial pressure of oxygen
TLC	Total lung capacity
VC	Vital capacity
VO ₂ max	Maximum oxygen uptake

Communicated by: Verena Peters.

Competing interests: None declared.

Shire provided funding for translation service. The views in the manuscript do not necessarily reflect those of Shire.

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Introduction

Hunter syndrome belongs to the group of mucopolysaccharidoses (MPS) and is characterized by increased accumulation in the tissues and urinary excretion of glycosaminoglycans (GAG), in particular dermatan sulfate and heparan sulfate (Burrow and Leslie 2008; Martin et al. 2008). MPS II is an X-linked trait, so that the disease affects almost exclusively boys and men (Neufeld and Muenzer 2001; Wraith et al. 2008). The genetic defect results in an iduronate-2-sulfatase deficiency, the key enzyme for degradation of GAG (Le Guern et al. 1990; Burrow and Leslie 2008).

The disease is very rare, with an incidence of 0.64 in 100,000 births and 1.3 in 100,000 male births in Germany (Baehner et al. 2005). Typical changes in the physiognomy occur in childhood, with coarseness in the facial features resulting from the accumulation of GAG: nose with flattened bridge, thick lips, large head, prominent forehead, short neck, widely spaced teeth, as well as frizzy hair and thickened skin. In addition, other characteristic changes or diseases as otitis, hernia, diseased heart valves, hepatosplenomegaly, joint stiffness and kyphoscoliosis are often observed (Beck 2011; Martin et al. 2008; Jones et al. 2009; Young and Harper 1982, 1983). Respiratory symptoms are typical and a common cause of clinical deterioration particularly as the disease progresses and in adulthood. The reason for this is the accumulation of GAG in the soft tissue, which causes enlargement of the tonsils and tongue and also narrowing of the upper respiratory tract (Kurihara et al. 1992; Kamin 2008). In some cases, this results in obstructive sleep-related breathing disorders even in childhood (Shapiro et al. 1985; Ginzburg et al. 1990; Leighton et al. 2001) and also difficult intubation (Kamin 2008; Muenzer et al. 2009). In addition, disease progression with tracheobronchomalacia (Morehead and Parsons 1993) and tracheal stenosis in childhood and also in adulthood (Young and Harper 1979; Davitt et al. 2002; Gross and Lemmens 2010) have been described.

Until now the life expectancy of patients with Hunter syndrome has been low, especially if the disease was the severe form (Young and Harper 1983). Attenuated cases with almost normal life expectancy have also been described, although very rarely (Young and Harper 1982; Jones et al. 2009). Only around 10% of all Hunter patients reached the age of 25 before the introduction of enzyme replacement therapy (Wraith et al. 2008; Jones et al. 2009).

Enzyme replacement therapy, which has been available in Europe since 2007 in the form of idursulfase, represents a starting point for potentially preventing the hitherto typical clinical course of the disease in young patients who die before reaching adulthood (Fenton and Rogers

2006; Young and Harper 1983). Study results and initial experience of therapy with idursulfase suggest that enzyme replacement therapy should be begun early (Wraith et al. 2008) before irreversible changes have manifested and ideally before significant progression of the disease.

However, there is little experience to date with enzyme replacement therapy in adult Hunter patients, who show a classic manifestation of the clinical picture. The current publication presents the clinical progression of an adult Hunter patient who was initially treated with noninvasive ventilation (NIV) and has additionally been receiving enzyme replacement therapy since its marketing authorization.

Case Report

The male patient was born in January 1971. A possible storage disease was suspected at an early age, although there was no evidence to verify this. A blind hepatic biopsy was carried out in September 1974 in response to suspected glycogenosis, although the result was inconclusive. In October 1974, there was evidence of increased urinary excretion of acid mucopolysaccharides and MPS II was diagnosed.

The patient is not intellectually compromised and, upon leaving school, he undertook vocational training and worked at a computer workstation. As he got older, he developed dyspnea on exertion, which manifested even when walking normally at ground level.

In October 2005, the patient was admitted to Hemer Lung Clinic for further diagnosis and therapy. At this time, he had severe restrictive ventilatory problems with an FEV₁ of 0.8 L (26% of target), a VC of 1.0 L, and a TLC of 2.6 L (53% of target) (Table 1). Blood gas analysis (BGA) showed respiratory global insufficiency with a pH of 7.38, a pO₂ of 52 mmHg, and pCO₂ of 81 mmHg. The pulmonary artery pressure was raised to a systolic reading of 55 mmHg. The interventricular septum (IVS) was also thickened to 1.30 cm, and there was a dynamic left ventricular outflow tract obstruction with a pressure gradient of 60 mmHg and grade II aortic valve insufficiency. Urinary excretion of acid mucopolysaccharides was elevated at 5.0 mg/0.1 g creatinine (norm < 2.8). Nocturnal polysomnography detected a disturbed sleep profile with reduced deep sleep and REM sleep. The average oxygen saturation was 75% and the respiratory disturbance index was raised at 60/h. Nocturnal BGA showed respiratory acidosis with a pH of 7.30. The pCO₂ was 81 mmHg and the pO₂ was 32 mmHg.

Treatment was initiated with gradual continuous positive airway pressure (CPAP) titration, adjusted to an ultimate

Table 1 Lung function and echocardiography prior to noninvasive ventilation therapy (10/2005), up to introduction of enzyme replacement therapy (2/2008) and after introduction of enzyme replacement therapy (9/2008)

Function parameter	Dates of assessments		
	10/2005	2/2008	9/2008
FEV1 (L)	0.8	1.5	1.6
VC (L)	1.0	2.0	2.1
TLC (L)	2.6	3.6	4.0
DLCO (% of target)		73.4	70.8
P0.1 (kPa)	0.59	0.47	0.30
Pimax (kPa)	3.42	4.56	4.23
pO ₂ (mmHg)	52	80	77
pCO ₂ (mmHg)	81	34	32
6MWT (m)	100(pO ₂ 44 (mmHg)/pCO ₂ 66 (mmHg))	280(pO ₂ 68 (mmHg)/pCO ₂ 43 (mmHg))	400(pO ₂ 76 (mmHg)/pCO ₂ 38 (mmHg))
PA syst.	55	45	30
IVS thickness	1.3	1.15	1.05

pressure of 11 cm H₂O to open up the upper respiratory tract at night. However, hypercapnea persisted in the course of CPAP titration, sometimes with pCO₂ readings up to 110 mmHg and a pH of 7.22. Treatment was therefore definitively adjusted to NIV with a pressure of 31/11 cm H₂O, a frequency of 18/min with the additional administration of 2 L O₂/min. This gradually achieved normalization of blood gas values, and the patient's sleep quality improved considerably.

NIV was subsequently used consistently. Pulmonary function results showed a clear improvement in February 2008 (Table 1). The FEV1 increased to 1.5 L, the VC to 2.0 L and the TLC to 3.6 L. Measurement of muscle power and respiratory pump load showed under NIV an increase in the Pimax from 3.43 kPa to 4.56 kPa and a simultaneous fall in the P0.1 reading from 0.59 kPa to 0.47 kPa. The blood gas readings at rest were pO₂ 80 mmHg and pCO₂ 34 mmHg. The distance covered in the Six-Minute Walk Test (6MWT) increased from 100 m in 2005 to 280 m in February 2008. The blood gas readings in the 6MWT test likewise showed a considerable improvement. Whereas in 2005 after walking 100 m, the pO₂ was found to decrease to 44 mmHg with an increase in pCO₂ to 66 mmHg, the pO₂ was 68 mmHg and the pCO₂ was 43 mmHg after walking a distance of 280 m (Table 1). The pulmonary artery systolic pressure was recorded as 45 mmHg.

In February 2008, supplementary therapy was initiated with idursulfase in a well-tolerated dosage of 0.5 mg/kg body weight. Under this treatment, the excretion of GAG was regularly monitored and found to have fallen to below half the upper limit of normal (58 µg/mg creatinine).

In September 2008, under idursulfase therapy an increase of the FEV1 to 1.6 L, of the VC to 2.1 L, and of the TLC to 4.0 L was detected, with a decrease in the P0.1 to 0.3 kPa and constant Pimax (Table 1). The BGA showed a tendency to hyperventilation (pO₂: 77 mmHg, pCO₂: 32 mmHg). The pulmonary artery pressure was normalized. Nocturnal polysomnography showed only a mild obstructive sleep-related breathing disorder. The nocturnal BGA readings were in the normal range. The NIV was maintained, and the therapeutic pressure was reduced to 20/9 cm H₂O. Administration of oxygen was no longer required.

In the six-minute walk test (6MWT), the distance covered had increased to 400 m. The BGA under exertion again showed an improvement (pO₂: 76 mmHg, pCO₂: 38 mmHg). At this point, spirometry was carried out for the first time, when a load of 80 W and a maximum oxygen uptake of 1,350 mL or 28.1 mL/kg body weight were achieved. The anaerobic threshold was 57% of the target maximum oxygen uptake. There were no indications of disturbed diffusion at an alveolar-arterial oxygen tension difference (AaDO₂) of 31 mmHg at maximum load.

The most recent follow-up examination in November 2010 under ongoing idursulfase therapy again showed an increase in the FEV1 to 1.6 L, of the TLC to 4.4 L, and of the VC to 2.3 L. The thickness of the septum had reduced further to 0.95 cm. Even if there have been only rather minor changes in the functional parameters from September 2008 to November 2010, a steady and clearly positive change has been recorded with regard to the joint and soft tissue situation and in particular to the physiognomy over the period of time in question. The joint contractures improved, especially in the area of the distal interphalangeal joints of the finger, so that the flexion which was previously fixed at 110° decreased to 85°, while the facial contours became smoother and the wrinkle formation in the face was reduced (Fig. 1). The previously frizzy hair appeared considerably straighter.

Polysomnography confirmed that the NIV was well adjusted, with a tendency to nocturnal hyperventilation and a consequent tendency to central apneas. The polysomnography without NIV showed only a mild obstructive sleep-related breathing disorder with no sign of nocturnal hypoventilation. Therefore, treatment was changed to nocturnal CPAP therapy with a constant pressure of 6 cm H₂O. Additional administration of oxygen was not required. With this therapy, the patient has been asymptomatic up to September 2011.

Fig. 1 Facial physiognomy of Hunter patient – in 2005 prior to idursulfase therapy (*left*) and in September 2011 after 3 years of idursulfase therapy (*right*)

Discussion

Until now only isolated case descriptions and clinical progression reports have been available for adult patients because of the typical progression of the disease – very few patients survive beyond the age of 30 (Pérez-Calvo et al. 2011). Most patients with Hunter syndrome have respiratory problems at an early age as a result of the progressive obstruction of the upper respiratory tract caused by an accumulation of GAG and restricted mobility of the mandibular joint. Some of these respiratory problems are associated with severe nocturnal sleep-related breathing disorders and frequent infections of the upper respiratory tract (Leighton et al. 2001; Orliaguet et al. 1999; Shapiro et al. 1985).

In many patients, these changes occur in the first or second decade of life, in particular when the clinical progression of the disease is severe, so that respiratory deterioration is a common cause of death (Young and Harper 1983). However, this type of severe obstruction of the upper respiratory tract is also described for attenuated forms of the disease, and this obstruction has been shown to determine the clinical progression (Young and Harper 1982). In isolated cases, there is also relevant thoracic restriction (Young and Harper 1982), as was also seen in the patient under discussion: in 2005, besides a disturbed sleep profile and sleep apnea, he also showed a severe restrictive ventilation disorder with hypoventilation.

In keeping with previous positive experiences in patients with Hunter syndrome (Leighton et al. 2001; Ginzburg et al. 1990), CPAP titration was primarily carried out to resolve the respiratory tract obstruction. This required a high CPAP level, although in comparative terms it was below previously reported CPAP levels of up to 20 cm H₂O (Ginzburg et al. 1990). Orliaguet et al. report an intolerance to CPAP pressures > 12 cm H₂O with the occurrence of dyspnea in their patients (Orliaguet et al. 1999). The cause was found to be a myxoma in the upper respiratory tract;

therefore, surgical resection of the myxoma in the area of the vocal cords was carried out. Only then, with the CPAP adjusted to 12 cm H₂O, were the AHI and the pCO₂ successfully normalized. Myxomatous changes of this type were not present in the case presented here, as well as other causes of obstruction described in the literature (Gross and Lemmens 2010; Young and Harper 1979; Davitt et al. 2002; Morehead and Parsons 1993), such as tracheal stenosis or tracheobronchomalacia. Although CPAP therapy effectively resolved the upper airway obstruction in the patient under discussion here, contrary to the case report of Ginzburg et al. in 1990, it did not remedy the accompanying hypoventilation, which had to be attributed to the severe restriction. However, the diurnal pCO₂ readings reported by Ginzburg et al. of a maximum of 51 mmHg were considerably lower.

Surgical therapy was not indicated due to the lack of evidence of surgically resectable myxomatous tissue. Therefore, the persistent hypoventilation with restrictive ventilatory disturbance and pronounced respiratory muscle weakness (raised p0.1 and lowered Pimax) presented an indication for initiating NIV. Blood gas levels were successfully normalized in the course of the NIV only after high inspiration pressures and a longer adaptation phase were selected. This avoided the need for a tracheotomy, as has been described in isolated cases with the most severe respiratory tract obstructions (Sasaki et al. 1987; Yoskovith et al. 1998), particularly as tracheotomy would also have been associated with an increased operative risk.

In contrast to CPAP therapy in Hunter syndrome with respiratory tract obstruction or sleep apnea, the use of NIV is not documented in the literature. Besides the rarity of these types of processes in adulthood, this is because the application of NIV has only become more widespread in the last two decades. Therefore, the functional improvements achieved under NIV in the course of 3 years cannot be compared to a similarly treated group. At any rate it is clear that, particularly in comparison with the functional

improvements under the enzyme substitution initiated in February 2008, effective ventilation alone can achieve a considerable increase in lung volume, with a virtual doubling of the FEV1 and VC, and an increase of 1 L in the total lung capacity (TLC). The normalization of blood gas levels at rest and on exertion as well as the increase in the distance covered in the 6MWT are also to be attributed to the effect of relieving the burden on the respiratory muscles and to the demonstrable increase in respiratory muscle strength in the course of the disease as a result of the systematic application of NIV.

In contrast to the central sleep apnea in untreated patients with Hunter syndrome described by Kurihara et al. as a consequence of the accumulation of gangliosides in the respiratory center (Kurihara et al. 1992), the central apneas seen under NIV are to be interpreted as a consequence of hyperventilation with a drop in the $p\text{CO}_2$ below the apnea threshold and are thus an indicator of effective therapy.

The adult patient described here has been receiving a combination of NIV therapy and enzyme replacement therapy with once weekly 0.5 mg/kg idursulfase since February 2008. The improvement achieved in the symptoms, but also the persistence of the functional improvements initially achieved by the NIV after ending the NIV are clearly attributable to the enzyme replacement. After a first six-month check-up under enzyme replacement therapy and in the further clinical course until September 2011, accompanied by normalization of the urinary excretion of GAG, there was further improvement in the lung function values FEV1, VC, and TLC and the BGA under exertion, normalization of nocturnal hypoventilation and clear improvement in the obstructive sleep-related breathing disorder.

The functional improvements in lung function and in the load tests are considerably greater than the increases in lung volume and distances walked reported to date in therapeutic studies with idursulfase. The Japanese study (Okuyama et al. 2010) reported an increase in the distance walked of 54.5 m and in the FVC of 3.8% after 12 months, comparable with the data specified by Muenzer et al. 2006. They saw after 1 year of idursulfase therapy an increase of 37 m in the 6MWT ($P = 0.013$), a percentage increase in the predicted FVC of 2.7% ($P = 0.065$) and an increase in the absolute FVC of 160 mL ($P = 0.001$), compared to a 30%-increase (i.e., 120 m) in the 6MWT seen in our patient.

Since the functional improvements achieved primarily by the NIV also persisted after changing from NIV to CPAP therapy under enzyme substitution, there is much to suggest that these improvements could also have been achieved by enzyme replacement therapy alone, if it had been available at the time.

Likewise the normalization of the left ventricular wall thickness and the pulmonary artery pressure are attributable

to enzyme replacement therapy, even if a clear reduction in right ventricular load and left ventricular hypertrophy had already been recorded under NIV.

Nevertheless, this is an unusual clinical improvement, especially since it occurred in an adult Hunter patient with long-established disease and severe respiratory impairment, in whom it would not have been primarily expected in this way before starting enzyme replacement therapy.

The increase in joint mobility which is impressive in a patient with long-standing disease duration was described in a similar way by Pérez-Calvo et al. in a 31-year-old male patient (Pérez-Calvo et al. 2011) and emphasizes that joint mobility can be improved by enzyme replacement therapy even in older patients, which has a significant effect on the use of the fingers in everyday life. The pronounced change and rejuvenation of the facial features is unusual for the age of the patient and is another indication of success of enzyme replacement therapy.

To sum up, the case presented here demonstrates that adult Hunter patients can benefit from enzyme replacement therapy, and in the case of a restrictive ventilatory disturbance with hypoventilation can benefit from symptomatic therapy with NIV. These treatments in adults can potentially achieve considerable functional improvements as well as changes in the physiognomy and joint mobility.

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