Children with Type I Gaucher Disease: Growing into Adulthood with and without Enzyme Therapy

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Thirty years ago DeDuve suggested that lysosomal storage disease may be treated by enzyme replacement [1]. Twenty years later, National Institutes of Health researchers together with the Genzyme Corporation made it a reality for patients with Gaucher disease [2]. Since the original end-points for the various clinical trials with both the placental derived alglucerase (Ceredase®, Genzyme Corporation, Cambridge, MA, USA) and the recombinant form imiglucerase (Cerezyme®, Genzyme) dealt with reduction of organomegaly and improvement in hematological and biochemical parameters [2–4], many manifestations of severe disease that were less common were not as completely investigated, an example of which is growth and development in children with Gaucher disease.

Therefore, the retrospective study by Kauli et al. in this issue of the Journal [5], describing the effect of splenectomy and enzyme replacement therapy on parameters of linear growth and sexual development in young patients with Gaucher disease, is noteworthy for two interrelated reasons. First, there is documentation of growth retardation that is apparently inimical to many children with Gaucher disease. The anticipated impact of splenectomy, which was often a medical imperative for severely affected patients in the era before the advent of enzyme replacement, was noted to be transient and partial at best. On the other hand, enzyme treatment resulted in attaining final height potential as well as inducing onset of puberty within expected time frames. The second, almost paradoxical finding is that there was a compensatory growth spurt irrespective of treatment modality in these children, thereby setting this population apart from other children with chronic diseases.

The above study confirms the findings reported by our group almost 7 years ago [6] regarding the effect of Gaucher disease on growth in 34 children with type I Gaucher disease. As in the findings of Kauli et al., growth retardation was shown to be a common feature of Gaucher disease and usually correlated with severity of other signs and symptoms of the disease. Addressing this issue, Meyer and researchers from our clinic reported their findings at the Pediatric Binational Hematology-Oncology Conference, held in Eilat, Israel last year. In their study, 43 children with Gaucher disease were further evaluated to ascertain both the degree of discrepancy from mid-parental height and whether growth retardation was correlated with hormonal growth markers. Levels of insulin growth factor and insulin growth factor binding protein 3 were within the normal ranges. Here too, children both untreated and those treated with enzyme replacement enjoyed compensatory growth, particularly at puberty.

Table 1. Comparison between children who presented with symptomatic Gaucher disease before and after the availability of enzyme replacement therapy

	Pre-ERT*	Post-ERT
No. of patients	67	13
M:F	27:40	6:7
Age at diagnosis	5.5 yr	2.6 yr
Splenectomy	22+5 partial	0
Avascular necrosis	15	0

* 55 of these patients (82%) are currently receiving ERT.
ERT = enzyme replacement therapy

Puberty may be delayed in some children with Gaucher disease, as seen in other populations with chronic diseases, but more importantly, in other children with poor dietary/nutritional histories. In the case of many young patients with Gaucher disease and massive organomegaly, early satiety and chronic fatigue preclude good eating habits. Nonetheless, it has been shown in a group of 53 women with Gaucher disease that despite delayed puberty (after age 14 years) in 35 of these patients (66%), there was normal onset of menarche and no evidence of subsequent infertility [7].

Taken together, one may perhaps extrapolate from these studies that despite a nearly universal finding of linear growth retardation in children with symptomatic Gaucher disease, it is in fact for many patients a self-correcting feature. Thus, a preliminary conclusion may be to reevaluate an earlier suggestion that growth retardation alone may be an indication for enzyme therapy [8]. In addition, since none of these young patients evinced hor-

monal or endocrine abnormalities, the implication may be that growth hormone stimulation tests such as arginine and clonidine diagnostic testing may be withheld unless specific problems, beyond simple linear growth retardation, are seen.

Enzyme replacement therapy has indeed been a milestone in the medical management of patients with Gaucher disease. Nowhere are the benefits more readily appreciated than in those who present with symptomatic disease at a very early age [Table 1]. One notes that the real advantage of enzyme therapy was in virtually eliminating the need for splenectomy, since enzyme replacement — whether as the placental derivative or the recombinant form — efficiently reduces hepatosplenomegaly and improves secondary hypersplenism and other hematological parameters [2,3]. Parenthetically, this was axiomatic in Israeli patients as well, who in almost all instances were started on the low dose regimen and achieved therapeutic responses comparable to those on dosage regimens two or four times as high [4,19]. Treated children, who have not undergone splenectomy and have received enzyme therapy prior to skeletal involvement, appear to remain free of the more devastating forms of bone disease, including episodes of periodic pain ("crises") and avascular necrosis of the large joints. Hence, a further extrapolation may be that enzyme replacement prevents overt skeletal damage when treatment predates bone involvement.

We would like to conclude with a comment on a further comparison: namely between the children in the study reported by Kauli and colleagues, and other young patients with Gaucher disease who are equally deserving of the benefits of enzyme replacement but are unable to receive this treatment. To date there are three Palestinian children under the age of 10, living a short car-ride from the Schneider Children's Medical Center of Israel, two of whom had been treated for a short time with enzyme therapy by virtue of a now defunct system of payment by the Israeli government. Since the establishment of the Palestinian Autonomy, these children can no longer enjoy the benefits of the prior arrangement because of the exorbitant per unit cost of the enzyme. All three children are now doing very poorly. Unfortunately the Palestinian Autonomy cannot commit itself to the high cost of therapy, and it has not been deemed an "emerging new market" by the manufacturer. This is in striking contrast to Egypt, India and China, where patients with symptomatic Gaucher disease are given enzyme therapy on a compassionate basis. Thus, it is within the context of indications for treatment in children, and within the forum of a medical journal that is read by most clinicians in Israel, that we would like to raise this humanitarian issue. In closing, we welcome any constructive thoughts from the readership as to how to further the cause of these very sick children with Gaucher disease.

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Two farmers each claimed to own a certain cow. While one pulled on its head and the other pulled on its tail, the cow was milked by a lawyer.

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