INVITED COMMENTARY

β-Thalassemia and normal growth: are they compatible?

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The cause of growth retardation in the inherited blood disorder β-thalassemia major (β-thal) has long been a subject of debate. This has become an issue in the last few years since children with β-thal are undergoing hypertransfusion and iron chelation therapy, and now living well into their thirties and forties. Therefore, in addition to growth retardation, many of the endocrinopathies such as hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus, which were not apparent before, are now being diagnosed and treated. Despite the fact that much has been learned in the past few years about the etiology of growth retardation in children with β-thal, treatment is still difficult in many cases.

Normal growth of β-thal children during the first 10 years of life depends upon the maintenance of hemoglobin levels above 8.5 g/dl. During this period of the child’s life hypoxia may be the main factor retarding growth. and the maintenance of hemoglobin levels above 10–11 g/dl together with adequate iron chelation therapy makes the β-thal patients indistinguishable from their non-thalassemic peers (1). If deferoxamine, which is used for iron chelation therapy, is used before the age of 3 years it also produces marked stunted growth with a clinical and radiologic rickets-like syndrome (2). This is because, before there is iron overload from the blood transfusions, deferoxamine is thought to also chelate other essential minerals besides iron. After the age of 10 though, despite the fact that adequate levels of hemoglobin are maintained, many of the β-thal children start having decelerated growth. In the pubertal children there may be a reduced growth spurt with marked deceleration, for which iron overload may be responsible (3). In this age group truncal shortening, most likely due to hypogonadism secondary to iron deposition, may also be found.

The hormonal cause of growth retardation in β-thal children is complex. Besides hypothyroidism and hypogonadism it has become apparent that growth hormone (GH) also plays a role in their abnormal growth. It still remains unclear, though, how the GH and insulin-like growth factor-I (IGF-I) axis may play a role. Several authors have reported reduced serum concentrations of IGF-I in the presence of a normal GH response to provocative studies (4, 5) and this led to the speculation that GH insensitivity is most likely the cause of the abnormal growth. Others have found, though, that classic GH deficiency and GH neurosecretory dysfunction (6) are the causes of the low IGF-I and short stature in many patients. The β-thal patients may have subnormal spontaneous GH secretion and an impaired GH response to GH-releasing hormone. Histologic examination at autopsy of the endocrine glands of β-thal patients has shown mild to moderate siderosis and a reduced number of cells in the pituitary gland together with fibrosis and siderosis of the thyroid gland and gonads (7). This is consistent with the view that many β-thal patients may have primary or secondary endocrine gland dysfunction. Undernutrition is also an important cause of low IGF-I and associated growth disturbances in this group. This may be compounded in certain cases of undernutrition by zinc deficiency.

In the article by Soliman and coworkers (8), the authors studied the GH response to clonidine and glucagon, and the levels of IGF-I, insulin-like growth factor-binding protein-3 (IGFBP-3) and ferritin, and they also evaluated the levels of IGF-I after 1 day of GH administration. They also followed the growth velocity of three groups of children, β-thal patients, children with GH deficiency (GHD) and children with constitutional short stature (CSS), after 1 year of hGH therapy. They found that the β-thal children had a reduced IGF-I response after 1 day of GH administration, compared with the IGF-I response in the GHD and CSS groups. They also noted that the β-thal children did not respond to 1 year of hGH therapy (in their growth velocity and circulating IGF-I levels) as well as did the GHD and CSS groups, who also received the same dose of hGH. They also evaluated the levels of IGF-I after 1 day of GH administration. They also followed the growth velocity of three groups of children, β-thal patients, children with GH deficiency (GHD) and children with constitutional short stature (CSS), after 1 year of hGH therapy. They found that the β-thal children had a reduced IGF-I response after 1 day of GH administration, compared with the IGF-I response in the GHD and CSS groups. They also noted that the β-thal children did not respond to 1 year of hGH therapy (in their growth velocity and circulating IGF-I levels) as well as did the GHD and CSS groups, who also received the same dose of hGH. From this they concluded that the β-thal children probably have partial GH resistance.

What those authors noted though, was that despite the fact that growth after GH in the thalassemic children was slower, they did double their growth velocity and therefore they did respond to the GH therapy, albeit not as dramatically as the CSS or GHD children. The reason that the β-thal children did not respond as well as the children with CSS and GHD, though, may not necessarily be GH resistance.

The IGF-I generation test used by the authors was not the standard one, so the results cannot be fully interpreted. IGF-I usually increases to its maximum level after approximately 3–4 days of GH administration (9) and therefore after only 1 day of hGH administration, as was used by the authors, one may wonder whether the GH receptor had had a chance to respond adequately, thus giving the impression that there was
GH resistance. In a group of 27 short prepubertal β-thal children who underwent a 5 day IGF-I generation test there was a greatly increased response of IGF-I and IGFBP-3 after the 3rd or 4th day of administration of GH, as compared with controls (10). This group also had normal GHBP levels as compared with controls, and 17% of the patients had classic GH deficiency, while the majority of the remaining severely growth-retarded patients had GH neurosecretory dysfunction (11).

It is possible that the reason for the inadequate response of Soliman and coworkers’ β-thal children to GH may ultimately be found beyond the GH receptor, in the dysfunction of IGF-I itself, as even in children with β-thal who have a normal IGF-I response to GH during the 4 day IGF-I generation test (10) their growth after 1 year is not optimal, and is comparable to that found in the β-thal children studied by Soliman and coworkers. There is no information available as to the possibility of iron deposits at the level of the growth plates of the bones in children with β-thal. If there are iron deposits interfering with the action of GH and IGF-I at this level of the epiphyseal plate then the β-thal children may need higher doses of GH to respond in the same way that non-β-thal children with GHD respond to GH therapy. With all the information available concerning the actions of GH, not only on growth but also on lipid and protein metabolism and on normal long-term cardiac function, it is imperative to identify the β-thal children who may benefit from GH and treat them effectively long-term so that they may have a better quality of life and possibly a longer survival rate.

References


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