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JIA-associated growth failure and exogenous growth hormone therapy

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Abbreviations: juvenile idiopathic arthritis, JIA; growth hormone, GH; insulin-like growth factor, IGF; height standard deviation score, HSDS; growth velocity, GV; growth velocity standard deviation score, GVSDS; anti-tumor necrosis factor alpha, anti-TNF α ; interleukin-6, IL-6

Abstract

Children with juvenile idiopathic arthritis (JIA) are often growth delayed, in particular, those with long-standing systemic onset disease. Total body inflammation and corticosteroid therapy are strongly implicated as causes of growth failure in JIA. Treatment of JIA-associated growth failure with growth hormone (GH) therapy has been successful to varying degrees. The financial cost and

potential for disease exacerbation should be considered when utilizing GH therapy in JIA. The benefits afforded by novel biologic disease modifying agents may obviate the perceived need for GH therapy.

Introduction

Growth failure in juvenile idiopathic/rheumatoid/chronic arthritis (JIA) has been well described (1). The majority of children with JIA and growth failure are of the systemic onset subtype, with smaller numbers of polyarticular and even less oligoarticular subtypes [1, 2]. Growth failure is almost certainly multi-factorial and several potential mechanisms have been proposed.

Inflammation and corticosteroid therapy are the most commonly implicated factors in JIA-associated growth failure. Glucocorticoids alone are well-known inhibitors of growth [3]. Difficulty exists in differentiating the contributions of inflammation from the increased corticosteroids that often accompany it. However, growth failure has been shown to occur in children with JIA independent of corticosteroid treatment [4] and even in the total absence of steroid therapy [5]. The role of exogenous growth hormone (GH) therapy in growth failure in children with JIA is controversial and herein, reviewed.

Growth hormone and the pituitary axis in JIA

Both inflammatory cytokines and corticosteroids influence GH production and its effects. Abnormalities of the GH-pituitary axis have been described in children with JIA. Depending on the testing method employed, 20-50% of JIA patients with poor growth and chronic steroid therapy are GH deficient [6-8]. Studies have shown that corticosteroids likely inhibit the GH axis on several levels, including suppression of GH releasing hormone-stimulated GH release, decreased GH pulsatility, suppression of transcription of GH receptor, and decreased GH and insulin-like growth factor-1 (IGF-1) receptor binding [9].

The primary mediators of GH effects are IGF proteins, and children with JIA with growth failure have impaired IGF production [6, 10-12]. Both height standard deviation scores (HSDS) and growth velocity (GV) correlate with IGF levels in these patients [13]. In addition, IGF levels have been shown to correlate inversely with erythrocyte sedimentation rate (ESR) [14], but not steroid dose [13, 14]. During treatment with exogenous GH, IGF levels are negatively correlated with C-reactive protein (CRP) levels [10]. IGF levels have also been shown to correlate inversely with interleukin-6 (IL-6) levels [15], which are known to be elevated in systemic onset JIA [16]. Thus, IGF levels may be a surrogate marker for growth in JIA.

Growth failure in JIA

Growth failure occurs relatively frequently in JIA. The natural history of growth failure in 24 children with systemic onset JIA treated with steroids for at least two years showed that the mean

HSDS decreased significantly from -0.03 at time of diagnosis to -2.4 over four years and the mean final adult HSDS was -2.0, with 41% of subjects' height more than 2 SD below the mean. Eighty-seven percent of subjects finished below target height based on mid-parental height, though if mid-parental heights were used as a target height, the HSDS loss was smaller at -1.7. Actual male final mean height was 1.64 m (range 1.45 to 1.80) [or 5'5" (4'9" - 5'11")], and actual female final mean height was 1.50 m (range 1.34 to 1.65) [or 4'11" (4'5" - 5'5")]. These final heights demonstrated significant growth failure in many of these children. [17]

This study demonstrated a strong positive correlation between mean HSDS loss during prednisone therapy and duration of prednisone therapy [17]. This correlation has also been shown for cumulative steroid dose [18]. Conversely, following discontinuation of prednisone an average increase in HSDS of 0.45 was observed. However, this catch-up growth was dichotomous; 70% experienced catch-up growth and increased their HSDS by a mean of +1.0 to a final of -1.5, while the other 30% had further mean HSDS loss of -0.8 for a final of -3.6. The factors contributing to the presence of catch-up growth are unclear, but appear to partially depend on the genetic potential for growth [17].

Observational growth hormone studies in JIA

Observational studies of exogenous GH therapy for JIA-associated growth failure are shown on the Table 1.

Table 1– Studies analyzing growth hormone therapy for JIA

<u>Ref.</u>	<u>Author</u>	<u>Year</u>	<u>Study type</u>	<u>(n)</u>	<u>Summary</u>
19	Butenandt	1979	Observational	20	↑ in GV by 4.3 cm/yr in 75%.
20	Davies	1994	Observational	20	↑ in GV by 4.1 cm/yr.
21	Touati	1998	Observational	14	↑ in GV by 3.5 cm/yr.
6	Al-Mutair	2000	Observational	10	↑ in GV by 3.0 cm/yr in 6 of 10
22	Simon	2003	Observational	13	↑ in GV by 3.9 cm/yr.
18	Bechtold	2003	Controlled	18	Increase in GV compared to controls.
8	Saha	2004	Controlled	25	Increase in GV compared to controls.

GV, growth velocity.

In 1979, Butenandt described 20 children with JIA with growth failure given GH therapy. Mean GV increased from 1.9 cm/year to 6.2 cm/year in the 75% of subjects who responded [19].

More recently, Davies et al. reported on 20 children with polyarthritis (10 systemic onset, 8 polyarticular onset, 2 pauciarticular onset) and a growth velocity standard deviation score (GVSDS) < -1.0. Subjects were randomized to receive two different doses of GH for one year and were then followed for six additional months. The higher dose GH increased GV by a mean of 4.1 cm/yr (mean GVSDS increased from -2.9 to +0.5). There was no statistical correlation between prednisone dose and response to GH, although a decrease in GV was noted in individuals when steroid doses were increased. Additionally, there was a highly significant negative correlation between mean serum CRP levels and GV. Lastly, children with polyarticular and pauciarticular onset experienced greater improvement in GV than those with systemic onset [20].

Touati et al. reported on GH therapy for 14 children with systemic or polyarticular onset JIA who were on chronic oral steroids and exhibited growth failure (GV was at least 1 SD below the mean and height was more than 2 SD below the mean). At one year of therapy, the mean GV had increased from 1.9 cm/year to 5.4 cm/year. As expected, there was a highly significant inverse correlation between GV during treatment and steroid dose [21]. Similarly, Al-Mutair et al. reported 10 patients with growth failure on prednisone therapy for polyarticular or systemic onset JIA. Mean GV in the first year of treatment increased significantly from 2.45 cm/year to 4.79 cm/year and, in a subset of 6 children who continued on GH therapy for a second year, it continued to improve to 5.43 cm/year [6].

A recent observational study by Simon et al. described 13 children with polyarticular or systemic onset JIA and growth failure who received GH for 3 years. Patients continued to have active disease throughout the study as evidenced by persistently elevated ESR and prednisone doses >0.2 mg/kg/day. Nevertheless, median GV increased significantly during the first year of GH therapy. However, the median HSDS did not change. Seven of the 13 children (54%) experienced catch-up growth and increased their mean HSDS by +0.6, but 4 of 13 (all of whom had high ESR or high steroid dose) had no catch-up growth and had a decreased mean HSDS of -0.4 [22].

These results suggest that improved disease control, with resultant lower steroid doses, is perhaps the most important approach to improving growth in children with JIA.

In summary, multiple observational studies have shown a short-term statistically significant increase in GV with GH therapy. Both active disease and steroid therapy likely decrease the effectiveness of GH, and upon discontinuation of GH there is a significant fall in GV toward pretreatment levels [20], perhaps as low as pre-treatment levels [21]. Taken together, all these observational GH study results appear encouraging for improving GV for children with JIA, but there is no convincing data on final adult height. All the same, the stage is set for randomized controlled trials of GH for the treatment of growth failure in children with JIA.

Controlled trials of growth hormone therapy in JIA

In addition to observational studies, two controlled trials of GH for growth failure in JIA have

been published. Saha et al. studied 25 children with active JIA, height below mean, and GV more than 1.5 SD below mean [8]. In this crossover study, patients served as their own controls. Each received either GH or placebo for 6 months followed by 6 months of the other therapy. The distribution of diagnoses was, in contrast to most other studies: 12% systemic, 40% pauciarticular, and 48% polyarticular onset JIA. Only 56% were taking daily steroids.

In this cohort, GH therapy resulted in a >50% increase in GV, versus placebo, in 75% of the patients. In those treated with GH, mean HSDS also increased from -2.08 to -1.79, compared to an increase from -2.18 to -2.02 for placebo. Additionally, children with GH deficiency as measured by L-dopa stimulation had a similar pattern of response to GH therapy as those without deficiency. Of note, this study excluded patients with “labile” arthritis requiring steroid treatment several times daily or those with recent activation of arthritis likely to require such therapy during the trial period. Thus, the benefit of GH therapy for patients with notably active JIA was not adequately addressed.

In 2001, Bechtold et al. published a 2-year controlled study of children with established JIA and a stable corticosteroid dose for >6 months whose GV was below the 30th percentile for chronological age [7]. Thirty-three of the 35 children had systemic onset JIA. The patients were divided into 3 groups. Subjects found to be GH deficient were given physiologic GH replacement for two years, and those without GH deficiency were randomized to receive either supra-physiologic exogenous GH for 2 years or no GH therapy.

The GH study group showed improved GV compared to controls ($P<0.012$). Specifically, the study group mean GVSDS was -2.9 at onset, improved to +0.85 at one year of therapy, and was +0.25 at two years. In comparison, the control group mean GVSDS was -3.2, -2.2, -1.2 during the same time intervals. The GH deficient group receiving GH replacement improved their GV, but not significantly ($P=0.07$) compared to the control group. In terms of clinical significance, the GH group grew a mean of 14.9 cm versus 8.0 cm for the control group for a mean actual height increase of 6.9 cm (2.7 inches). Assessing all patients together, both corticosteroid dose and CRP showed a significant inverse correlation with GV, as predicted from the observational studies.

These same patients, with a few additions, were published again by Bechtold and colleagues in 2003 [18]. At four years of GH therapy, the GH treatment group had an increased mean HSDS from -3.3 to -2.3, whereas the control group mean HSDS decreased from -2.3 to -3.0, for a net increase of 1.7 SD for the treatment group. The controls did increase their GVSDS through the four years from -2.6 to -0.8. Multiple regression analysis revealed that height gain was most influenced in an inverse fashion by mean ESR, mean CRP, and mean prednisone dose. Specifically, GH treatment resulted in a higher GV for a given prednisone dose, but high doses of prednisone tended to negate the effects of GH and resulted in smaller height gains. A significant inverse correlation was found between GV and joint activity score. This again suggests that effective disease control is requisite for optimal growth.

Although the study by Bechtold et al. is perhaps the most useful study yet reported regarding exogenous GH therapy for growth failure in juvenile arthritis, it has limitations. The obvious major limitation of this study, freely admitted by the authors, is the lack of follow-up to adulthood, i.e., final height. Delayed puberty in these patients may require follow-up into their early twenties, particularly for males, to assure final height. Also presented but less explicitly mentioned was the fact that although the control and study groups did not have statistically different mean steroid doses at the onset of the study, by the fourth year the control group was on a higher steroid dose (0.17 mg/kg/d of prednisolone equivalent versus 0.10 mg/kg/d, $P < 0.05$). Similarly, the control group contained more individuals receiving > 0.2 mg/kg/d of prednisolone equivalent (7 of 20 versus 3 of 18). This makes it more difficult to directly compare the benefit of GH therapy for GV in JIA since corticosteroids have clearly been shown to inhibit growth. Even so, the studies by Saha and by Bechtold and their colleagues suggest that GH therapy may improve GV in children with active JIA.

Indications and risks of growth hormone therapy for JIA

The indications for GH therapy in JIA-associated growth failure are still not clear and the current use of GH for growth failure outside of GH deficiency remains very controversial [23]. GH therapy is not currently FDA approved for use in JIA in the United States and, as with any therapy, there are risks to exogenous GH use. Fortunately, adverse events have been shown to be rare during GH therapy for a variety of causes of growth failure [24]. Whether GH poses unique risks to children with JIA and other autoimmune disorders is not known.

The potential for GH-induced activation of the immune system is an interesting consideration. Most studies state that disease activity and/or joint scores were unaffected by GH therapy [7, 8, 18, 20, 21]. However, two patients failed to complete one study because of severe disease flare on GH therapy [20]. One study excluded patients with “labile” arthritis who may have been more likely to flare [8]. In another study, one patient developed fever and flare of disease at the onset of GH therapy [7]. Additionally, there is a case report of systemic lupus erythematosus flare thought to be related to exogenous GH [25]. Although these cases may implicate GH in disease flares, they are certainly not proof of cause.

In addition to anecdotal reports, there are several observations that raise concern that GH may possibly contribute to flares of autoimmune disease. IGF-1 has been shown to be increased by exogenous GH therapy [7, 10, 21, 22], and both IGF-1 and GH have numerous effects on mouse thymocytes, including stimulating proliferation and augmenting trafficking [26]. Similar effects on human thymocytes would not be surprising, as GH and its receptor are known to be expressed by human thymic cells [27]. GH may also have positive effects on the functional activity of circulating phagocytic cells as suggested by the correction of phagocyte dysfunction in GH deficient children who received GH therapy [28]. Finally, transgenic mice expressing bovine GH

develop an arthritic disorder with disability and significant thickening of synovial tissue. The arthritis is presumed autoimmune in nature based on the concomitant presence of multiple autoantibodies [29]. This animal model perhaps raises suitable concern for the use of GH in children with JIA.

The available literature suggests that in addition to medical considerations, families and physicians often take into account age and maturity of the patient, societal and perceptual factors, and financial considerations when making decisions about GH therapy (30, 31). With regards to financial considerations, the current cost of a one year supply of GH for a 30 kg patient is in excess of \$15,000 (23). This cost is on par with the current annual cost for TNF α inhibitors used to treat JIA (32). Given the important role of disease activity in growth failure, limited resources would likely be better spent on therapies aimed at controlling inflammation.

Disease control and growth

Since growth has been shown to improve with better disease control and/or lower doses of corticosteroids, the introduction of more effective biologic agents may greatly decrease the incidence of growth failure and obviate the need for GH therapy. In one of the observational GH therapy studies, 2 patients went into remission during the pretreatment observation period and had a subsequent growth spurt, thus disqualifying them from the study [20].

Moreover, a retrospective study reviewed the growth of 71 patients with polyarthritis; only 2 had systemic onset JIA. Their growth was reported for 2 years before and 2 years after instituting anti-tumor necrosis factor alpha (anti-TNF α) therapy. In 53 children with growth impairment prior to therapy, the mean change in HSDS per year was +0.45 SD. Additionally, the mean total dose of corticosteroids for all patients decreased from 3.2 gm in the preceding 2 years to 1.6 gm in the 2 years following treatment (50% reduction) [33]. Thus, in the absence of exogenous GH, children with JIA improved their growth when their disease activity was controlled.

In addition to anti-TNF α therapy, other novel biologic strategies are becoming available. One example is interleukin-6 (IL-6), which has been strongly implicated in the pathogenesis of systemic onset JIA [16], and anti-IL-6 receptor antibodies have shown promise in the treatment of this condition [34, 35]. Similarly, a mouse model of IL-6 over-expression has been shown to result in stunted growth which can be partially overcome with the administration of anti-IL-6 antibodies [15]. Lastly, in a human study, four children with systemic onset JIA and a starting height ranging from -0.4 to -7.1 SD experienced a height increase of between +0.2 and +1.6 SD during a 2 to 3.5 year course of anti-IL-6 receptor therapy [36]. With newer, more effective therapies available for difficult to treat JIA, growth failure may become less of a co-morbidity for these children.

Conclusions

There is no doubt that growth failure occurs in JIA, especially in children with long-standing systemic onset disease. Growth failure is likely multi-factorial, although cytokine aberrations and

sustained corticosteroid therapy seem to play a central role. Exogenous GH therapy has been shown to promote growth in these children, even in the absence of a measurable GH deficiency. The clinical significance of this growth varies on an individual basis, and the effect of GH on adult height remains unclear. Although few concerning side effects of GH therapy have been reported in clinical trials, there are theoretical risks of disease exacerbation by many mechanisms. Irrespective of GH therapy, disease remission has been shown to promote growth. Hopefully, the advent and use of directed biologic agents will bring about more effective disease control and an end to growth failure associated with JIA.

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