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Short children with familial short stature show enhancement of somatotroph secretion but normal IGF-I levels

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ABSTRACT. The aim of the present study was to evaluate the GH status in children with familial, idiopathic short stature (FSS). To this goal we evaluated the GH response to GHRH (1 µg/kg iv) + arginine (ARG) (0.5 g/kg iv) test which is one of the most potent and reproducible provocative tests of somatotroph secretion, in 67 children with FSS [50 boys and 17 girls, age 10.8±0.4 yr, pubertal stages I-III, height between –3.6 and –1.6 standard deviation score (SDS), target height <10° centile, normality of both spontaneous and stimulated GH secretion as well as of IGF-I levels]. The results in FSS were compared with those in groups of children of normal height (NHC) (42 NHC, 35 boys and 7 girls, age 12.0± 0.5 yr, pubertal stages I-III, height between –1.3 and 1.4 SDS, height velocity standard deviation score (HVSDS)>25° centile, GH peak >20 µg/l after GHRH+ARG test, mean GH concentration [mGHc]>3 µg/l) and children with organic GH deficiency (GHD) (38 GHD, 29 boys and 9 girls, age 11.2±3.7 yr, pubertal stages I-III, height between –5.7 and –1.3 SDS, GH peak <20 µg/l after GHRH +ARG test, mGHc <3 mg/l). Basal IGF-I levels and mGHc were also evaluated in each group over 8 nocturnal hours. IGF-I levels in FSS (209.2±15.6 µg/l) were similar to those in NHC (237.2±17.2 µg/l) and both were higher (p<0.0001) than those in GHD (72.0±4.0 µg/l). The GH response to GHRH +ARG test in FSS (peak: 66.4±5.6 µg/l) was very marked and higher (p<0.01) than that in NHC (53.3±4.5 µg/l) which, in turn, was higher (p<0.01) than in GHD (8.2±0.8 µg/l). Similarly, the mGHc in FSS was higher than in NHC (6.7±0.5 µg/l *vs* 5.1±0.7 µg/l, p<0.05) which, in turn, was higher than in GHD (1.5±0.2 µg/l, p<0.0001). In conclusion, our present study demonstrates that short children with FSS show enhancement of both basal and stimulated GH secretion but normal IGF-I levels. These findings suggest that increased somatotroph function would be devoted to maintain normal IGF-I levels thus reflecting a slight impairment of peripheral GH sensitivity in FSS.

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INTRODUCTION

GH and IGF-I secretions are markedly impaired in children with severe GH deficiency but also slight insufficiency of 24 h somatotroph secretion and IGF-I levels leads to growth failure and needs GH replacement (1-5). In spite of no clear evidence of GH and IGF-I insufficiency, a considerable number of short children with idiopathic short stature (ISS) benefit from GH treatment and are defined as non-classical GH deficient (5, 6-9).

Key-words: GH, IGF-I, GHRH+arginine test, familial short stature.

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It is well known that parental height is a major determinant of final height and that many children with ISS have familial short stature (FSS) (10, 11). The pathophysiological mechanisms underlying short stature in ISS and FSS are very likely multiple but still unclear. In particular, hormonal parameters are assumed as normal and, in fact, these conditions are generally classified as due to non-endocrine causes (10-15). Recent evidence suggested that slight impairment in peripheral GH sensitivity could explain short stature in a number of children with ISS and FSS (16-20).

The aim of the present study was to evaluate the activity of GH/IGF-I axis, particularly the GH releasable pool, in short children with FSS. To this goal, we studied the GH response to GHRH+arginine (ARG) test which has been shown to be one of the most powerful and reproducible tests to evaluate the maximal

secretory capacity of somatotroph cells (4, 5, 21-24). We also studied the spontaneous nocturnal mean GH concentration as well as IGF-I levels in order to have more general information about the activity of GH/IGF-I axis. The results in FSS were compared with those in normal heigt children (NHC) and in children with organic GH deficiency (GHD) as control groups.

SUBJECTS AND METHODS

One hundred and forty-seven children (117 boys and 30 girls) were studied. They were classified as follows on auxological and hormonal criteria by means of: 1) 67 children with FSS (50 boys and 17 girls, age 10.8±0.4 yr, pubertal stages I-III, height between –3.6 and –1.6 standard deviation score (SDS), target height <10° centile, GH peak>20 µg/l after GHRH+ARG test, mean GH concentration (mGHc)>3 µg/l); 2) 42 NHC (35 boys and 7 girls, age 12.0±0.5 yr, pubertal stages I-III, height between –1.3 and 1.4 SDS, height velocity standard deviation score (HVSDS)>25° centile, GH peak >20 µg/l after GHRH+ARG test, mean GH concentration (mGHc)>3 µg/l); 3) 38 children with organic GHD (29 boys and 9 girls, age 11.2±3.7 yr, pubertal stages I-III, height between –5.7 and –1.3 SDS, GH peak <20 µg/l after GHRH+ARG test, mGHc <3 µg/l). Malnutrition, organic disease, other endocrine abnormalities and psychosocial dwarfism were ruled out in all children.

The study protocol was approved by local Ethical Committee and informed consent was obtained from all parents.

All children underwent testing with GHRH (GHRH1-29, GEREF Serono, Rome Italy; 1 µg/kg iv at 0 min) +ARG (ARG hydrochloride, SALF, Bergamo, Italy; ARG, 0.5 g/kg iv over 30 min, from 0 to +30 min). Blood samples were taken every 15 min from 0 to +90 min. The test was performed in the morning after an overnight fasting and in recumbent position.

In 56 FSS, 16 NHC and 19 GHD the spontaneous mean GH secretion over 12 nocturnal h (from 20:00-08:00 h sampling every 30 min). Basal IGF-I levels were evaluated in all subjects.

Serum GH levels (µg/l) were assayed by IRMA assay (HGH-CTK, Sorin, Italy). The sensitivity of the method is 0.15 µg/l. The inter- and intra-assay coefficients of variation are 5.1-7.5% and 2.6-5.4%, respectively, at GH levels of 2.9-42.4 and 2.8-41.2 Mg/l, respectively. It should be noticed that the definition of the cut-off limits depends on the GH assay used (25); thus the present data could differ if evaluated by double antibody IRMA.

Serum IGF-I levels (µg/l) were assayed by IRMA (Nichols Institute of Diagnostics, San Juan Capistrano, U.S.A.) after acid-ethanol extraction, to avoid interference by binding proteins. The sensitivity of the method is 0.1 µg/l. The inter- and intra-assay coefficients of variation are 8.8-10.8% and 5.0-9.5%, respectively, at IGF-I levels of 79.6-766.4 and 79.4-712.5 µg/l, respectively. The results are expressed as mean±SE of absolute values (µg/l) for both GH and IGF-I levels. The statistical evaluation was performed by paired and unpaired Student's *t* test and Spearman correlation test.

RESULTS

Total IGF-I levels in FSS were similar to those in NHC (209.2±15.6 *vs* 237.2±17.9 µg/l) and both were higher (p<0.0001) than those in GHD (72.0±4.0 µg/l) (Fig. 1).

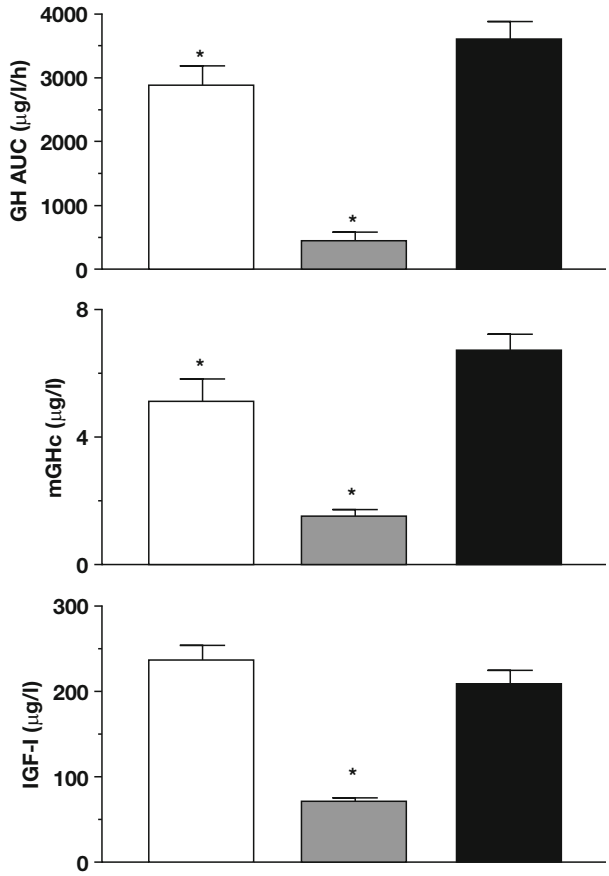

Fig. 1 - *Mean (±SE) GH AUC after GHRH+arginine (upper panel), mGHc (medium panel) and IGF-I levels (lower panel) in normal children (□), in children with GH deficiency (■) and in children with familial short stature (■).*

The administration of GHRH+ARG induced a clear GH increase in normal children and children with FSS (Fig. 2).

The GH response in FSS (peak 66.4±5.6 µg/l) was significantly higher (p<0.001) than that in NHC (peak 53.3±4.5 µg/l). On the other hand, GHD showed an almost absent GH response to GHRH+ARG (peak 8.2±0.8 µg/l) and lower than in NHC (p<0.001) (Fig. 3). The same differences were found when the GH response to GHRH+ARG was evaluated as AUCs (Fig. 1).

The nocturnal mean GH concentration in FSS was higher (p<0.05) than in NHC (6.7±0.5 µg/l *vs* 5.1±0.7 Mg/l). As expected, these levels were higher (p<0.0001) than those in GHD (1.5±0.2 µg/l) (Fig. 1).

The GH response to GHRH+ARG did not show any association to height and height velocity. On the other hand, the GH response to GHRH+ARG was positively associated to spontaneous mGHc (r=0.3,

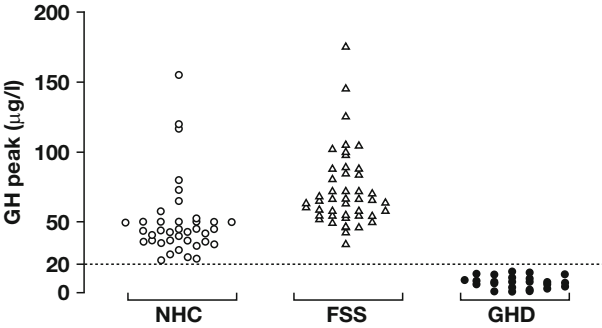

Fig. 2 - *Individual peak GH response to GHRH+arginine in normal height children (NHC) (○), in children with organic GH deficiency (GHD) (●) and in children with familial short stature (FSS) (△).*

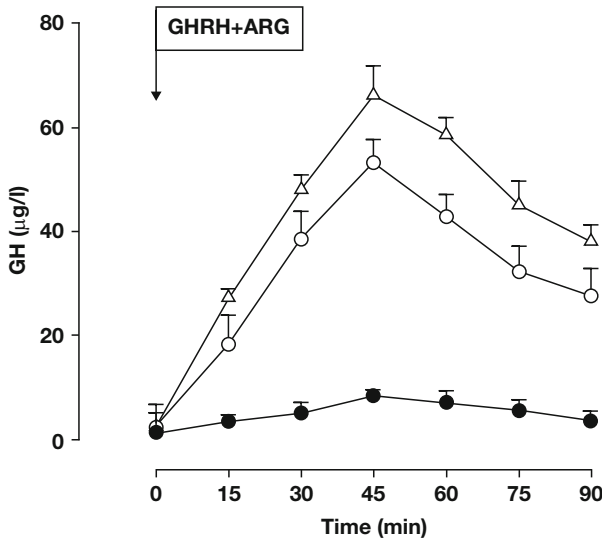

Fig. 3 - *Mean (±SE) GH responses curves after GHRH+arginine (ARG) in normal children (○), in children with GH deficiency (●) and in children with familial short stature(△).*

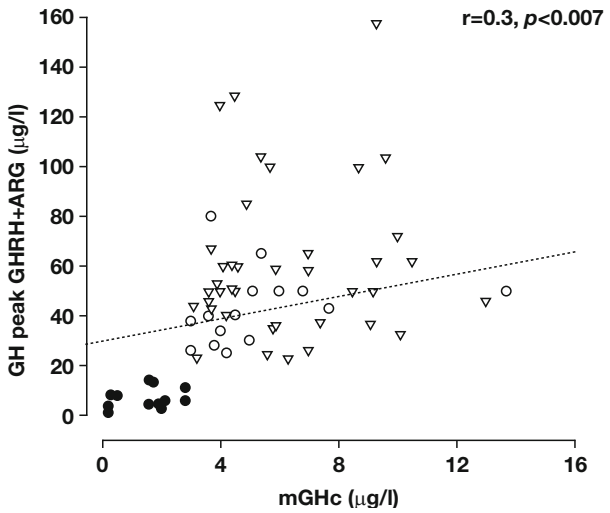

Fig. 4 - *Linear correlation between spontaneous mean GH concentration and GH peak after GHRH+arginine (ARG) test in normal children (○), in children with organic GH deficiency (●) and in children with familial short stature (▽).*

$p<0.007$) (Fig. 4). Neither the peak GH response to GHRH+ARG nor the mGHc were associated to IGF-I levels.

DISCUSSION

The results of the present study demonstrate that, with respect to NHC, short children with FSS show a significant increase in the maximal secretory capacity of somatotroph cells which, as expected, is negligible in hypopituitaric children with GHD. This secretory pattern is coupled with the same difference in terms of nocturnal spontaneous GH secretion. On the other hand, IGF-I levels in children with FSS are similar to those in NHC but markedly reduced in hypopituitaric patients with organic GHD. It is an obvious finding that the GH releasable pool is severely impaired in hypopituitaric children with GHD and, particularly in patients with multiple hypopituitarism including GHD. In fact, the diagnosis of severe GHD is usually straightforward (4, 5, 26). It has been recently shown that it is slightly reduced even in slow growing children with GH neurosecretory dysfunction (23), a condition that is characterized by low spontaneous GH secretion in the presence of some GH response to provocative tests (1-4, 27).

GH neurosecretory dysfunction (GHNSD) and FSS are considered as subgroups of the ISS by many Authors (10, 11, 14). In this wide category there are many short and/or slow growing children who show normal GH response to classical provocative tests but, nevertheless, often benefit from GH treatment (5-9). By definition, FSS includes short children with predicted short adult height within the parental target coupled with normal GH and IGF-I secretion (10, 11, 15).

Our present data agree with the assumption that GH and IGF-I levels in FSS are not below normal limits. In fact, our study indicates that the maximal secretory capacity of somatotroph cells even increases in this condition. Furthermore, the GH response to GHRH +ARG, one of the most powerful single tests to evaluate the maximal secretory capacity of somatotroph cells (4, 5, 21-24, 28), was significantly enhanced with respect to children growing normally. Moreover, the enhanced GH responsiveness to GHRH+ARG was coupled with a significant increase in spontaneous, nocturnal mGHc. This evidence indicates that FSS

may show enhanced spontaneous and stimulated GH secretion and this seems contradictory with the presence of IGF-I levels overlapping with those in NHC. In fact, there is agreement that IGF-I is the best marker of GH status (12, 29-33) though IGF-I synthesis and release are also under the important influence of the nutritional status (34-36).

To explain the uncoupling between GH and IGF-I secretion in children with FSS, a slight reduction in peripheral GH sensitivity could be hypothesized. In fact, there is already evidence showing that in a subgroup of children with ISS the pathophysiological mechanism underlying short stature is likely to include reduction in peripheral sensitivity to GH (17, 18, 20). Thus, in our present study IGF-I levels in FSS could have been maintained normal as an effect of enhanced GH secretion needed to overcome a slight impairment of peripheral GH sensitivity. This hypothesis could be confirmed only by molecular evaluation (37, 38).

Independently of pathophysiological mechanisms, our present findings further confirm that, testing with GHRH+ARG distinguishes hypopituitaric children with organic GHD from children with normal growth. However, FSS children as well as children with GHNSD (23) are not distinguished by NHC. This evidence agrees with previous studies (4, 21, 27) indicating that single testing with GHRH+ARG reliably evaluates the pituitary GH releasable pool but normal GH response to this test does not rule out the existence of GH insufficiency.

In conclusion, this study shows that FSS is characterized by enhanced secretory capacity of somatotroph cells but IGF-I levels overlap with those in NHC; this evidence fits well with the hypothesis that slight peripheral GH resistance could play a role in the pathogenesis of some forms of ISS and FSS.

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