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ORIGINAL ARTICLE

Outcome of type III Gaucher disease on enzyme replacement therapy: Review of 55 cases

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Summary The European Task Force for Neuronopathic Gaucher Disease (NGD) met in 2006 to review its 2001 guidelines. Fifty-five patients from five European countries were reviewed; 29 were male and 26 female. The majority of the patients were homozygous for the L444P mutation. All had been on enzyme replacement therapy (ERT). However, there was considerable variation in the dose of ERT, as well as an uneven distribution of risk factors. Thus, the oldest patients were on the lowest doses, and several had had a total splenectomy, while the youngest patients had a high proportion of compound heterozygosity and were on the highest doses, and very few had had a splenectomy. This heterogeneity rendered analysis very difficult. However, some observations were possible. The older patients appeared to remain relatively stable despite a low dose of ERT. In the younger patients, there was no clear effect of high-dose ERT. However, the period of follow-up was too short in many patients to draw valid conclusions. These data will be used to draw up revised guidelines.

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References to electronic databases: Neuronopathic Gaucher disease: OMIM #231000. Gaucher disease type II: OMIM #230900.

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Abbreviations

ERT	enzyme replacement therapy
FSIQ	Full Scale Intelligence Quotient
LSD	lysosomal storage disorder
NGD	neuronopathic Gaucher disease
PIQ	performance intelligence quotient
SST	Severity Scoring Tool
VIQ	verbal intelligence quotient

Introduction

The original EU Task Force guidelines for the management of neuronopathic Gaucher disease (NGD) (OMIM #231000) were published in 2001 (Vellodi et al 2001). However, by 2005 it was felt that these guidelines needed reviewing.

The authors of this paper met in June 2005. The primary objective was to evaluate the effect of high-dose

enzyme replacement therapy (ERT) on the neurological outcome of type III (chronic neuronopathic) Gaucher disease. Type II Gaucher disease (OMIM #230900) was not discussed.

Sixty patients were presented and discussed at the meeting. It was difficult to evaluate the data in a meaningful way, for several reasons:

- Not all centres were performing the same assessments.
- Important data were missing, e.g. data yielded by the Rostock Neuro Score that was used in the 2001 study. This was in fact not used for further analysis as the score had not yet been validated or published. A new scoring system has been devised, one that has been validated and peer-reviewed (Davies et al 2007).
- Baseline neurological assessment did not always provide sufficient information for later comparison.
- There were significant differences in data interpretation between groups.
- Financial constraints meant that, despite the recommendations, very few patients with type III disease were being treated with Cerezyme 120 IU/kg every two weeks.

It was felt that data quality could be considerably enhanced by a systematic collection of data, albeit retrospectively, from patient records in each country. It was decided that one person (E.H.D.) should visit all the centres for this purpose. The centres involved were based in hospitals in Lumea, Sweden; Warsaw, Poland; Mainz, Germany; and London, United Kingdom. Forty-five patients were seen in clinic between November 2005 and February 2006, and the notes of a further 10 patients reviewed, making 55 in all. Although 60 patients were discussed at the first meeting, five patients had type II disease and were therefore excluded from further analysis. Some of the UK and Polish patients were on the OGT-918 study being conducted by Actelion. For such patients, only data up until 2003 (the time the study commenced) was analysed.

Definition

For the purposes of this study, neuronopathic Gaucher disease was defined as the presence of neurological involvement in patients with biochemically proven Gaucher disease, for which there was no explanation other than Gaucher disease.

Data collection

The following data were collected:

- Basic demographics: sex, ethnicity, age at diagnosis and assessment.
- Genotype.
- Splenic status, i.e. whether intact, partially removed or totally removed
- Seizure history.
- Current neurological features
  - Eye movements
  - Ataxia (collected but not analysed; see Discussion)
  - Pyramidal and/or extrapyramidal (collected but not analysed; see Discussion).
- Neuropsychometric scores.
- Treatment details: age of starting ERT, current dose.
- Concurrent medication,, e.g. anticonvulsive drugs.
- Chitotriosidase levels as a measure of visceral disease.

Statistical methods

Descriptive tests (mean, and median when not normally distributed) were used to describe the demographic characteristics of the patients, ERT and chitotriosidase. A multiple regression analysis was performed to determine the effect of ERT on patient outcome as measured by Neuropsychometric assessments and chitotriosidase, adjusting for a number of independent clinical variables including genotype and spleen status.

Demographic data

The data are summarized in Table 1. There were 55 patients in all; 29 male and 26 female. The distribution was 12 each from Sweden and Germany, 18 from Poland and 13 from the UK. The Swedish patients were the oldest at assessment and the German and UK patients the youngest. There were three pairs of siblings.

The two factors known to be associated with an adverse neurological outcome, genotype and splenectomy, were analysed. The majority of the patients (n=40, 71.4%) were homozygous for the L444P mutation. Five had L444P/D409H, five L444P/rare allele and a further four rare allele/rare allele. In one patient neither mutation was identified. The majority

Table 1 Demographic data

	Sweden	Poland	Germany	UK	Total
Number	12	18	12	13	55
Median age (years)	38.9	15.6	12.0	10.0	13.96
Male	7	8	7	4	26
Female	5	10	5	8	29
L444P/L444P	11	13	6	10	40
L444P/D409H	1	2	2	1	5
L444P/other	1	1	2	1	5
Other/other genotype	0	2	2	1	5
Total splenectomy	8	3	2	–	13
Age at total splenectomy (years)	(*n*=6) 9.3 (SD 8.1)	(*n*=6) 5.2 (SD 3.9)	(*n*=2) 5 (SD 4.24)	*n*=0	(*n*=14) 6.9 (SD 6.10)

of the Swedish patients were L444P/L444P, but only 50% of German patients. Full sequencing had not been performed in all cases. However, the incidence of 71.4% homozygosity for the L444P mutation is almost identical to the 72% incidence reported by the Neurological Subregistry of the ICGGR (data in preparation). While this does not validate our findings, nevertheless it suggests that they can be used for purposes of comparison.

Fourteen patients (25%) had had a total splenectomy. The majority (75%) of Swedish patients had been splenectomized, while none of the UK patients had.

Comments

- The significantly older age of the Swedish patients might indicate milder disease.
- The young German cohort had a high proportion of compound heterozygotes; this might indicate more severe disease.
- The higher incidence of splenectomized patients in the Swedish cohort might predispose to a more severe neurological burden in this cohort.

Treatment

The data are summarized in Table 2. All patients were receiving enzyme replacement therapy (ERT) with Cerezyme at the time of assessment. The median age at start of therapy was 4.6 years (mean 11.67 years, SD 13.63). The median age at assessment was 13.9 years (range 2.3–54.8). The mean duration of treatment at the time of assessment was 7.85 years (SD 4.0). The

Table 2 Treatment data

	Sweden	Poland	Germany	UK	Total
Median age at start of ERT (years)	26.6	6.75	4.75	1.25	4.66
Duration on ERT (years)	11.1 (SD 3.98)	6.37 (SD 3.07)	5.99 (SD 3.91)	8.55 (SD 3.79)	7.85 (SD 4.0)
Starting dose of ERT (IU/kg per 2 weeks)	59.7	39	89	69.5	61.4 (SD 34.24)
Dose of ERT at time of assessment (IU/kg per 2 weeks)	70.0 (SD 50.86)	48.1 (SD 31.74)	95.4 (SD 43.86)	146.1 (SD 109.95)	86.4 (SD 73.14)
Chitotriosidase at diagnosis (nmol/h per ml)	Converted from nKat/L[a]				(*n*=15) 17042.2 (SD 16 518.6)
Chitotriosidase at start of treatment (nmol/h per m)	(*n*=9) 28 601 (SD 19 059)	(*n*=11) 15 812 (SD 6430)	(*n*=9) 23 266 (SD 21 158)	(*n*=7) 12 237 (SD 2867)	(*n*=36) 19 119 (SD 15 277)
Chitotriosidase at assessment (nmol/h per ml)	3492 (SD 5168)	3795 (SD 4305)	2621 (SD 4927)	1014 (SD 877)	2803 (SD 4174)
% reduction in chitotriosidase	87.8	76.0	88.8	91.8	85.4

[a] See Appendix 1 for conversion used.

mean starting dose of ERT was 61.4 IU/kg per 2 weeks (SD 34.24). The mean dose of ERT at time of assessment was 84.3 IU/kg per 2 weeks (SD 70.82).

Comments

- The age at start of treatment was not the same for all countries.
- The youngest patients (UK and Germany) were on the highest doses at assessment.
- The oldest patients were on the lowest doses at assessment.
- Only in one country (UK) were all patients on 100–120 IU/kg per 2 weeks or greater at assessment.

Treatment outcomes

Eye movements

Only two of the patients assessed were historically thought to have had normal saccades. One was L444P/L444P but presenting with a normal to high IQ and had no neurological manifestations apart from mild kyphosis. The assessor, however, felt that the patient definitely had a horizontal gaze palsy. The other was L444P/1138A and was phenotypically indistinguishable from type I, and was therefore excluded from further analysis.

Between November 2005 and February 2006, 45 patients were assessed by a single assessor, and for the purposes of this study horizontal gaze palsy was divided into two groups, either 'horizontal saccades absent, vertical saccades present' or 'horizontal and vertical saccades absent'. Nine patients were assessed to have both horizontal and vertical saccades absent with the remaining 34 having only absent horizontal saccades. Clinical severity was independent of age at assessment, age at start of ERT, genotype or splenectomy status. The subjective nature of eye movement assessment, relying as it did entirely on clinical observation, rendered this parameter unreliable and its relationship to ERT was therefore not assessed.

Seizures (Table 3)

Nine patients (16.3%) assessed suffered from epilepsy. Four were L444P/L444P and one each F213I/L444P, L444P/G202R and D409H/G202R. Three developed myoclonic epilepsy, either in isolation or in association with generalized tonic-clonic seizures.

The effect of the following factors on seizures was studied: age at start of ERT and at assessment, duration and mean dose of ERT, genotype, and total splenectomy.

Comments

- Patients developing seizures were older at start of treatment by nearly 6 years, and at assessment by nearly 11 years
- The dose of ERT appeared to have no effect.
- Splenectomy appeared to be the only significant predisposing factor.

Neuropsychometric assessments

The Full Scale Intelligence Quotient (FSIQ) has been utilized as the main outcome measure in other published studies(Altarescu et al 2001). Fifteen Polish and British patients had their FSIQ assessed on two or more occasions. The tests used varied depending on the age of the patient, but included the Wechsler Intelligence Scale for Children (WISC-III) and Wechsler Adult Intelligence Scale – III (WAIS-III) or its predecessors. Separate verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) scores were not available for all patients. Fourteen out of the 15 were L444P/L444P, one was R433S/R433S. Three had had a total splenectomy. The time interval between first and last recorded FSIQ ranged from 1 to

Table 3 Seizure data

	Age at assessment (years)	Age at start of ERT (years)	ERT (IU/kg per 2 weeks)	Years on ERT	Genotype	Splenectomy
Patients with epilepsy (*n*=9)	Median 23.5 Mean 26.3 (SD 16.3)	Median 11.7 Mean 17.1 (SD 15.6)	94.5 (SD 52.4)	Median 11.7 Mean 9.27 (SD 5.3)	(6=66.7%) L444P/L444P	*n*=4 (44.4%)
Patients without epilepsy (*n*=46)	Median 12.5 Mean 18.1 (SD 13.4)	Median 4.5 Mean 10.6 (SD 13.1)	82.4 (SD 81.4)	Median 7.7 Mean 7.5 (SD 3.7)	(35=76.0%) L444P/L444P	*n*=9 (19.5%)

7 years (mean 3.78). The mean age at first assessment was 8.28 years (SD 6.64), and at the second assessment was 12.92 years (SD 7.47). The mean ERT dose for this group was 77.4 IU/kg every two weeks (SD 61.5), which is slightly lower than the group as a whole. A total of eight patients were receiving ERT at a dose of less than 60 IU/kg/every two weeks with four patients receiving close or above to the recommended dose of 120 IU/kg every two weeks. Six patients were receiving 120 IU/kg per 2 weeks or higher at the time of assessment for 5 years or more. The mean FSIQ for this sub group of six patients was 98.4 (SD 5.6), which dropped to 77.6 (SD 15.4) at the repeated assessment. One patient, however, demonstrated a significant drop from 93 to 51, which skews the data.

A difficulty in analysis is that the average age of patients receiving a higher dose of >62.25 IU/kg per 2 weeks is considerably younger (4.88 years (SD 1.63) at first assessment; 8.52 years (SD 1.33) at second assessment) than the age of those receiving the lower dose of <62.25 IU/kg per 2 weeks (12.17 years (SD±8.18) at first assessment; 17.32 years (SD 8.58) at second assessment). This suggests that the youngest patients, i.e. those most recently diagnosed, have been prescribed ERT in accordance with the guidelines where possible. However, it leaves us without a homogenous cohort to analyse.

A further problem was the small number in this group. We therefore attempted to include the Swedish patients. Nine Swedish patients had been assessed cognitively on two or more occasions. Eight of these patients have been reported previously (Erikson et al 2006). The FSIQ of these patients had been calculated using standard tests. However, these had then been converted to a stanine score (Bendig 1957). The original scores were not readily available, and hence these patients could not be included in the initial analysis. Therefore, the FSIQ scores of the British and Polish patients were transferred to stanine scores of 1–6, using the conversion table shown in Appendix 2.

Table 4 Change in FSIQ. Multiple regression result of mean dose of ERT, age at start of ERT, spleen status, chitrotriosidase and effect on change in FSIQ (n=16)

	Regression coefficient (95% CI)	p-value
Baseline FSIQ	−3.22190	0.3824
Mean dose of ERT	−1.77435	0.3724
Age at start of ERT	6.33916	0.2629
Splenectomy	1.65286	0.8779
Chitotriosidase at assessment	−4.47659	0.3507

Table 5 Change in bracketed FSIQ/stanine score. Multiple regression result of mean dose of ERT, age at start of ERT, spleen status, chitrotriosidase and effect on change in bracketed FSIQ/stanine score (n=24)

	Regression coefficient (95% CI)	p-value
Baseline FSIQ/stanine	−1.77435	0.2590
Mean dose of ERT	6.33916	0.4288
Age at start of ERT	1.10895	0.2173
Splenectomy	1.65286	0.7874
Chitotriosidase at assessment	−4.47659	0.3918

While this reduced the sensitivity of the score to change, it allowed a larger sample size to be compared. The mean scores demonstrate a 0.48 drop; however, the overall scores remains in the Low Average bracket. The exact dates when Swedish assessments were performed were not available at the time, and therefore the mean age could not be calculated for first and latest assessment separately. The mean ERT dose in the older patients (age >14 years) was lower than in the younger patients (45 vs 85.2 IU/kg per 2 weeks). Younger patients may have included those with potentially more severe disease. While the older patients tended to receive lower doses, they were more likely to have milder disease.

A multiple regression analysis model was performed to include average ERT dose, age at start of ERT, chitotriosidase, and splenectomy status. Genotype was not included as a variable, as all but two patients were L444P homozygotes. This allowed all the data to be analysed without losing the sensitivity to change that can occur when data are grouped.

Based on 16 patients, none of the variables above are significantly related to the change in FSIQ over time (Table 4). The same is true based on 24 of 25 patients (one chitotriosidase value missing) when results are bracketed into FSIQ/stanine scores, with none of the variables significantly related to the change over time (Table 5).

The large age range of this cohort and small sample size dictate that the results should be interpreted with caution.

Age at start of therapy and total splenectomy

Total splenectomy has been reported to have an adverse effect on neurological outcome (Erikson 1986; Erikson et al 1987). Patients commencing ERT at a later age demonstrated an increase in their bracketed FSIQ/stanine scores. The same applied to

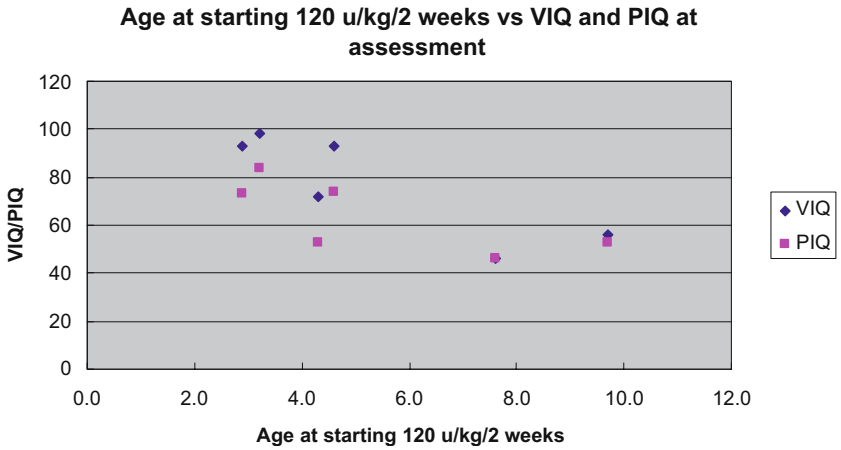

Fig. 1 Age at start of ERT dose of 120 IU/kg per 2 weeks vs VIQ and PIQ at assessment (n=6)

those who had had a total splenectomy. As six out of the seven who had a complete splenectomy were also older than 14 years when they started ERT, this is consistent across both analyses. A possible explanation for this is that ERT improved the general visceral health of patients allowing them to perform better during psychological assessments.

Effect on FSIQ of high-dose ERT (120 IU/kg per 2 weeks)

One of the most important recommendations in the original paper was that the ERT dose in all patients with type III GD should be 120 IU/kg per 2 weeks. It was therefore important to see whether this had made a difference. In order to ensure homogeneity it was felt that only data on L444P homozygote patients should be analysed. There were six such patients (all UK) who had had 100–120 IU/kg per 2 weeks for 5 years or more at assessment and who had had two or more FSIQ assessments. For each patient, the age at commencing ERT at 120 IU/kg per 2 weeks and IQ at assessment were plotted against each other. Separate plots were obtained for VIQ and PIQ as there was significant discrepancy between the two. The results are shown in Figure 1. It would appear that the younger the age, the better the outcome. However, it should be emphasized that the three youngest patients were all under the age of 10 years at the time of assessment, and therefore the period of follow-up was probably too short to allow comment.

Visceral disease

One biomarker of visceral disease was also evaluated. As all centers measured chitotriosidase activity, this was therefore chosen. It was measured as nmol/h per ml in Poland, Germany and the United Kingdom. In Sweden measurement was calculated in ncat/L and converted to nmol/h per ml using the formula in Appendix 1. Chitotriosidase levels at diagnosis were only available for 15 patients. The mean level for 36 patients at the start of ERT was 19119 nmol/h per ml (SD 15277). This demonstrated an overall reduction of 85.4% by the time of assessment to a mean of 2803 nmol/h per ml (SD 4174).

The details for each country are as shown in Table 2. Swedish patients, who were on the lowest dose, showed the smallest fall, while the UK patients, who were on the highest dose, showed the greatest fall. In the UK group, the level at assessment also had the lowest standard deviation.

Multiple regression was used to explore these data further including ERT dose at start of therapy, ERT at assessment and years on ERT Predicting the level of (log)chitotriosidase, years on ERT comes close to significance (p=0.07), while the start dose of ERT is less so (p=0.11). Current ERT dose is far from achieving significance (Table 6).

Both splenectomy (p=0.03) and genotype (marginally, p=0.09) are significant when included with years on ERT (p=0.004). Spleen is coded 0 for N (n=34),

Table 6 Predicting the level of (log)chitotriosidase. Multiple regression result of years on ERT, ERT dose at start, ERT dose at assessment and effect on chitotriosidase (n=52[a])

	Regression coefficient (95% CI)	p-value
Years on ERT	−0.072403	0.0656
ERT dose at start	−7.75788	0.1118
ERT dose at assessment	7.28058	0.7519

[a] Some missing data.

Table 7 Predicting the level of (log)chitotriosidase. Multiple regression result of years on ERT, spleen status and genotype (n=54)

	Regression coefficient (95% CI)	p-value
Years on ERT	−0.123365	0.0039
Spleen status	0.375299	0.0347
L444P/L444P	0.621826	0.0895

1 for P (n=5) and 2 for Y (n=16). L444P is coded 1 for L444P/L444P (n=41) and 0 otherwise (n=14). The interpretation is that chitotriosidase falls by 15% per year on ERT, while splenectomy and homozygous L444P cases have appreciably higher values (Table 7).

Discussion

The primary objective of the study—to investigate the effect of high-dose ERT on neurological outcome—could not be achieved, at least from the data available.. A number of factors may have contributed to this.

1. There was considerable skewing of data across the four cohorts. Importantly, the majority of older patients received lower doses, and the majority of younger patients received higher doses. Therefore, dose comparison within age groups was not possible.
2. There was no follow-up information on the data obtained using the Rostock Neuro Score in the first study, for the reasons mentioned in the Introduction.
3. The only data that we have reported are the IQ scores, as they were the only longitudinal data available. However, these may not be representative of the disease as a whole. Furthermore, many of the early assessments had been performed using appropriate age-related tests. Such data cannot be compared with more recent data using other tests. They therefore could not be used in the analysis. Important data on ataxia and pyramidal involvement were collected and analysed. However, they were cross-sectional and therefore did not provide the information required for analysis. i.e. change over time, although future systematic analysis may be feasible.
4. Despite the Task Force recommendations, only a small number of patients had been treated with high-dose ERT, mostly for financial reasons, and with the period of follow-up it was not possible to draw any conclusions from the data available.
5. There was no statistical significance in any of the analyses.

Despite these shortcomings, it was possible to make some observations.

Older patients

In this group, the FSIQ data had to be converted to Stanine scores for the reasons discussed above. In doing so, some sensitivity may have been lost. However, the data suggest that, while the scores tended to show a downward trend, they remained within the low average bracket. Since none of them was on high doses at the time of assessment, we can say that they did not appear to require high doses of ERT, at least not from a neurological point of view.

Younger patients

In this group, there was no evidence that high-dose ERT had a favourable effect. However, the follow-up period in the key cohort was too short to allow us to be categorical about this. A longer period of follow-up, using the newly available Severity Scoring Tool, may help to clarify this contentious issue.

Visceral disease

Control of visceral disease, as reflected by the chitotriosidase activity, was perhaps not as good in the older patients, but it may be that this is not necessary to achieve such control in this group. Visceral disease was well controlled in the younger group. The only factors that significantly affected it were the length of time on treatment and the splenectomy status. There was no effect of ERT dose, either at commencement or at assessment.

Recent reports in animal models of other lysosomal storage disorders indicate that intravenously administered enzyme results in clearance of stored material in the CNS (Dunder et al 2000; Matzner et al 2005; Roces et al 2004). While this may not apply to Gaucher disease, it is important to keep an open mind on the subject, although assessment of the effects of ERT may be confounded in future by the arrival of new therapies.

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Appendix 1 Conversion of chitotriosidase activity

Chitotriosidase activity in Sweden is measured in nKat/L, where nKat stands for nanokatal, while other countries measure it in nmol/h per ml.
The conversion is:

1 nmol/h per ml = 3.6 nKat/L

Appendix 2 Relationship of stanine bracket score intervals to FSIQ bracket definitions

Stanine score intervals	FSIQ bracket definitions
1 = IQ < 70	<70 = Exceptionally Low/Learning Difficulties range
2 = IQ interval 70–81	70–80 = Low/Borderline Learning Difficulties
3 = IQ interval 82–88	80–90 = Low Average
4 = IQ interval 89–96	90–110 = Average
5 = IQ interval 97–103	110–120 = High Average
6 = IQ interval > 103	120+ = High/Superior

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