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Chapter Seven

Efficacy of enzyme replacement and substrate reduction therapy in three siblings with Gaucher disease type III

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Abstract

We report on three siblings with Gaucher disease type III, born between 1992 and 2004. During this period, new developments resulted in different potential therapies, changing clinical practice. The two eldest siblings received enzyme replacement therapy (ERT) from the age of 24 and 5 months respectively, later followed by an increase in dosage. ERT was combined with substrate reduction therapy (SRT) from the age of 12 and 8 years, respectively. In the youngest sibling the combination of high-dose ERT and SRT was already given from the age of 5 months. The two eldest siblings showed significant neurological impairment from the age of 1.5 years, starting with a convergent strabismus and partial occulomotor apraxia, followed by cognitive decline and an abnormal EEG and BAER. In strong contrast, the neurological development in the youngest sibling is almost completely normal. At the age of three years, cognitive development, EEG and BAER are all normal. Disturbed saccadic eye movements, which were already present at the start of therapy, remained stable. In addition to the clinical efficacy, we report on the biochemical response to therapy. Based on our results, the combination of high-dose ERT and SRT should be considered as a promising therapy for GD III, especially if started at a young age. Further follow-up studies are necessary to explore the long-term therapeutic effects.

Introduction

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase (GBA; EC 3.2.1.45), which catalyzes the degradation of glucosylceramide into ceramide and glucose. Glucosylceramide accumulates massively in macrophages of patients with GD. The so-called Gaucher cells invade various tissues and may thereby result in organ dysfunction.

Three phenotypic subtypes of GD are distinguished. GD type I (OMIM # 230800) is the most common and mildest variant. Patients with GD type I develop progressive symptoms, such as hepatosplenomegaly, anemia, thrombocytopenia and skeletal lesions. In GD type II and III, the central nervous system (CNS) is involved in addition to the visceral complications. This can become apparent already soon after birth (acute neuronopathic form, GD type II; OMIM # 230900) or later in life with a more protracted course (chronic neuronopathic form, GD type III; OMIM # 231000).

Two treatment modalities are approved for GD. Firstly, enzyme replacement therapy (ERT), which is based on chronic intravenous administration of recombinant GBA, aims to increase the residual capacity to degrade glucosylceramide. Secondly, substrate reduction therapy (SRT), which is based on chronic oral administration of an inhibitor of the biosynthesis of glucosylceramide and higher glycosphingolipids, aims to balance glucosylceramide synthesis and residual degradation capacity. Over fifteen years of experience with ERT has learned that ERT resolves hepatosplenomegaly and improves hematological and bone disease in the majority of patients with GD type I, thereby greatly improving quality of life [1]. In GD type III a similar visceral response to ERT can be observed [2-4]. However, ERT is incapable to prevent patients with GD type III from CNS complications, as the blood-brain barrier blocks the passage of the 60 kDa enzyme. Nevertheless, it has been suggested that high dose ERT (i.e. ≥ 120 U/kg biweekly) might stabilize neurological manifestations in some patients with GD type III by either 'forced' penetration of recombinant GBA into the cerebrospinal fluid (CSF) due to systemic overload (reviewed in Zimran et al. 2007 [5]) or by clearance of perivascular Gaucher cells located outside the blood-brain barrier [6].

In 2002 SRT, in the form of the immunosugar *N*-butyldeoxynojirimycin (miglustat), became available as a new therapeutic option for patients with mild to moderate GD type I in whom ERT is either not tolerated or not accepted. Administration of miglustat improves visceral complications in GD type I patients and is generally well tolerated [7,8].

In contrast to the recombinant enzyme, miglustat is partly capable to cross the blood-brain-barrier [9] and, therefore, might be a potential drug to treat the central nervous system (CNS) complications in GD type III. SRT for treatment of neurological complications in GD type III is appealing, but so far only has been investigated in a few studies. The outcome of a multi-center study on the efficacy of SRT in combination with ERT in GD type III patients has not yet been published. However, the first results were considered to be disappointing (Schiffmann, oral presentation EWGGD 2006 [10]), resulting in premature termination of the trial (www.actelion.com). Nevertheless,

therapeutic efficacy has been demonstrated in a single case [11].

Along with the development of new therapies, potential biomarkers have been studied to monitor the burden of disease in relation to treatment. Increased plasma chitotriosidase reflects the presence of Gaucher cells in viscera of GD patients [12,13], and monitoring of plasma chitotriosidase is commonly used to assist in decision making regarding initiation and optimization of therapy [12]. More recently, the chemokines macrophage inflammatory protein (MIP)- 1α and β , have been reported to be also elevated in plasma of patients with GD type I [14]. MIP- 1α might be of particular interest in GD type III, since it was suggested that induction of this chemokine might be related to brain pathology in both hexosaminidase B and β -galactosidase-deficient mice [15-17].

In the present study we report the clinical findings in three siblings with GD type III who received different therapeutic regimens during the course of their disease, including ERT monotherapy, the switch from ERT monotherapy towards combined ERT and SRT therapy as well as direct and early initiation of this combined therapy. In addition, attention is focused to biochemical markers in plasma and CSF in relation to therapy and clinical outcome.

Patients and methods

Patients

Three siblings were diagnosed with GD type III based on enzymatic deficiency of GBA activity in leucocytes and mutation analysis. The patients were all homozygous for the L444P mutation, which is known to be associated with a neuronopathic course of GD [18]. All children receive ERT (Cerezyme®, Genzyme, Boston, USA) through an intravenous access device (Port-a-Cath). Between 1990 and 2001 the dosage of ERT was based on visceral parameters (i.e. liver- and spleen size, hematological parameters) in combination with the response of chitotriosidase in plasma. From 2001 all patients were treated with high-dose ERT, i.e. 120 U/kg/biweekly, based on the European consensus on neuronopathic GD [19].

The study on combined ERT and SRT was approved by the local medical ethical committee.

The dosage of *N*-butyldeoxynojirimycin (miglustat, Zavesca®, Basel, Switserland) was based on the body surface of the patient according to Gerald and O'Bannon [20].

Clinical assessments

Oculomotor apraxia (OMA) characterized by an initiation failure of rapid eye movements (saccades) is often the earliest neurological sign in GD type III. Initially, eye movements were assessed on ophthalmologic and neurological evaluation. Saccadic movements of both eyes were regularly monitored using an electromagnetic eye recording method (DMI) from 2003 onwards [21]. In addition, eye movements were documented on video. Particularly vestibular testing (passively rotating the eye), OMA, head nodding, blinks and ocular alignment could be evaluated from the video afterwards.

Hearing was assessed by brainstem auditory evoked responses (BAER). Psychomotor development was assessed by either the BSID-II or the SON-R, depending on the age of the patient. Neurological examination and electroencephalography (EEG) regularly were included in the follow-up. Liver and spleen size were measured by abdominal ultrasound.

Biochemical assays

Biochemical parameters were analyzed in both plasma and CSF samples, which were stored at -20°C. CSF samples could be obtained before initiation of SRT in patient 2 and 3 and at one year after starting SRT in all. The activity of plasma and CSF chitotriosidase was determined using 4-methylumbelliferyl-deoxychitobiose as substrate [22]. The carrier status for chitotriosidase was determined. In case the patient was a carrier, measured chitotriosidase values were doubled.

Levels of MIP-1 α and MIP-1 β in both EDTA plasma and CSF were measured by ELISA as previously described [14].

Results

Clinical parameters: Case descriptions

Case 1

This female child was diagnosed with GD type III at the age of 1.5 years, after presentation with failure to thrive and hepatosplenomegaly (GBA activity: 2,5 nmol/mg.hr). Neurological evaluation revealed partial OMA with a convergent strabismus. The EEG showed diffuse slowing with focal abnormalities in both temporal regions. The BAER was normal. At the age of two years ERT was started at an initial dose of 25 U/kg twice a week. Hepatosplenomegaly markedly improved and normalization of the platelet count and hemoglobin level was observed within 3 months. The changes in treatment over time are shown in Table 1. Neuropsychological testing at the age of 4 years revealed severe developmental delay (verbal and performal IQ both 48). Strabismus surgery was performed twice, at the age of six and ten years. Neurological examination at the age of 9 years revealed a horizontal and vertical gaze palsy. She had normal coordination and muscle strength and disturbance of the fine motor movements. The BAER was abnormal with absence of wave IV and V and prolonged latencies of waves I to III. Cognitive testing revealed a stable IQ of 48. At the age of 14 years mean saccadic velocities were tested and found to be abnormal (horizontal, downward and upward velocities at 12 degrees of 80, 90 and 210 degrees per second; normal: 350 ± 25 horizontal and 350 ± 50 vertical).

Over the last two years, while receiving SRT in addition to ERT, the neurological situation, including the reduced velocity of saccadic eye movements, has remained stable. Despite epileptic discharges on the EEG recording, no clinical signs of epilepsy are present. The child has severe thoracic kyphosis of 60° , with no progression over the last years. She visits a school for mentally disabled children.

Case 2

The second child of this family, also a girl, was diagnosed with GD immediately after birth on the basis of enzymatic testing (GBA activity: 1,7 nmol/mg/h). Antenatal diagnosis was not requested because of religious motives. ERT was initiated at the age of five months (Table 1), because of a gradual enlargement of liver and spleen size in combination with an increasing concentration of chitotriosidase in plasma (Figure 1). Hematological parameters were normal. Neurological and ophthalmologic examination did not reveal any abnormalities at that time. The EEG recording was normal. However, from the age of 1.5 years partial OMA in combination with a convergent strabismus was observed, which was surgically corrected at the age of 4 years. Neuropsychological testing performed at the age of 4 years showed severely impaired mental development (verbal and performal IQ of 53 and <48, respectively), comparable to her older sister at that age. She had reduced muscle strength, disturbed fine motor movements and signs of ataxia with a wide based gait. At the age of 6 years the EEG revealed general background slowing with a predominant rhythm of 4-7 Hz with epileptic discharges over the right centroparietal region. Clinically, no epilepsy was observed.

Table 1. Different doses of ERT (U/kg/2 weeks) and combination with SRT (+) in patient 1-3 over time.

Age (Years)	Patient 1	Patient 2	Patient 3	
5/12	-	100	120+	
1	-	30	120+	
2	100	40	120+	
3	50	40	-	
4	50	70	-	
5	40	70	-	
6	40	120	-	
7	40	120	-	
8	60	120	-	
9	60	120	-	
10	120	120+	-	
11	120	120+	-	
12	120	-	-	
13	120	-	-	
14	120+	-	-	
15	120+	-	-	
16	120+	-	-	

From the age of 10 years SRT was added to ERT. Clinical assessment before the start of combination therapy revealed the same abnormalities on the EEG. The BAER was grossly abnormal and revealed only a clear wave I and V. Velocity of saccadic eye was even more reduced than in her sister (horizontal, downward and upward velocities at 12 degrees of 65, 55 and 130 degrees/sec). Two years after initiation of combination therapy repeated EEG, BAER and assessment of saccadic eye movement velocity revealed the same abnormalities as two years previously. Clinically she is in a stable condition and visits the same school as her older sister.

1.5 yrs

17

Patient	Age	Time after start ERT ERT and SRT		chitotriosidase	
Patient 1	15 years	13 years	1 yr	1272	
Patient 2	5 months	baseline	_	68	
	10 years	9.5 years	_	838	
	11 years	10.5 years	1 yr	816	
Patient 3	5 months	baseline	_	39	

1.5 years

Table 2. Chitotriosidase activity (nmol/mL/h; normal 6-64) in CSF.

2 years

Case 3

Enzymatic analysis immediately after birth confirmed the diagnosis of GD in this third, male child (GBA activity: 1 nmol/mg.hr). At the age of 5 months combination therapy with high-dose ERT and SRT was started. Slight liver and spleen enlargement was observed on physical examination, which was confirmed by abdominal ultrasound. Hematological parameters were normal. The EEG was normal. The BAER showed slightly prolonged latencies. Ophthalmologic evaluation revealed a gaze evoked nystagmus in the upward direction. Saccadic eye movement assessment showed partial OMA with slow horizontal saccades with a mean saccade velocity at 12 degrees of 160 degrees/sec. Vertical saccade velocity could not be reliably tested.

During the first half year of combination therapy diarrhoea was observed as gastrointestinal side effect of SRT. This was well controlled by temporary dietary adjustments. No other side effects occurred.

Three years after the start of combination therapy, at the age of 3.5 years, the following results were obtained. Ophthalmologic and neurological examination revealed no abnormalities, especially no nystagmus. Saccadic eye movements showed no further deterioration (horizontal, downward and upward velocities at 12 degrees of 210, 170 and 300 degrees per second). Both the BAER and EEG were normal. Psychomotor development was completely age-appropriate (mental and motor developmental quotients of 92 and 91, respectively).

Biochemical parameters: Chitotriosidase, MIP-1 α and MIP-1 β in plasma and CSF

Chitotriosidase, MIP-1 α , and MIP-1 β were analyzed in serial plasma specimens of all three siblings. The two sisters were both heterozygous for the chitotriosidase mutation, whereas the youngest boy had a wildtype genotype. The response of plasma chitotriosidase to therapy is illustrated in Figure 1A-C. Plasma chitotriosidase levels rapidly declined in all siblings after initiation of therapy (Fig. 1A-C). Decreasing the dosage of ERT in the two eldest siblings resulted in a significant increase in plasma chitotriosidase, being reduced again after increasing the dosage of ERT (Fig. 1A&B).

The response of plasma levels of MIP- 1α and MIP- 1β in relation to therapy is shown in Figure 1D-F. At baseline plasma MIP- 1β was increased in all patients compared to controls (median 17 pg/mL, range: 1-122 pg/mL, n=39). During ERT or combined ERT and SRT

in patient 3, levels of MIP- 1β reached values below the detection limit. Plasma MIP- 1α was only clearly elevated in the eldest sibling at baseline and decreased while treated with ERT (control values: MIP- 1α : median 9 pg/mL, range 0-208 pg/mL, n=39).

Only limited samples of CSF were available for biochemical analysis. Both MIP-1 α and β were undetectable in the CSF samples. Chitotriosidase activity was markedly elevated in the most recent CSF samples from the two neurologically affected sisters (Table 2). In sharp contrast, chitotriosidase activity in the latest CSF sample from the youngest male sibling, obtained at the age of two, was still within the normal range (Table 2).

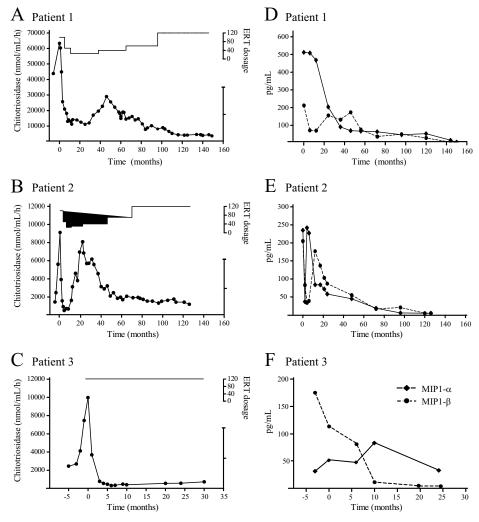


Figure 1. Biochemical parameters in patient 1-3 over time. (A-C) Chitotriosidase activity in plasma. (D-F) MIP-1 α and MIP-1 β levels in plasma. Detection limit: 5 pg/mL

Discussion

We report on three siblings with GD type III who were treated with different therapeutic regimens as a result of the emergence of new therapeutic insights and options over time. Our data support the hypothesis that SRT in addition to high-dose ERT may have a beneficial effect on the neurological course in GD type III if initiated at an early age.

High-dose ERT improves the visceral signs and symptoms in GD type III. However, although a possible attenuation of the neurological course due to high-dose ERT has been suggested, relentless neurological deterioration has been frequently reported [2,4,6,23,24]. The two eldest siblings in this study indeed showed progressive neurological deterioration during ERT monotherapy. However, they did not receive a high-dose regimen from the start of treatment. In line with previous reports [2,4,6], the visceral disease manifestations responded well to ERT, as also reflected by the marked reduction in plasma chitotriosidase.

The very different clinical course in the youngest sibling, who was treated with both SRT and high-dose ERT from the age of 5 months, suggests a neuroprotective effect of this treatment in GD type III. Despite abnormal eye movements, which were already present before initiation of treatment, physical examination and additional investigations, including neurocognitive testing, did not reveal any abnormalities at the age of 3.5 years. At that age both sisters had clear OMA at physical examination, as well as strabismus, which is an important feature of neuronopathic GD [25]. Moreover, severe developmental delay was already noticed at that age in both girls. Nevertheless, it can not be completely ruled out that the clinical course would have varied between these three children, unrelated to differences in therapy as it has been shown that the phenotype may vary within families, even between monozygotic twins [26].

In the two sisters who already showed major CNS involvement at the time SRT was added to ERT, the combined therapy appeared to have limited but potentially valuable effects, as neither improvement nor deterioration of neurological complications occurred within two years. In addition, recently an adult patient with GD III was reported, who showed a significant decrease in the number of seizures and improved speech after SRT was added to ERT [11].

Only few mechanisms are known by which the accumulation of glucosylceramide may result in devastating brain pathology [27]. Interestingly, in both the Sandhoff (hexosaminidase B deficiency) and the GM1-gangliosidosis (β -galactosidase deficiency) mouse model, induction of MIP-1 α seems to play a critical role in brain pathology [15-17]. This marker was recently shown to be elevated in plasma of patients with GD type I [14]. Plasma MIP-1 α and MIP-1 β are indeed increased in patients with GD type III as reported here, and both levels decreased upon therapy. Unfortunately we were unable to detect MIP-1 α and MIP-1 β in the CSF by ELISA as the sensitivity for detection of both chemokines with the presently available methods is relatively low. Therefore, we can not rule out that these chemokines might play a role in the brain pathology. Studies in mouse models of GD type II/III will allow a more thorough analysis of potential local elevations and effects of the MIP-1 α and MIP-1 β in brain. Fortunately, chitotriosidase can be extremely sensitively

detected by measuring its enzymatic activity towards a fluorogenic substrate [28]. Only a limited number of CSF samples were available for analysis in the present study. The two neurologically affected sisters both showed markedly elevated chitotriosidase concentrations in CSF at age 10 and 11 years. In contrast, chitotriosidase in the CSF of the youngest sibling was still normal after 1.5 year of SRT and ERT. However, no age-matched samples from his affected siblings were available. The increased CSF chitotriosidase is of interest as it suggests a potential value as marker for neurological involvement in GD type III. Indeed, neurological involvement in GD patients may be accompanied by increased chitotriosidase levels in CSF as previously also reported by Schiffmann et al [4]. However, as the youngest child in our study already displayed abnormal slowing of saccadic eye movements despite normal CSF chitotriosidase, it is apparently not a sensitive marker for early neurological involvement.

Although the results of a multi-center study trial on efficacy of SRT and ERT in GD type III have not (yet) been published, early analyses were disappointing resulting in termination of the trial (www.actelion.com). However, we speculate that the potential benefits of combined ERT and SRT in GD type III should be sought in prevention rather than in improvement of neurological symptoms.

In summary, based on our results high-dose ERT in combination with SRT may be regarded as a potential efficacious therapy for GD type III, especially if started at a young age. Further follow-up studies will need to demonstrate that the potential beneficial effects of SRT in combination with ERT are sustained, resulting in preservation of cognitive function over time.

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