Impaired social status of growth hormone deficient adults as compared to controls with short or normal stature

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Summary

OBJECTIVES In adults with growth hormone deficiency (GHD) social problems have been reported, but so far the relative contributions of GHD, additional pituitary deficiencies and short stature have not been distinguished. We therefore compared social data from GHD patients with social data from controls with short or normal stature. Furthermore we investigated whether social problems are caused solely by the deficiency of GH or also by the associated absence of other pituitary hormones.

DESIGN A questionnaire was sent to patients and controls with items on education, profession, income, partner and living situation.

PATIENTS Two hundred and ten GHD patients treated in childhood but not in adulthood (93 isolated GHD (IGHD), 111 patients with multiple pituitary deficiency (MPD)) were compared with 53 short controls (height in childhood < third percentile for population) and 39 normal stature controls.

RESULTS There were no differences between short and normal controls. There were also no differences between IGHD and MPD patients in any of the investigated items. GHD patients did not differ from controls on education level, but scored lower on the profession scale, had a lower income and had a partner less often; if they had a partner they less often had children; also, more of them lived with their parents.

CONCLUSION Since patients with multiple pituitary deficiency did not differ from patients with isolated growth hormone deficiency, this suggests that the lower scores on the social parameters are the result of the growth hormone deficiency itself. Since short stature controls had higher scores than patients with growth hormone deficiency and did not differ from normal stature controls in any of the aspects investigated, it seems unlikely that the problems of the patients with growth hormone deficiency can be attributed to short stature.

Growth hormone deficiency (GHD) is an uncommon disorder defined by insufficient secretion of GH. If it starts in infancy or childhood, it is characterized by several symptoms, principally short stature. In 75% of the patients the cause is unknown and in most known cases there are brain abnormalities (Albertsson-Wikland, 1992). It affects twice as many boys as girls and 22% of the affected children have other hormonal deficiencies (particularly those children with brain anomalies).

A number of cognitive and psychosocial problems have been reported in GHD children and adults (Björk et al., 1989; Frisch et al., 1990; Siegel et al., 1991). An essential weakness in all these studies is the lack of control groups with short stature. This makes it difficult to determine whether the effects observed are due to short stature or to GHD itself. Furthermore, most of the studies concern patients treated in a period when GH was scarce and when the doses were lower than those given today.

In this study we investigated whether the social status of GHD adults is similar to that of healthy persons with normal stature and to that of healthy persons who had experienced short stature during childhood. To discriminate between the effects of GHD and other pituitary deficiencies, patients with isolated GHD (IGHD) and multiple pituitary deficiencies (MPD) were studied separately. Social status was assessed by evaluating the following aspects: (1) educational level, (2) job level, (3) living situation, (4) marital status, and (5) the ability to have children.

Patients

GHD patients

From the files of the Dutch Growth Foundation, which controlled GH treatment in the Netherlands until 1986, and
from the database of the National Registry of GH therapy, which contains the data of GH treated patients since 1989, we collected the names of 578 patients who were born between 1946 and 1974 and had been treated with GH. One hundred and seventy-one patients were excluded because they were under the age of 18, and 145 were excluded for a variety of other reasons (diagnosis GHD not validated, still receiving or again receiving GH therapy, mentally retarded or deceased). A total of 262 patients remained. Patients were divided into an IGHD group and a MPD group on the basis of the hormonal therapy they were receiving at the time of the questionnaire.

Until 1985, patients were treated with pituitary extracted hGH; from 1986 they were treated with recombinant hGH. From 1967 until 1983 the standard regimen was 4 IU twice a week intramuscularly (i.m.), from 1983 to 1986 2 IU 4 times a week subcutaneously (s.c.), and from 1986 2 IU/m²/day s.c. 6 or 7 times a week. If other deficiencies were present, hormonal substitution was given.

Control groups
A cohort of 3481 healthy individuals born between 1959 and 1974 who had been enrolled in 1977 as children in an epidemiological study about cardiovascular disorders (Hoes et al., 1993) formed the basis for two control groups. The first group was formed by selecting randomly 90 persons whose height in 1977 was above the third percentile (P₃) for the national population (Roede & Van Wieringen, 1985) (normal controls NC). The second control group was formed by all 83 persons whose height in 1977 was below the P₃ (short controls SC).

Methods
Patients and controls were asked to complete a questionnaire containing items on their final height (FH), current medical treatment and several social parameters. Addresses were checked from the national population registry. To assess the validity of the reported FH we measured FH in a random selection of 28 patients. The mean of these 28 reported heights was 166.7 ± 9.1 cm and the mean measured height 166.3 ± 9.1 cm. Twenty-three of the 28 patients reported a FH within 2 cm of measured FH and the median of the absolute difference was 0.7 cm. We therefore considered the reported FH to be a good estimate of actual FH.

Education, profession and income
Education was evaluated on the basis of the highest level of education attained. In the Netherlands, 8 levels can be distinguished. Professions were rated on a social prestige scale (van Berkel-van Schaik & Tax, 1990), which ranges from 13 (refuse collector) to 89 (surgeon). Professions not on this list were scored independently by 4 investigators, whose scores were subsequently averaged. This 'actual profession' score was compared with the professions of the father and mother. The highest score of father or mother was used as parental score. The difference between this parental score and the patient's score was calculated. Because the differences in profession might be attributed to a difference in education, subjects were also asked to state the profession for which they had been trained ('educated profession' score). This educated profession score was compared with the 'actual profession' score. Analysis of these items was restricted to those patients for whom parental and educated as well as actual profession score were available.

Patients were also asked whether they had a paid job, whether their health or their height had influenced their choice of job, and whether their height had an influence on the way in which they performed their current job.

Additionally, they were asked to rate their net family income (including income of their partner, if they had a partner) according to one of the 6 percentile categories of national reference data (income below 10th percentile (P₁₀) for population; P₁₀–P₂₅; P₂₅–P₅₀; P₅₀–P₇₅; P₇₅–P₉₀; >P₉₀) (Centraal Bureau voor de Statistiek, 1990).

Partners, children, living situation
Patients were asked whether they had a partner. Persons with a partner were asked whether they had children. To investigate the living situation they were asked whether they lived alone, with parents, or with a partner.

Statistical analysis
Heights were expressed in centimetres and as standard deviation score (SDS). The SDS was calculated with the formula SDS = (height - mean population height)/SD population height, using national references (Roede & Van Wieringen, 1985). Between the four groups the age and height were analysed with an analysis of variance (ANOVA). In the case of significant differences the least significant differences (LSD) method was used to examine which means differed from others. For all ordinal parameters, a χ²-test was used to screen for differences within the patient groups (IGHD vs MPD) or within the control groups (SC vs NC). Because no significant differences were found, data from the two patient groups were combined as were data from the two control groups.

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Social status of GH deficient adults

Table 1 Response, sex, age and height characteristics of the participants (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. in file</th>
<th>Response (%)</th>
<th>No. of responses (M:F)</th>
<th>Age (years)</th>
<th>Mean height (cm) (M)</th>
<th>Mean height (cm) (F)</th>
<th>Height SDS (M:F combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGHD</td>
<td>262*</td>
<td>78</td>
<td>93 (67:26)</td>
<td>24.6 ± 4.0</td>
<td>166.9 ± 8.9</td>
<td>153.5 ± 7.0</td>
<td>−2.29 ± 1.26</td>
</tr>
<tr>
<td>MPD</td>
<td></td>
<td></td>
<td>111 (70:41)</td>
<td>27.0 ± 4.8†</td>
<td>168.9 ± 7.9</td>
<td>156.6 ± 9.8</td>
<td>−1.93 ± 1.33†</td>
</tr>
<tr>
<td>SC</td>
<td>83</td>
<td>67</td>
<td>53 (23:30)</td>
<td>28.6 ± 3.6†</td>
<td>172.4 ± 4.2†</td>
<td>157.1 ± 4.7†</td>
<td>−1.64 ± 0.72†</td>
</tr>
<tr>
<td>NC</td>
<td>90</td>
<td>43</td>
<td>39 (21:18)</td>
<td>29.2 ± 3.7†</td>
<td>181.5 ± 5.4†</td>
<td>168.6 ± 4.1†</td>
<td>−0.02 ± 0.74†</td>
</tr>
</tbody>
</table>

* It was not known beforehand whether patients had IGHD or MPD.
† P < 0.05 compared to IGHD; † P < 0.05 compared to MPD; § P < 0.05 compared to SC (ANOVA with LSD method).
IGHD, Isolated growth hormone deficiency; MPD, multiple pituitary deficiency; SC, short controls; NC, normal controls.

To study the differences between patients and controls for the various outcome parameters, we had to take into account differences in sex ratio and age between the patients and the controls. For parameters with a binary outcome (having a paid job, having a partner, having children, living with a partner, living alone, or living with parents) a logistic regression analysis was performed using groups (patients vs controls), sex and age as independent variables. For the parameters education and income and for the profession scores a multiple linear regression (MLR) analysis was performed using group (patients vs controls), sex and age as independent variables.

Results

The number of patients, sex, age and height data for the patients and the control groups are summarized in Table 1. Lower response rates were obtained from the control groups (particularly the normal controls) than from the patients. In the SC group there were more women than men, whereas in the other 3 groups there were more men than women. The control groups were significantly older than the patient groups (P < 0.01). The MPD patients were significantly older than the IGHD patients. The height of MPD patients, calculated as SDS, was significantly greater than the height of the IGHD patients. The short controls were also significantly taller than IGHD patients, but not significantly taller than MPD patients. Although the inclusion of those in the SC group was defined by being <P3 upon entry to the epidemiological study (when they were children) their mean height as adults is >P3, which shows that their height had caught up substantially.

Education

There was no difference in the education of IGHD and MPD patients (P = 0.37) or in the education of short and normal controls (P = 0.59). Table 2 shows that the education of the combined patient groups was similar to that of the combined control groups, and there was no difference between the age cohorts. Multiple linear regression analysis showed that none of the three variables used

Table 2 Outcome of the education, profession and income scores of patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scale range</th>
<th>GHD Patients (mean ± SD)</th>
<th>Controls (mean ± SD)</th>
<th>Significance between patients and controls (MLR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>1–8</td>
<td>5.80 ± 1.90 (n = 200)</td>
<td>5.77 ± 1.93 (n = 92)</td>
<td>NS</td>
</tr>
<tr>
<td>Profession</td>
<td>13–89</td>
<td>(n = 106)</td>
<td>(n = 44)</td>
<td></td>
</tr>
<tr>
<td>Actual profession</td>
<td></td>
<td>39.3 ± 15.0</td>
<td>47.7 ± 14.1</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Parental profession</td>
<td></td>
<td>45.0 ± 15.1</td>
<td>47.9 ± 13.3</td>
<td>NS</td>
</tr>
<tr>
<td>Educated profession</td>
<td></td>
<td>41.3 ± 15.5</td>
<td>45.6 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Income class</td>
<td>1–6</td>
<td>2.18 ± 1.23 (n = 161)</td>
<td>3.50 ± 1.32 (n = 68)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

In the multiple linear regression analysis (MLR) the difference between the patient and control groups was adjusted for sex and age.

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(patient group, sex, age) had a significant correlation with the level of education.

Profession

In the patient groups 13% of the IGHD and 38% of the MPD patients reported that their health had influenced their choice of job, whereas in the control groups the corresponding figures were 10% (SC) and 0% (NC) \((P < 0.001)\). There was no difference between groups with respect to reporting that their health was currently impairing the way they did their jobs (IGHD 16%, MPD 25%, SC 21%, NC 14%, \(P = 0.31\)).

All profession scores were available for 106 patients and 44 controls. There was no difference between the IGHD and MPD group \((38.8 \pm 14.4 \text{ vs } 39.7 \pm 15.6, \ P = 0.46)\) or between the SC and NC groups \((47.4 \pm 15.8 \text{ vs } 48.2 \pm 12.3, \ P = 0.46)\). Table 2 shows that the patients had significantly lower actual profession scores than the controls, whereas the parental profession score and the educated profession score were not different.

Income

There was no difference in the income of IGHD and MPD patients \((P = 0.25)\) or in the income of short and normal controls \((P = 0.90)\). Table 2 shows that the controls have a higher income than the patients \((P < 0.001)\). A higher age was also significantly \((P < 0.001)\) correlated with a higher income. Gender did not correlate with income. Also, if the fact that more controls had a partner was taken into the MLR analysis, income remained significantly higher in the control than in the patient groups.

Employment

There was no significant difference in the percentage of IGHD patients being employed \((55.9\%) \text{ and } MPD \text{ patients } (55.0\%, \ P = 0.89)\) or between short and normal controls \((49.1 \text{ and } 64.1\% \text{ respectively, } P = 0.15)\). The logistic regression procedure revealed that being in paid employment is not significantly dependent on patient group \((\text{GHD vs control, } P = 0.35)\), whereas being in paid employment was significantly related to age \((\text{more paid jobs with increasing age, } P < 0.001)\) and sex \((\text{more males than females in employment; } P = 0.002)\). The probability of being employed, as a function of age, as calculated by the logistic regression procedure, is visualized in Fig. 1.

Partners, children

There was no significant difference between the percentage of IGHD patients having a partner \((32.6\%) \text{ and } \text{the percentage of MPD patients having a partner } (23.4\%, \ P = 0.15)\) or between the proportion of short and normal controls having a partner \((86.5 \text{ and } 82.1\% \text{ respectively, } P = 0.56)\). Figure 2 shows the predicted probability of having a partner. Group (controls more than patients, \(P < 0.0001\)), age (more older than younger patients having a partner, \(P = 0.0003\)) and sex (more women than men having a partner, \(P = 0.0001\)) had a significant correlation with the chance of having a partner.

When data only of patients with a partner were analysed to find out how many of them had children, no differences were found between IGHD and MPD patients \((13.8 \text{ vs } 28.0\% \text{ having children, } P = 0.20)\), or between SC and NC \((48.9 \text{ and } 65.6\% \text{ respectively, } P = 0.15)\). Figure 3 shows the outcome of the logistic regression analysis; the predicted
Table 3 Living situation of patient and control groups

<table>
<thead>
<tr>
<th></th>
<th>IGHD (%)</th>
<th>MPD (%)</th>
<th>P (IGHD vs MPD)</th>
<th>SC (%)</th>
<th>NC (%)</th>
<th>P (SC vs NC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living with parents</td>
<td>51.1</td>
<td>50.0</td>
<td>0.88</td>
<td>11.5</td>
<td>10.3</td>
<td>0.85</td>
</tr>
<tr>
<td>Living alone</td>
<td>30.7</td>
<td>31.7</td>
<td>0.88</td>
<td>9.6</td>
<td>7.7</td>
<td>0.74</td>
</tr>
<tr>
<td>Living with partner</td>
<td>18.2</td>
<td>18.3</td>
<td>0.98</td>
<td>78.8</td>
<td>82.1</td>
<td>0.70</td>
</tr>
</tbody>
</table>

IGHD, Isolated growth hormone deficiency; MPD, multiple pituitary deficiency; SC, short controls; NC, normal controls.

The probability of having children is adjusted for age and sex. Here again an older age ($P = 0.005$), being a woman ($P = 0.024$) and belonging to the control group ($P = 0.004$) are significantly associated with a higher chance of having children.

**Living situation**

Table 3 shows that there are no differences with respect to the living situation between the MPD and the IGHD group or between the control groups. The logistic regression procedure revealed that even after correction for age and sex, more patients lived with their parents (Fig. 4) whereas more controls lived with partners (Fig. 5).

**Discussion**

This study shows that patients with childhood onset of GHD (irrespective of whether they also have other pituitary deficiencies) are significantly more socially disadvantaged than controls with respect to their living situation (more patients living with parents), partnership (fewer with a partner), offspring (fewer children), profession (having jobs with lower social prestige, although the proportion of people having a paid job was normal) and income (lower income). The results of other studies on similar patients are remarkably similar. GHD adults have a reduced quality of life with less energy and more depression, are more socially isolated with a lower chance of having a partner and lower marriage rates, and have normal educational but lower employment rates (Dean et al., 1985; Björk et al., 1989; Galatzer et al., 1987).

It is still open to discussion whether the causes for this impaired social status of patients with childhood onset GHD stem from childhood or adolescence or whether they emerge in adulthood, after GH treatment was stopped. Adults with GHD are usually not treated with GH and it is known that they experience physical and psychological problems (reduced strength and exercise capacity, lack of vitality and energy, anxiety, depression) (Lamberts et al., 1992; Cuneo et al., 1992), which may also lead to the observed differences in our study population. One study in which adults with adult onset GHD were treated with GH or placebo showed that before treatment the patients scored significantly worse on the Nottingham Health Profile (which amongst other factors measures social isolation) and that after a short-term treatment period (6 months) the GH treated patients had normalized their scores whereas the scores in the placebo treated group remained impaired (McGauley et al., 1990).
Our study shows that GHD patients differ in their living situation and in their relationships compared to short and normal controls. These aspects are associated with psychosocial independence and maturity, elements that develop during puberty and adolescence. This would give support to the hypothesis that the difficulties arise during that period of life.

It was also not known whether the psychosocial problems are related to the deficiency of GH itself or to one or more confounding factors such as short stature, deficiencies of other pituitary hormones, or the burden of a chronic illness in youth. Since short controls in our study did not differ in any respect from controls with normal stature, it appears likely that short stature alone is not disadvantageous with regard to the social items investigated. However, because of the slightly lower final height of GHD patients in comparison to the short controls, it is not possible to rule out the possibility that the observed effects in the GHD groups are caused to some degree by their short stature.

We also have demonstrated that isolated GHD patients do not differ from GHD adults with multiple pituitary deficiencies. Most patients in the latter group lack gonadotrophins, resulting in disturbed pubertal development. Physical disturbances during this important phase in development can easily lead to social disturbances, but apparently this did not lead to more social problems for this group than for isolated GHD patients.

Another factor which might be hypothesized is the burden of a chronic illness in youth. The children have been treated for many years and it might be that the effect of being regarded as not healthy during a long and crucial period of development has had a negative influence on their psychosocial development. However, studies on adults with cystic fibrosis who had been treated during childhood for comparably long treatment periods failed to reveal social problems, although their educational career was slightly different (Sinnema et al., 1983).

The hypothesis that the deficiency of GH itself might be an important determinant which caused the differences found is supported by the fact that it is known that the brain has binding sites for GH (Lai et al., 1993). Furthermore, the fact that psychosocial parameters improved during GH-treatment in adult onset GHD patients (McGauley et al., 1990) supports this concept.

In conclusion, we found that growth hormone deficient patients, irrespective of whether they have other hormonal deficiencies, have an unfavourable social outcome which seems not be associated with their short stature. Further research is needed to discover in what phase of life these problems originate and whether GH treatment or psychosocial intervention can lead to improvement.

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References


