Delayed Growth and Puberty in Patients with Gaucher Disease Type 1: Natural History and Effect of Splenectomy and/or Enzyme Replacement Therapy

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For Editorial see page 80

Abstract

Background: Growth retardation in childhood was only recently recognized as a prominent feature of Gaucher disease type 1, but there are few data on both the pubertal development and the final outcome of growth and sexual maturation.

Objective: To investigate the natural pattern of growth and puberty in patients with Gaucher disease type 1 and the effect of splenectomy and enzyme replacement therapy.

Methods: We retrospectively analyzed growth and puberty in 57 patients with Gaucher disease type 1; 52 were followed since childhood and/or prepuberty and 42 have reached sexual maturity and final height. In the analysis we considered severity of disease, time of splenectomy, and start of enzyme replacement therapy.

Results: Deceleration of growth at age 3–5 years was observed in 30 of 57 patients followed since early childhood while untreated: height-SDS decreased from –0.34±0.42 at age 0–3 years to –1.93±0.95 ($P<0.01$) at age 7–10 years and was more pronounced with severe disease. A high prevalence (59.6%) of delayed puberty, which was more frequent with severe disease, was observed in 47 patients followed before and throughout puberty. No primary endocrine pathology was found. All patients, untreated as well as treated, with growth and pubertal delay had a spontaneous catch-up, achieved full sexual maturation, and most (83.3%) reached a final height within the range of parental height–standard deviation score. Splenectomy (partial and/or total) performed in 20 patients while still growing had a beneficial effect on growth, which was temporary in some and did not affect puberty. ERT improved growth in 11 patients who started therapy before puberty, as evidenced by a progressive increase in the height-SDS, and seemed to normalize the onset of puberty.

Conclusions: Growth retardation in childhood and delay of puberty are characteristic of Gaucher disease type 1 and are more frequent with severe disease. There is a spontaneous catch-up later in life and most patients reach a final height within their genetic growth potential. Enzyme replacement therapy apparently normalizes growth and possibly also the onset of puberty.

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Gaucher disease is a well-defined metabolic disease and probably the most common lipid storage disorder [1]. Nevertheless, despite the long-recognized suppressive effect of chronic systemic disease on growth [2,3] and puberty [4,5], Gaucher disease type 1 has not been included in those described. As early as 1965, Matoth and Fried [6] mentioned stunted growth in 34 children with Gaucher disease type 1 but they did not consider it to be a striking feature of the disease. It was only recently that the high prevalence of growth retardation among children with Gaucher disease type 1 was reported [7–11], and the data are sparse regarding pubertal development [8,11] and the final outcome of growth and puberty in affected individuals.

The aim of the present study was to investigate the natural history and outcome of growth and sexual maturation in 57 patients with Gaucher disease type 1, most of whom were followed continuously since childhood. The study also evaluated the effects of splenectomy and enzyme replacement therapy.

Subjects and Methods

Subjects

The study population included 57 patients (26 males) with Gaucher disease type 1 who were treated and/or followed

ERT = enzyme replacement therapy

SDS = standard deviation score

at the Department of Oncology/Hematology at our hospital from 1964 to 1999. Twenty-five had also been evaluated at our Institute of Endocrinology and Diabetes. All patients were Ashkenazi Jews except for one whose mother was Sephardic. According to the pubertal stage [12] at the time of this study, 10 (7 males) were prepubertal (age 3.8–11.5 years), 2 (males) were in mid-puberty (ages 15.1 and 15.7 years), and 45 (17 males) were postpubertal (age 19.3–40 years). Of these 45 patients 42 (16 males) had reached final height, including 2 (males) who were followed since childhood, had complete growth charts, and had died as mature adults (at age 30.4 and 33 years). The mean age at diagnosis and/or start of follow-up was 5.1±2.2 years (range 0.5–15). All but five patients were first seen before age 8.5 years and about half (30 of 57) before age 5 years. Of the 57 patients, 26 belonged to 10 families with 2–4 children with Gaucher disease type 1, and in 15 of them the diagnosis was reached (at age 0.7–11) by screening the families after one child had been diagnosed. They were asymptomatic at the time of diagnosis.

Severity of disease

Similar to other investigators [11], we found that the severity score index for Gaucher disease, as suggested by Zimran et al. [1], is inappropriate for children. Therefore, we used a retrospective 4-point scale to define the severity of the disease as follows: bone involvement = 1 point, splenectomy = 1 point, and ERT = 1 point (total score 0–3 points). A score of 0–1 was defined as mild disease (25 of 57 patients) and a score of 2–3 as severe disease (32 patients). This severity score easily distinguishes mildly from severely affected patients with Gaucher disease type 1. Indications for splenectomy and the use of ERT are often debatable — not every splenectomy performed in the past would be endorsed as appropriate at present, and there are patients not approved for ERT in one medical center who transferred themselves to another in order to receive therapy. However, we believe that all would agree that a patient is severely affected when bone involvement, splenectomy, and ERT (or at least two of them) are present. Moreover, it is accepted that Gaucher disease type 1 is severe when it appears with symptomatic disease in childhood. Our present severity score also overcomes the factor of age at diagnosis, since asymptomatic children can be diagnosed following the diagnosis of a sibling. This was the case with 15 of our patients.

Genetics

The genotype was known for 55 patients (the two deceased patients included in the study had died before genotype determinations became available). All except one carried the mutation N370S. Thirteen patients (6 males) were homozygous for this mutation (2 with severe disease), and the remaining 42 had compound heterozygosity: N370S/84GG in 28 patients (23 with severe disease), N370S/L444P in 5 patients, N370S/V394L and N370S/IVS2+1 in 3 patients each, N370S/R285C and N370S/Ex8INS in 1 patient each, and 1 patient carried the genotype 1604A/84GG.

Splenectomy

Splenectomy due to progressing pancytopenia was performed in 26 patients (9 males), of whom 12 had total splenectomy (at age 7–20 years). Fourteen had partial splenectomy (at age 6.3–17.3 years) according to our policy since 1983 [13], and 4 of them underwent total splenectomy (after 3–8 years) because of recurrent massive splenomegaly with pancytopenia. Data on growth before and after splenectomy were available only on 20 patients (7 males) who were operated on while still growing, i.e., before and during puberty.

Enzyme replacement therapy

At the time of the study, 36 patients (15 males) were receiving ERT (age at start 3.9–38 years) as approved by the Gaucher Committee at the Israel Ministry of Health. Of these, only 15 (11 prepubertal) had started therapy while they were still growing. The patients were treated with glucocerebrosidase, initially with alglucerase (Ceredase®, Genzyme Corporation, Cambridge, MA, USA) and since 1998 with imiglucerase (Cerezyme®, Genzyme), with a lower dose high frequency regimen of 2.3 U/kg three times weekly, i.e., 30 U/kg/month. The dose was modified according to the response of bone crisis, i.e., in children whose bone disease had worsened the dose was increased to 30 U/kg every 2 weeks [14].

Growth and puberty

In addition to the follow-up evaluation specific for Gaucher disease (clinical and auxiliary), height and weight were measured and pubertal stage was defined according to Tanner [12]. To enable a comparison between the heights of both sexes and at different ages, height was expressed as a standard deviation score, thus the height-SDS was calculated for each patient according to Tanner et al. *$SDS = x\text{-}x^1/Sx$, while x = height measurement, x^1 = mean height for age and sex, Sx = SD for age and sex.* Bone age was estimated by X-ray of the wrist and hand according to Greulich and Pyle [16].

Individual retrospective evaluation of growth and puberty was done for each patient. Changes in the Ht-SDS were determined within age subgroups from infancy through childhood for untreated patients and after each year of treatment for patients receiving ERT. Changes in the Ht-SDS and in linear growth after splenectomy (partial and/or total) were determined in patients operated on while still growing, i.e., before and during puberty. The heights of both parents of all patients except one (deceased) were available, and in patients who had completed their growth the achieved final height was compared to the parental Ht-SDS range and to the target height, i.e., the corrected mid-parental height according to Tanner et

Ht-SDS = height SDS

al. [17]. *THt for boys = (father's height + mother's height+13)/2; THt for girls = (mother's height+father's height-13)/2.* THt is used in an attempt to assess the genetic growth potential of a child [17].

Endocrine investigations

These were performed in 25 patients and comprised: basal blood values of free thyroxine, thyroid-stimulating hormone, prolactin, sex hormones (testosterone and 17-beta-estradiol) and insulin-like growth factor I. Basal and stimulated plasma levels of growth hormone and gonadotropins (luteinizing and follicle-stimulating hormones) were assessed by standard dynamic tests: for GH, the insulin-induced hypoglycemia or the clonidine stimulation test or the GH-releasing hormone stimulation test; and for LH and FSH, the standard GnRH stimulation test. The specific tests performed were determined individually according to clinical evaluation and follow-up. All hormonal examinations were performed using standard radioimmunoassays, and IGF-1 testing was performed by a radioimmunoassay developed in our laboratory with established norms for age and pubertal stage [18].

Statistical analysis

The Student *t* test, repeated measure analysis of variance (ANOVA) and the Chi-square (χ^2) test were used as appropriate.

Results

Growth

Of the 57 patients who were followed since infancy or early childhood while untreated, linear growth data were available for 30; of these, 20 (10 males) had severe disease (score 2–3) and 10 (4 males) mild disease (score 0–1). In these patients a gradual deceleration of growth was observed at age 3–5 years [Table 1A] and the Ht-SDS decreased significantly in later childhood, from –0.34±0.42 at age 0–3 years to –1.93±0.95 at age 7–10 years ($P<0.01$, ANOVA repeated measures). The growth rate decreased more markedly toward adolescence (to –1.98±0.6 at age 10–13 years, measured in 24 patients) and was accompanied by a decrease in bone maturation rate leading to a bone age retardation of 2–4 years [Figure 1].

Puberty [Table 2A]

At the time of study, 47 of the 57 patients (19 males) had entered puberty or were past puberty, but had been followed since prepuberty. Among these patients there was a high prevalence (n=28, 59.6%) of delayed puberty, i.e., no signs of puberty in males at age 14 and in females at age 13 [4,5]. The rate of delayed puberty was similar for

Table 1. Height-SDS of prepubertal patients with Gaucher disease type I on longitudinal follow-up: 30 untreated vs. 11 patients receiving ERT

A. Ht-SDS of untreated patients (n=30*)

Age range (yr)	No. of patients	Ht-SDS M±SD**
0–3	9	–0.34±0.42
3–5	18	–1.23±1.12
5–7	22	–1.71±0.82
7–10	25	–1.93±0.95

B. Ht-SDS of patients receiving ERT (n=11***)

Duration of ERT	N	Ht-SDS M±SD
At start	11 (ages 3.9-14.5)	–1.42±1.02
1 yr	11	–1.17±1.09
2 yr	10	–1.02±1.14
3 yr	8	–1.00±0.80
4 yr	8	–0.85±0.91
5 yr	7	–0.74±0.93
6 yr	3	–0.14±0.78
7 yr	2	–0.18±0.68

* Patients followed longitudinally since infancy or early childhood, untreated (30/57)

** Decrease of Ht-SDS is significant: $P<0.01$, ANOVA repeated measures

*** Patients who started therapy before puberty (11/57) followed longitudinally

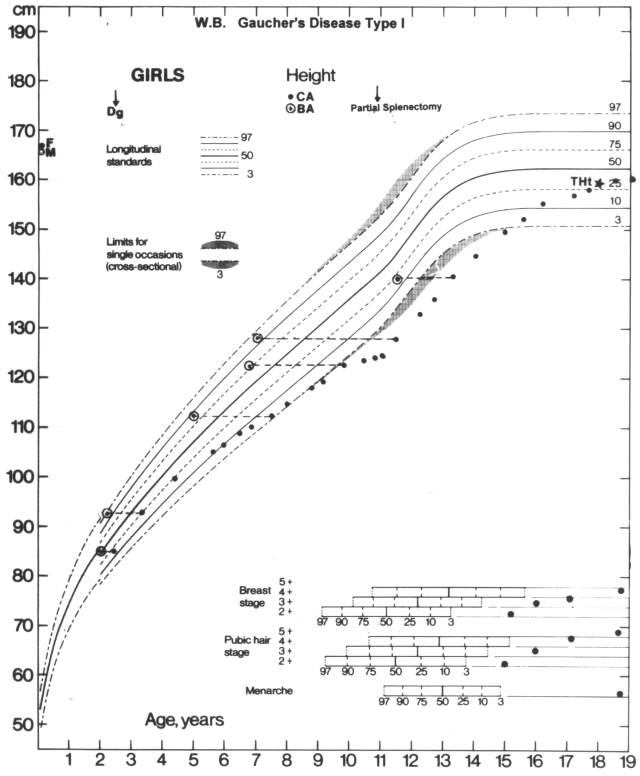

Figure 1. Representative growth chart of a patient with severe Gaucher disease type I (score 2) followed since diagnosis at age 2.5 years until adulthood. Growth rate decreased in childhood and improved after partial splenectomy. Puberty was delayed with menarche at age 18.8 years. Catch-up growth was complete and final height reached target height. ERT was begun only at age 23 years. CA = chronological age, BA = bone age, M = mother's height, F = father's height.

THt = target height
GH = growth hormone
LH = luteinizing hormone
FSH = follicle-stimulating hormone
GnRH = gonadotropin releasing hormone
IGF-1 = insulin-like growth factor-1

Table 2. Prevalence of delayed puberty and achieved final height vs. target height among patients with Gaucher disease type 1: correlation with severity of disease

	All patients	Patients with mild disease	Patients with severe disease
	n	n	n
A. Prevalence of delayed puberty +			
Pubertal patients *			
Total	47	18	29
Male	19	5	14
Female	28	13	15
Delayed puberty			
Total	28 (59.6%)	6 (33.3%)	22 (75.9%)
Male	12 (63.1%)	1 (20%)	11 (78.6%)
Female	16 (57.1%)	5 (38.4%)	11 (73.3%)
B. FHt vs. THt (M±SD) ++			
Total **	42	17	25
Within parental Ht-SDS range, n (%)	35 (83.3%)	15 (88.2%)	20 (80%)
Male	6	4	12
FHt, M±SD (cm)	172.8±6.3	176.1±7.7	172.0±5.6
THt, M±SD (cm)	174.8±4.6	174.2 ±4.4	175.1±4.5
Female	26	13	13
FHt, M±SD (cm)	160.5±6.5	159.3±7.6	161.2±4.7
THt, M±SD (cm)	161.2±6.1	159.4±7.0	163.2±4.3

+ Prevalence of delayed puberty is significant: $\chi^2 = 8.4$, $P<0.003$
* Patients followed before and throughout puberty (47/57)
++ FHt vs.THt not significant in all groups
** Patients who had reached FHt (42/57)

males (12 of 19, 63.1%, with first pubertal signs at age 14.5–17.5) and females (16 of 28, 57.1%, with first pubertal signs at age 13.5–17) and was significantly higher for patients with severe disease ($\chi^2=8.4$, $P<0.003$). Delayed puberty aggravated further growth and bone maturation delay (bone age retardation 3–5 years), and caused significant psychosocial distress to the patients and their families. However, when puberty ensued, all affected patients showed a marked spontaneous catch-up growth [Figure 1] and eventually all reached full sexual maturation. Moreover, fertility appears to be normal, and to date, 8 of our patients (7 females, 1 male) have become parents to 10 normal children.

Relationship of genotype to growth and puberty

The majority of patients with growth retardation in childhood (19 of 30) and/or delayed puberty (16 of 28) had the genotype N370S/84GG. This was the most frequent genotype among our patients, most of whom had severe disease (23 of 28 with score 2–3), as mentioned earlier and previously reported [13]. Six patients with growth delay in childhood (four of them with a pubertal delay) had the genotype N370S/N370S, i.e., the second largest genotype group among our patients and mostly with mild disease (11 of 13 with score 0–1).

Effect of splenectomy on growth and puberty

Of 20 patients who underwent splenectomy while still growing, 14 were prepubertal and 6 were in puberty; 7 had undergone total splenectomy (at age 5.5–17.7) and 13 partial splenectomy (at age 6.3–5.8). Of the 13, 3 developed massive recurrent splenomegaly with pancytopenia and also underwent total splenectomy 3–8 years later (2 were already in puberty at re-operation).

Of the 14 patients operated before puberty, 12 showed a beneficial effect of splenectomy on growth (7 after partial splenectomy and 5 after total splenectomy) by gradually normalizing linear growth within 1–2 years after surgery [Figure 1]. The growth rate improved in parallel to the improvement in the patients' clinical condition and hematological parameters after both partial and total splenectomy. In 5 of the 14 (all after total splenectomy), growth improved only temporarily after surgery and slowed down again when their clinical condition worsened. In 2 of the 14 prepubertal patients (both after partial splenectomy) no benefit on growth was observed.

In the six patients who underwent surgery during puberty, the benefit of splenectomy on growth could not be determined because the increase in growth velocity coincided with their pubertal growth spurt. The effect of splenectomy on growth was also difficult to evaluate in one of the pubertal patients and in four prepubertal patients since ERT was begun 3–16 months after surgery. In the remaining 15 growing splenectomized patients (10 prepubertal and 5 in puberty), ERT was instituted only 8.5–19.5 years after the operation, i.e., as adults.

We did not observe any effect of splenectomy (partial or total) on the time of onset of puberty. Puberty was delayed in 12 of 14 patients who underwent splenectomy before puberty, and only 2 of 14 had normal puberty.

Effect of ERT on growth and puberty

Of 15 (6 males) of the 36 patients who started ERT while still growing, 11 were prepubertal and 4 were in advanced puberty. On longitudinal follow-up a clear and steady beneficial effect of ERT on growth was observed in the 11 prepubertal patients, and the growth velocity gradually increased, thereby improving their Ht-SDS [Table 1B, Figure 2]. However, to date, the number of our patients treated for longer periods is too small for this to reach statistical significance.

In the four patients who started ERT during puberty, the effect of therapy on growth could not be evaluated because its initiation coincided with their pubertal growth spurt.

In the four prepubertal patients who had undergone splenectomy relatively close to the time of ERT initiation (3–16 months) there was some uncertainty in the interpretation of their improved growth during the first 2 years of the therapy. However, the steady and progressive increase in growth velocity and in the Ht-SDS during the following years indicated that these patients had clearly benefited from ERT and they had normalized their growth similarly to the other prepubertal treated patients.

Puberty appeared during ERT in 7 of the 11 treated prepubertal patients. It is noteworthy that puberty ap-

peared within the physiological age range in four of the seven [Figure 2], and was delayed in three. Two of these three patients (females) started ERT at later ages (13.2 and 14.5 years) and already had a pubertal delay. All patients on ERT reported an improved quality of life, and all had a definite though variable gain in weight.

Final height [Table 2B]

Forty-two patients (25 with severe disease) had reached their FHt at the time of writing and 34 (18 with severe disease) had completed their growth without ERT. All 42 patients, with mild or severe disease, achieved a mean FHt not significantly different from their mean THt. On individual analysis the majority of patients reached their parental Ht-SDS range (35 of 42, 83.3%). Only seven (16.7%) ended growth below the parental Ht-SDS range, of whom five had severe disease (score 2–3). The four adult patients who received ERT since prepuberty did not appear to have any advantage in the FHt achievement compared to those who reached FHt without it.

Endocrine evaluation

Twenty-five patients (13 males) underwent endocrine evaluation because of marked delay in growth and puberty. Blood values for free thyroxine and TSH were within normal limits in all patients, as was basal plasma prolactin examined in 15 patients. In seven patients, dynamic endocrine tests were performed to assess GH and gonadotropin secretions. All showed normal stimulated levels for GH, whereas IGF-I levels (examined in five of the seven) were in the lower range for age and pubertal stage [18]. In all seven, basal and stimulated plasma levels of LH and FSH, performed at Tanner stages 1 and 2, corresponded to pubertal stage according to the norms in our laboratory, while the basal plasma levels of sex hormones were in the prepubertal range.

Discussion

Our data confirm the observation reported by other investigators [7–11] that growth delay during childhood is a prominent clinical feature of Gaucher disease type 1. This study also documents for the first time the high prevalence of pubertal delay associated with this disease, and provides data on the final outcome of growth and sexual maturation in patients with Gaucher disease type 1. We found no evidence of any primary endocrine pathology among our patients.

Analysis of the growth data in 30 patients followed from infancy through childhood, while untreated, showed that the decline in linear growth, as expressed by the Ht-SDS, begins in early childhood and becomes more prominent in later childhood [Table 1A]. We believe that this impairment in growth is related to the disease itself and seems to be more pronounced in its more severe forms. Nevertheless, despite the retarded growth in childhood, the FHt of the patients was not compromised. The majority of our 42 adult patients (35, 83.3%) reached their parental Ht-SDS range.

Delayed puberty was observed in 59.6% of our patients [Table 2A]. It increased the growth delay and aggravated the height deficit at the time of adolescence, showed no gender predominance, and was more prevalent among patients with severe disease compared to those with mild disease (75.9 vs. 33.3%). Eventually, though later in life, all affected patients achieved full sexual maturity and had no apparent fertility problems. However, the delay in growth and physical maturity at the age of adolescence, in comparison with their peers, was a source of significant anxiety and distress to them and their families.

The mechanism whereby growth and puberty are delayed in Gaucher disease type 1 is not clear, but it can be assumed that the underlying metabolic disorder is the main factor, as in other chronic metabolic diseases [2–5]. Studies have shown that the average resting energy expenditure of patients with Gaucher disease type 1 is increased for age, gender, height and weight, presumably due to the increased metabolic burden from accumulated undegraded glucosylceramide in large masses of Gaucher's cells [8,19,20]. This hypermetabolic state was shown to improve with ERT [21]. Thus, the increased

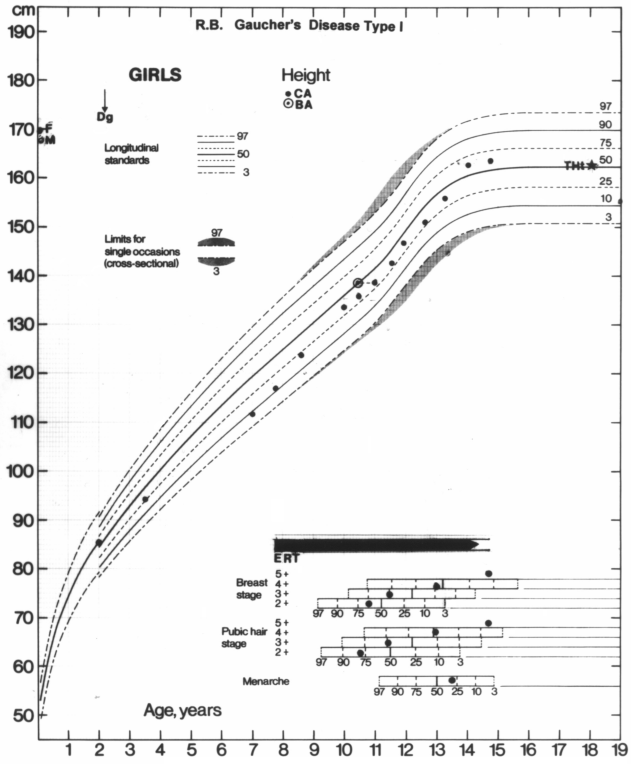

Figure 2. Representative growth curve of a patient with severe Gaucher disease type 1 (score 2) followed since diagnosis at age 2 years. Growth rate decreased in childhood and a steady catch-up growth appeared after ERT was begun at age 7.7 years. Puberty was normal with menarche at age 13.5 years. Final height reached target height.

FHt = final height
TSH = thyroid-stimulating hormone

caloric requirement of the patients may be responsible for a state of relative malnutrition — a well-recognized causative factor of growth and pubertal retardation [2–5]. The association of low levels of IGF-I with normal secretion of GH has indeed been reported in children with malnutrition of various etiologies [3,22], as we found in the five patients in whom IGF-1 was examined.

The beneficial effect of splenectomy on growth, total as well as partial, seems to be related to the clinical and hematological improvement following this operation. Splenectomy is a palliative therapeutic measure in Gaucher disease type 1; it improves the clinical condition of the patients but does not change the basic metabolic abnormality of the disease. The beneficial effect on growth was temporary in some of our patients and it had no recognizable effect on puberty. Since the introduction of ERT in Gaucher disease type 1, the indications for splenectomy have been largely reduced [23].

It is less than a decade since ERT became available for clinical use. Our data confirm that ERT normalizes growth during childhood, as already reported [7,9,10], and seem to indicate a possible normalization of the onset of puberty. This may be due to the restoration of a normal metabolic state by the enzyme replacement. We also observed that the benefit of ERT on growth is sustained and progressive — the longer the treatment period, the greater the improvement in the Ht-SDS [Table 1B].

In summary, our data present the natural history of delayed growth and puberty in patients with Gaucher disease type 1, with a spontaneous catch-up later in life and achievement of full sexual maturity as well as adult height within their individual genetic growth potential. This is true even for patients with severe disease, without ERT. Our data reinforce the findings of Zimran et al. [1] that Gaucher disease becomes less progressive as the patients grow older and has a tendency of stabilization in adulthood. However, for young patients with Gaucher disease type 1, normalization of growth and puberty is of great psychosocial value and ERT contributes considerably to improving quality of life. Further studies of patients treated since early childhood and followed throughout puberty until adulthood will clarify the ultimate benefit of ERT in patients with Gaucher disease type 1.

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