Different Effects of GH Treatment on Cognitive Function in Girls with Turner’s Syndrome and in Adults with GH Deficiency

To the editor:

We read with great interest the paper by Ross et al. (1), concerning the absence of GH effects on cognitive function in girls with Turner’s syndrome. In our opinion, the statement that these results are in agreement with most of the previous studies that found no apparent GH treatment effects on cognitive function in patients with GH deficiency (GHD) needs a fair degree of caution.

In fact, although GH treatment is recommended worldwide for ameliorating the final height of girls with Turner’s syndrome, these patients are generally not classically GH-deficient. For this reason, we believe that the absence of GH effects on cognitive function, as clearly demonstrated by Ross et al. (1) in girls with Turner’s syndrome (without estrogen replacement treatment), is not easily comparable with the data obtained in GHD patients, in whom GH represents the “substitution” therapy.

Furthermore, the concern by Ross et al. (1) that the presence of multiple pituitary hormonal defects in adults with GHD could have a negative impact on brain development and could potentially interfere with the results of the psychological tests is not completely justified, as the majority of clinical studies [including the only mentioned (2)] have been performed in patients receiving stable and adequate hormonal replacement therapies.

As far as the effects of GH therapy on cognitive functions in adults with GHD are concerned, Degerblad et al. (3) actually found no significant effects of GH treatment; however, they suggested that the negative results could be tentatively explained by the difficulty in optimizing the measurement of subtle changes of mood and cognitive functions, rather than by a real lack of effects exerted by GH. In a short-term study (1 month) using GH treatment, Almqvist et al. (4) demonstrated that recombinant GH was able to improve cognitive psychometric testing, in particular the face recognition test, a test primarily for evaluating memory function.

Our experience in adults with childhood-onset GHD (5,6) showed that 6 months of GH treatment caused an overall improvement in their performance. In particular, the scores of the tasks in the nonverbal memory, e.g., the face recognition test, a test primarily for evaluating memory function, significantly improved compared to their performance at baseline.

In conclusion, as also stated by Ross et al. in their interesting paper (1), we agree that cognition in girls with Turner’s syndrome is more probably estrogen-dependent rather than GH-dependent, as the former actually represents the main feature of the syndrome. Further additional studies, aimed at correcting the real hormonal defects, are required to understand the potential reversibility (or not) of the neurocognitive deficits observed in Turner’s syndrome.

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References

Psychological Stress and Skydiving

To the editor:

Recently, two interesting papers dealing with psychological stress produced by skydiving appeared in The Journal of Clinical Endocrinology and Metabolism (1,2). Because in 1992 and 1993 we described the response of subjects about to make their first jump with a parachute (3,4), we would like to offer some comments.

The plasma concentrations of a number of hormones were found not to increase significantly during the period preceding the jump (1,2). However, in our hands, the skydiving test—before a novice enters the plane—induced a significant rise in plasma antidiuretic hormone and a similar tendency in serum cortisol (3,4). Also, there was a significant and positive correlation between the changes in cortisol and C-reactive protein.

One explanation for the negative findings could be that the responses of some hormones were blunted, as each stressor might induce its specific hormone pattern (5). More likely, the discrepancy between our results is due to the different design of the experiments, the selection of controls, and the influence of preanalytical factors (factors acting before a specimen is collected and analyzed). Stress responses are known to exhibit considerable interindividual variation. To increase the detectability of the response, we used each individual as his or her own control (during a stress-free situation some days before or after the jump) instead of different control individuals. In the articles quoted there is no mention of the possibility of preanalytical influences (e.g. time of day, posture, food intake, exercise, experiencing cold, and changes in altitude and speed, etc. during the flight and the fall). Because we have previously demonstrated that physical activity and changes in posture have strong effects (e.g. refs. 6–10), the investigators (1,2) may have been unable to keep the volunteers absolutely free of physical activity—parachutists need to change clothes, take on a harness, etc. Actually, we considered it important, as recommended (6), to collect the specimens after 15 min of sitting to achieve hemodynamic equilibrium and to eliminate the influence of many other preanalytical factors. Therefore, it would have been interesting to receive information on analytes that reflect physical activity (e.g. serum creatine kinase and lactate dehydrogenase) and hemococoncentration.

Because of ethical and legal considerations it is difficult to induce pure psychological stress experimentally. Therefore, imminent skydiving—before a novice enters the plane—seems to be an excellent model for such studies. However, later phases in the skydiving sport appear to involve so much somatic stress that one should be cautious in using them as models of pure psychological stress.

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Received October 21, 1997. Address correspondence to: Alessandro Sartorio, M.D., Endocrine Unit, Italian Institute for Auxology, Via Ariosto 13, 20145 Milan, Italy.
LETTERS TO THE EDITOR

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References


Psychological Stress and Sky Diving—Authors’ Response

To the editor:

We appreciate the comments of Dr. Dugué and colleagues, in the preceding letter, concerning a first-time parachute jump as a model for acute psychological stress. This model has been employed in a number of studies and has shown to induce a pronounced neuroendocrine stress response (1–5). The authors argue however, that physical activity before jumping; and in particular during the jump itself, influence the psycho-neuroendocrine response. Furthermore, it is argued that anticipatory stress of the novice jumper, incurred immediately before the first jump is a superior model for analyzing the effects of purely psychological stress on neuroendocrine parameters. However, in the studies cited as examples, the prejump psychological arousal did not significantly increase cortisol plasma concentrations (6, 7). This is in accordance with previously published observations in first-time tandem parachutists where the prejump stress did not increase cortisol, prolactin, GH, or TSH levels (3, 5). Both studies however, observed increased sympathetic activity before the jumps as indicated by elevated salivary amylase (5) and plasma noradrenaline levels (3). The blunted neuroendocrine response before the jump itself was most probably due to stress coping mechanisms of novice parachutists (5). These subjects appear to cope well with the forthcoming jump. However, after boarding the aircraft and during ascent of the plane, heart rate values and endocrine parameters start to increase, and they peak during the jump itself as this potentially life threatening situation elicits an emergency (fight-flight) response with a weakening of psychological coping mechanisms (2, 3, 8).

We agree that there is some physical activity involved in performing a tandem-parachute jump. However, physical exercise, is mainly associated with the release of noradrenaline. In contrast, psychological stress, primarily elicits an increase in adrenaline plasma concentrations. The much greater jump-induced increase in adrenaline (700%) plasma concentrations when compared with a 100% increase in noradrenaline levels, demonstrates that psychological stress is predominantly responsible for the neuroendocrine changes during parachute jumping (3).

Whereas for ethical reasons it remains difficult to induce psycholog-
cortisol progressively decreased significantly until mid-morning before skydiving, and we comment on this in relation to other studies in which a similar phenomenon was observed.

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To the editor:

The management of Graves’ disease in childhood is often difficult for both patients and their parents, and places a great deal of responsibility on physicians for appropriate treatment guidelines. Glaser and Styne (1) recently presented a retrospective investigation of 191 patients aged 1–19 yr treated for Graves’ disease at 5 pediatric hospitals in California from 1976–1996. They found that among patients with BMI scores above 0.5 sd and small goiters, 86% responded favorably to pharmacological treatment (remission, defined as normal T4 or FT4 concentrations when off medication for 6 months within 2 yr after initiation of therapy). In a group with lower BMI and larger goiters, remission was seen in only 13%. Despite the large number of patients the authors were unable to identify other predictive factors, possibly because several parameters were missing in the records reviewed. A total of 85/191 patients were excluded from the analyses. These patients had been subjected to radioiodine or surgical treatment, failed to achieve remission or were lost to follow-up. This seems to imply that the true number of patients who failed to achieve remission was larger than that of the final comparison between 27 remitters and 79 nonremitters. Moreover, the 6 month follow-up period was remarkably short, contributing additional bias to the study.

In their report, Glaser and Styne subscribe to previous claims that 25% of children with Graves’ disease enter remission every 2 yr on pharmacological treatment (2). We disagree, and we object to this frequently cited and oversimplified figure. In our experience, comprising 31 carefully monitored cases subjected to a long-term thyrostatic-thyroxine regimen, only 19% entered remission after a median of 6.5 yr (range 4.5–8 yr) (3). The mean age at diagnosis was 11 yr, and the majority of the patients were girls. Although our material was smaller, it was population-based, and all the patients were followed into adulthood. We argue strongly that a proper evaluation of therapeutic response must be based on long-term follow-up.

In our view, the majority of children with Graves’ disease are notoriously difficult to cure with pharmacotherapy, and even during long-term therapy only a small fraction will enter permanent remission. We therefore recommend a limited period of thyrostatic drug treatment. If the disease activity is not readily reduced (as reflected by the dose of thyrostatics required and the level of TSH receptor antibodies), extensive thyroid surgery is advised. We believe that this active strategy reduces the risk of exposing children with Graves’ disease (and their families) to complications of medical therapy, 12 (14%) opted to discontinue medical therapy because of dissatisfaction with frequent office visits and blood testing, and 3 (4%) chose surgical therapy for cosmetic reasons. Only 9 (11%) continued to have elevated T4 and/or T3 concentrations at the time of surgery or radioablation and thus could possibly be said to have failed medical therapy. Of these 9 patients, however, noncompliance was suspected. Thus, there is no clear indication that the exclusion of these 9 patients would have very likely to bias the results of the study.

Despite the limitations of our study as described above, we do not feel that the stated remission rate of 25% with every 2 yr of treatment is markedly inaccurate. The remission rate observed in our study agrees with that observed by Lippe et al. (2) and Collen et al. (3) in their previous prospective studies. In the initial study by Collen et al., the authors followed a cohort of 65 pediatric patients with hyperthyroidism for periods ranging from 3 months to 16 yr. They used life-table analysis methods to determine the distribution of remission times in the population. In that study, the authors defined remission as maintenance of clinical and biochemical euthyroidism for at least 1 yr without antithyroid medication. They determined that approximately 25% of patients achieve remission with every 2 yr of treatment. In a second study by Lippe et al., the same group followed the cohort of patients from the first study for an additional 5 yr. Even with this additional follow-up period, the remission rate remained the same. The authors note that only one of 36 patients who achieved remission experienced a relapse after remaining euthyroid for greater than 1 yr without antithyroid medication. The remaining 35 patients had been followed for a mean of 3.3 ± 2.9 yr (range 1–11.7 yr) without experiencing a relapse. Both the relatively long follow-up period in these studies as well as the concordance of the

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Received November 13, 1997. Address correspondence to: Professor F. Anders Karlsson, Section of Endocrinology and Diabetes, Department of Medicine, University Hospital, S-751 85 Uppsala, Sweden.

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References


Childhood Graves’ Disease—Remission Rate and Risk Factors—Authors’ Response

To the editor:

In the previous letter, Karlsson et al. raise several issues. Although determination of remission rate was not a primary aim of our study, they question whether the remission rate for pediatric hyperthyroidism is truly 25% with every 2 yr of medical therapy. They cite concerns regarding lack of long-term follow-up. In our study (1), we defined remission as maintenance of normal serum T4 or FT4 concentrations without medication for greater than 6 months. Because our study was retrospective in design, long-term follow-up was not available for many patients. Use of a definition of remission that required follow-up periods longer than 6 months in a retrospective study would have resulted in excessive restriction of the sample size. Because determination of the remission rate was not the primary objective of our study, we felt justified in using this definition. We acknowledge that our definition of remission may have resulted in some patients being misclassified, and this was clearly stated in the limitation section of the article. While we cannot exclude the possibility of selection bias in determining which patients continued medical treatment, of the 85 patients who were excluded, 35 (41%) were lost to follow-up, 7 (8%) preferred initial treatment with surgery or radioablation, 10 (12%) were non-compliant, 9 (11%) had complications of medical therapy, 12 (14%) opted to discontinue medical therapy because of dissatisfaction with frequent office visits and blood testing, and 3 (4%) chose surgical therapy for cosmetic reasons. Only 9 (11%) continued to have elevated T4 and/or T3 concentrations at the time of surgery or radioablation and thus could possibly be said to have failed medical therapy. Of these 9 patients, however, noncompliance was suspected. Thus, there is no clear indication that the exclusion of these 9 patients would have very likely to bias the results of the study.

We hope this clarifies our findings. We thank the editor for the opportunity to respond to this comment.

1. Received January 9, 1998. Address correspondence to: Nicole S. Glaser, M.D., Department of Pediatric Endocrinology, University of California, Davis, 2516 Stockholm Boulevard, Room 339, Ticon II, Sacramento, California 95817.
remission rate observed in these studies with that observed in our study argues strongly that the figure is likely an accurate one.

Karlsson et al. (4) state that, in their study of 31 pediatric patients with hyperthyroidism, only 19% entered remission after a median of 6.5 yr of medical therapy. The authors, however, do not report data regarding predictive variables such as goiter size and body mass, index which were determined in our study to influence the likelihood of early remission. In addition, the sample size for their study was small. Finally, 21% of the patients in their study were treated with antiathyroid medication for 2 yr or less before surgery and 67% were treated for 4 yr or less. We feel that determination of accurate remission rates from this small study group, many of whom were treated for relatively brief periods, is difficult.

Karlsson et al. favor the use of surgery after a brief attempt at medical management. While the optimal treatment for pediatric hyperthyroidism continues to be controversial, we feel that their strategy would subject many children to unnecessary surgical procedures and the risk of surgical complications. We continue to advocate medical therapy as the first line of treatment, particularly in patients who present with small goiters and body mass index > 0.5 s.d., indicative of a high likelihood of achieving remission within 2 yr.

As concerns the issue of increased risk of autoimmune thyroid disease in children with Down’s syndrome, this is a well-established fact. Children with Down’s syndrome constituted 3% of our study population. This information (along with information regarding other concurrent medical disorders in the study population) was not included in the manuscript merely because of the desire to keep the manuscript concise. Children with Down’s syndrome were not excluded from the analysis, and the care of children with Down’s syndrome in our clinics certainly is no different from that of other children.

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References

Why Nobody Has P450scC (20,22 Desmoslase) Deficiency*

To the editor:

Okuyama et al. (1) recently reported a case of congenital lipoaid adrenal hyperplasia (lipoid CAH) caused by a splicing mutation in the gene for the sterogenic acute regulatory protein (STAR). In citing the relevant literature, they pointed out that nearly all patients with the lipoid CAH phenotype have been found to have STAR mutations. In two large series, Bose et al. (2) and Nakae et al. (3) found STAR mutations in 39 of 40 patients with lipoid CAH. This was a well-established fact. Children with Down’s syndrome constituted 3% of our study population. This information was not included in the manuscript merely because of the desire to keep the manuscript concise. Children with Down’s syndrome were not excluded from the analysis, and the care of children with Down’s syndrome in our clinics certainly is no different from that of other children.

Okyuama et al. (1) recently reported a case of congenital lipoaid adrenal hyperplasia (lipoid CAH) caused by a splicing mutation in the gene for the sterogenic acute regulatory protein (STAR). In citing the relevant literature, they pointed out that nearly all patients with the lipoid CAH phenotype have been found to have STAR mutations. In two large series, Bose et al. (2) and Nakae et al. (3) found STAR mutations in 39 of 40 patients with lipoid CAH. This was a well-established fact. Children with Down’s syndrome constituted 3% of our study population. This information was not included in the manuscript merely because of the desire to keep the manuscript concise. Children with Down’s syndrome were not excluded from the analysis, and the care of children with Down’s syndrome in our clinics certainly is no different from that of other children.

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References

* Received November 24, 1997. Address correspondence to: Walter L. Miller, M.D., Professor, Department of Pediatrics, University of California, San Francisco, Bldg. MR-4, Room 209, San Francisco, California 94143-0978.

Serum Leptin Levels in a Patient with Pheochromocytoma

To the editor:

We read with great interest the report of Masuzaki et al. (1), which showed that serum leptin levels were increased in patients with Cush- ing’s syndrome. However, serum leptin levels in a patient with pheochromocytoma, another adrenal tumor, were not described.

A 72-year-old man complaining of episodic headaches, nausea, palpitations, and perspiration was referred to our department in October 1997. Physical examination showed that the patient was agitated and had striking peripheral vasoconstriction. Blood pressure varied between 240/130 and 80/40 mm Hg; the patient did not have orthostatic hypotension. Plasma noradrenaline and adrenaline levels were increased (2.20 ng/mL and 0.86 ng/mL, respectively), although serum cortisol and aldosterone levels were normal. Twenty-four-hour urinary noradrenaline and adrenaline were also increased (882 μg/day and 138 μg/day, respectively). A tentative diagnosis of pheochromocytoma was made. Computed tomography of the abdomen showed a mass measuring 240/130 and 80/40 mm Hg; the patient did not have orthostatic hypo-

Differential Expression of HGF and Met in Human Placenta

To the editor:

We read the paper by Kauma et al. (1) with interest. Their technique for separating and culturing trophoblast from villous core tissue showed that only the villous core tissue produces hepatocyte growth factor (HGF). This confirms evidence from previous in situ hybridization studies by ourselves and others, where HGF mRNA was localized to the villous core (2–4). They attribute the HGF production to villous core fibroblasts but are unable to explain why cultures of whole tissue produce 24 times more HGF than isolated villous core tissue: co-culture of whole tissue produces 2.1 times more HGF than isolated villous core tissue. This implies that...

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**TABLE 1.** Cathecholamine and serum leptin levels in a patient with pheochromocytoma

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Noradrenaline</td>
<td>2.20</td>
<td>0.26</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Adrenaline (ng/mL)</td>
<td>0.86</td>
<td>0.04</td>
<td>&lt;0.12</td>
</tr>
<tr>
<td>Urinary Noradrenaline (μg/day)</td>
<td>882</td>
<td>138</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Adrenaline (μg/day)</td>
<td>652</td>
<td>2</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

* Serum leptin levels were determined in duplicate by a radioimnunoassay kit (Linco Research, Inc., St. Charles, MO).

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*b* Received December 31, 1997. Address correspondence to: Toshihide Yoshida, Kyoto Prefectural University of Medicine, Kamikyo-ku, Kyoto 602, Japan.

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1. Received October 1, 1997. Address correspondence to: D. A. Somers, Academic Department of Obstetrics and Gynecology, Birmingham Women’s Hospital, Edgbaston, Birmingham, United Kingdom B15 2TG.
nearly 25% of total secreted protein was HGF, which is implausibly high and raises questions about the measurements reported.

The failure by Kauma et al. to immunolocalize HGF to the villous trophoblast is at odds with the previously published work of ourselves and others, showing co-localization of HGF and c-met protein to the vasculo-syncytial membrane in the third trimester (3, 6). One study in human placenta from the first trimester also failed to localize HGF to the trophoblast, but did localize it to the basal membrane area, where the cytotrophoblasts come into contact with the villous core (4). A fourth study failed to immunolocalize HGF to trophoblast throughout gestation (2). The reasons for this discrepancy may well lie in the specificity of the antibodies involved as, while the latter study (Clark et al., ref. 2) and Kauma et al. used the same monoclonal antibody, the other three studies all used different polyclonal antibodies. It is possible that the polyclonal antibodies may bind to forms of HGF not detected by the monoclonal antibody, which is likely to recognize a single epitope. Alternative forms of HGF likely to exist in the trophoblast layer include the inactive monomer, the active dimer, and the receptor bound or internalized HGF. A further difference identified between these studies lies in the tissue fixation used: both Wolf et al. (6) and ourselves (3) used Formalin-fixed wax embedded sections, whilst the other three studies used frozen sections, post-fixed in acetone. This may also affect antigen recognition, especially by monoclonal antibodies. It would be interesting to know if the authors were able to perform successful HGF immunolocalization using the Formalin-fixed, wax embedded sections that they used for the c-met immunohistochemistry.

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References

Differential Expression of HGF and Met in Human Placenta—Authors’ Response

To the editor:

We greatly appreciate the interest of Dr. Somerset and his colleagues (see preceding letter) in our paper concerning the production of hepatocyte growth factor (HGF) in placental villous core mesenchymal cells and the presence of the HGF receptor, Met, in placental trophoblast cells. They note that, in our study, intact placental villous explants produced 24 times more HGF than did isolated placental villous core tissues. Furthermore they speculate that possible damage to the perivascular smooth muscle in the villous core may result in decreased HGF production from these cells. We acknowledge that tissue damage to cells in the villous core during isolation may be one possible explanation for decreased HGF production in our studies.

That this effect would be selective for the perivascular smooth muscle cells seems unlikely, as the short Dispase digestion isolation procedure used is gentle and rapid, leaving the villous core tissue completely intact, including the perivascular tissues within the villous core (1).

Dr. Somerset raises into question our reported values of HGF production by intact placental villi stating in the letter that “25% of total secreted protein was HGF.” This interpretation would be correct if the denominator were μg total protein secreted. However, as stated in the Materials and Methods section, HGF production in this figure was standardized between samples by measuring the extractable protein from the tissue and cell samples and is not a value for total secreted protein. These procedures for standardizing in vitro cell and tissue secretion of proteins have previously validated (1, 2). Standardizing HGF secretion by total wet weight of cultured placent al villous explants demonstrates production rates of approximately 1 ng HGF/mg tissue/24 h.

Our study did not show immunolocalization of HGF to placental trophoblast. We initially attempted immunostaining with both polyclonal and monoclonal antibodies to HGF on formalin-fixed paraffin embedded tissue sections, but could not demonstrate any specific staining using these methods of fixation and processing. We would agree with Dr. Somerset et al. that they may have detected receptor-bound or internalized HGF on trophoblast cells, not detected by our HGF immunolocalization procedure, in their studies using their immunolocalization procedure. This explanation would be consistent with our findings that trophoblast do not produce HGF but do express Met.

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To the editor:

The article by Ghazali et al. (1) entitled “Low Bone Mineral Density and Peripheral Blood Monocyte Activation Profile in Calcium Stone Formers with Idiopathic Hypercalciuria” evokes substantial interest in relation to mechanisms that induce osteoporosis.

Secondary hyperparathyroidism has been described in patients with idiopathic hypercalciuria of renal origin (2). The authors have stated that they have excluded patients with hyperparathyroidism from their study. It would be of interest to know if those patients with renal hypercalciuria had higher the elevation in serum PTH or had high serum PTH levels in the upper limits of the reference range as compared to those patients with dietary dependent hypercalciuria or the normal controls.

PTH acts on cells other than those of bone and kidney, and mitosis of lymphocytes has been described (3, 4). It may be interesting to note if there is a positive correlation between the PTH levels and the cytokines of patients with renal hypercalciuria, and whether this was responsible for the reduction in bone density.

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1 Received January 13, 1997. Address correspondence to: Scott Kauma, Department of Obstetrics and Gynecology, MCV/VCU, 1101 East Marshall Street, Sanger Hall, RM 11-024, Richmond, Virginia 23298.

2 Received July 11, 1997. Address correspondence to: Dr. Nihal Thomas, Department of Endocrinology and Biochemistry, Royal Adelaide Hospital, IMVS, Adelaide 5000, Australia.
References


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