Quality of life of young adults with idiopathic short stature: effect of growth hormone treatment

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The aim of the study was to evaluate whether treatment with recombinant human growth hormone (rhGH) affects the quality of life of young adults who were diagnosed as idiopathic short stature (ISS) during childhood, and whether their quality of life and aspects of the personality are different from normal. Experiences and expectations concerning rhGH treatment of the subjects and their parents were also investigated. Eighty-nine subjects were included into the study: 24 subjects (16M, 8F) were treated with rhGH from childhood, whereas 65 subjects (40M, 25F) were never treated. At the time of the interview all subjects had attained final height [mean (SD) -2.3 (0.9) SDS for Dutch references], and the age of the treated subjects was 20.5 (1.0) y, and 25.7 (3.5) y of the control subjects (p < 0.001). The level of education was similar, but the treated subjects had less often a partner compared to the control subjects (adjusted for age and gender, p < 0.001). The Nottingham Health Profile and Short Form 36 Health Survey showed no difference in general health state between treated and control subjects, and the healthy Dutch age-specific references (norm group). Although 74% of the subjects reported one or more negative events related to their height, and 61% would like to be taller, only 22% and 11% were willing to trade-off at Time Trade-Off and Standard Gamble, respectively. The personality of the subjects, which was measured by the Minnesota Multiphasic Personality Inventory, was not different from the norm group. The satisfaction with the rhGH treatment was high, as it had caused 12 (8) cm and 13 (7) cm gain in final height according to the subjects and parents, respectively. Based on initial predicted adult height (Bayley & Pinneau), this gain was only 3.3 (5.6) cm. We concluded that although the treated subjects had a partner less often when compared to the control subjects, the quality of life of subjects with ISS at adult age is normal and appears not to be affected by rhGH therapy. The treated subjects were very satisfied with the treatment, probably by overestimation of the final height gain.

Growth, growth disorders, growth hormone, idiopathic short stature, quality of life

During the last decade, clinical trials with recombinant human growth hormone (rhGH) were initiated in children with idiopathic short stature (ISS), in order to improve growth and adult height. Although there is little evidence that children with ISS are psychosocially disadvantaged (1, 2), it is often assumed that as a consequence of the improvement of growth, the quality of life improves (3). Recently the first results of treatment with rhGH on final height became available, showing that the average gain in final height is only 2–4 cm (4, 5). Whether rhGH treatment influences quality of life in this group of patients was previously only studied during rhGH treatment. The results were controversial, as some studies reported an improvement (6, 7), while another study did not (8).

It is unknown whether the quality of life of young adults with ISS who underwent rhGH treatment and attained final height, is affected by this treatment. rhGH treatment might have had beneficial effects, because in most subjects growth accelerated during the first years of rhGH treatment (9), making their height more similar to that of their age mates. On the one hand, subjects may be satisfied with their actual height, as they have done everything possible to improve it. On the other hand, quality of life might be reduced at adulthood, because they have had negative experiences with the long-lasting treatment and are still short in comparison to the general population (10).

Busschbach et al. compared the quality of life of untreated short adults diagnosed as ISS in a paediatric clinic with that of short adults from the general population (11). The complaints of short adults with ISS presenting at a paediatric clinic appeared to be the result of unsuccessful coping, as these adults attribute many of their day-to-day difficulties to their short stature.
problems to their short stature, in contrast to short adults from the general population (12). This suggests that some aspects of their personality, like negativity, shyness or extroversion, may be different from a norm group.

In the present study we investigated whether the quality of life of young adults with ISS who completed rhGH treatment was different from untreated young adults with ISS. The quality of life and personality of rhGH-treated and untreated subjects with ISS were compared to a population based reference. Finally, we evaluated treatment experiences and expectations of the young ISS adults and their parents.

Patients and methods

Patients

We selected 102 subjects who were diagnosed as ISS before the onset of puberty at Dutch paediatric departments. They were at least 19 y old, and had attained final height. Final height was attained if the height velocity <0.5 cm/y calculated over at least 6 months, or if height was determined at an age of at least 19 y in females (F), and at least 20 y in males (M). The measurement of final height was performed at the local paediatric department or at the patient’s home following detailed written instructions. All subjects were invited by letter to participate in the study. Eight subjects could not be traced (incorrect address), two were mentally retarded, two refused to participate and one was severely ill. The remaining 89 subjects were included into the study (response 87%). Twenty-four of them (16M, 8F) were treated with rhGH according to two prospective multi centre studies (Study 1 and Study 2, “treated ISS group”) (9, 13), and 65 (40M, 25F) subjects were never treated and participated in a retrospective study (Study 3) on the spontaneous growth of children with ISS (“control ISS group”) (14).

The inclusion criteria of Studies 1, 2 and 3 were almost similar; height >2.5 standard deviations (SD) below the mean of the Dutch reference (15) (Study 1) or >2 SD below the mean of the British reference (16) (Studies 2 and 3), prepubertal state, and stimulated GH peak ≥15 mU/l (Study 1) or ≥20 mU/l (Studies 2 and 3), no organic cause of growth failure or dysmorphic syndrome. The studies were approved by the ethical committees of the participating centres.

Growth hormone treatment

The 13 children (6M, 7F) included in Study 1 were treated with rhGH (Somatorm, Genotropin; Pharmacia & Upjohn, Sweden; subcutaneously, 7× per week; 1 IU = 0.37 mg) in a dose of 14 IU/m²/week, which was doubled to 28 IU/m²/week if the height velocity became insufficient (n = 11). The 11 children (10M, 1F) in Study 2 were randomized into three dosage regimens groups of rhGH (Humatrope; Eli Lilly, Indianapolis, USA; subcutaneously, 6× per week; 1 IU = 0.37 mg). The first group received 18 IU/m²/week, the second group 27 IU/m²/week, and the third group 18 IU/m²/week during the y 1 and 27 IU/m²/week thereafter. Expressed per kg body weight, the rhGH dosages of both studies ranged from 0.2 to 0.3 mg/kg/week. rhGH treatment was started at a mean (SD) age of 11.6 (1.1) y (range 9.4–13.6). After 5.6 (1.1) y (range 3.8–8.1) the treatment was completed. At the time of this study the treatment was stopped 3.3 (1.4) y (range 0.1–6.3) ago.

Data collection

All subjects were asked to be interviewed at home. Seventy-one percent of the treated subjects and 72% of the control subjects agreed, and an extensive interview took place, which lasted about 1 h.

The quality of life of the subjects was estimated using three sets of measurements. The first set referred to the last completed level of education and presence of a partner. An age and gender adjusted comparison with the level of education and presence of a partner in the general Dutch population was made (17, 18). The second set consisted of multi-dimensional questionnaires of quality of life: the Nottingham Health Profile part I (NHP) (19) and the Short Form 36 Health Survey (SF-36) (20). Both questionnaires are generic and measure a person’s health state in six and eight dimensions, respectively. The NHP scores of the ISS subjects were compared to a healthy Dutch reference group, aged 21–50 y (norm group) (19). The SF-36 scores of the ISS subjects were compared to a Dutch reference group, aged 18–24 y (norm group) (20). The third set of measurements was uni-dimensional, including items that concerned the impact of short stature on the quality of life. The subjects were asked if they wanted to be taller at present (as an adult) and in the past (as a child). Then the strength of this wish was measured by means of two validated methods, Time Trade-Off (TTO) and Standard Gamble (SG), which both ask the respondent’s preference in a hypoethical situation (21). First, subjects were asked if they would be willing to take lifelong, once a day medication (TTO), or rather be subjected to surgery and 1 week hospitalization (SG), to attain the average height for Dutch adults (M: 182 cm; F: 168 cm), assuming that this would be without any risk. If so, the subjects had to indicate the maximum number of life-y they were willing to give up (TTO), or the maximum risk to die during the operation they were willing to accept (SG), to attain this goal. These questions were repeated, while assuming that the present height of the subject was at the 3rd percentile for Dutch adults (M: 169 cm; F: 157 cm). In this context, the maximum number of life-years given up, or the maximum risk to die are valid expressions of the disability of short stature (21).

Personality aspects of the subjects were investigated by means of the Dutch short form of the Minnesota Multiphasic Personality Inventory (NVM) (22), which consists of five subscales: negativism, somatization, shyness, severe psychopathology and extraversion.

Finally, the rhGH-treated subjects and their parents were
asked about their experiences with the treatment. The final height gain that was expected by the patients and parents at the start of the treatment, was compared with the final height gain as perceived by them. These values were also compared with the final height gain defined as the difference between final height and predicted adult height at start (23). The subjects who refused an extensive interview were willing to answer the main questions of the study by telephone (short interview). This lasted about 15 min. As reasons for refusing an extensive interview the subjects mentioned no interest (n = 14), no time (n = 7), or other reasons (n = 4). The questions were derived straight from the extensive interview and were about highest level of education, partnership, satisfaction with their height at childhood and adulthood, preferred height as an adult, positive and negative experiences of their height as a child or as an adult, and the TTO and SG questions. The rhGH-treated subjects and their parents were also asked about their satisfaction with the rhGH treatment, positive and negative effects of the treatment, side effects, omission of the rhGH injection, and height gain in cm caused by rhGH. Age, height, level of education, and level of satisfaction concerning their height at present or as a child were similar for the subjects with a short or an extensive interview. Thus, it is reasonable to believe that the subjects with a short interview are representative for the total sample.

Statistics

Differences between the rhGH-treated and control subjects were tested by Student’s unpaired t-tests, in case of normally distributed variables, or Mann–Whitney’s U and Pearson’s χ² tests, in case of a skewed or ordinal variables. Comparison of the educational level and partnership with the Dutch general population was also performed by Pearson’s χ² tests. Differences in the quality of life measures between the treated and control subjects were adjusted for age and gender (confounding) in a linear or logistic regression analysis. The mean and standard deviation (SD) were presented, unless otherwise indicated. Significance level α was 0.05.

Results

Table 1 presents the baseline parameters, partnership and level of education. There was no significant difference with respect to gender distribution or height between the rhGH-treated and the control group. The number of subjects with a present height above the 10th percentile for Dutch references, was 3 in the treated group (13%), and 5 in the control group (8%). The mean height gain of the treated subjects, based on the initial predicted adult height, was 3.3 (5.6) cm (range -9.9–13.4 cm). At the time of the interview the age of the treated subjects was on average 5.2 y younger than the age of the control subjects. The proportion of subjects with a partner was lower in the rhGH-treated group than in the control group (Table 1; M: p = 0.001; F: p < 0.01). After adjustment for age and gender in a logistic regression analysis, the difference in presence of a partner remained significant (p < 0.001). Comparison of partnership of the treated and control ISS subjects with the Dutch general population, with correction of gender and age, revealed no significant differences. The last completed level of education did not differ between treated and control subjects. The educational level of subjects was similar to the age and gender adjusted level of education in the Dutch general population.

Multi-dimensional quality of life

The general health state of the subjects was measured by the NHP and SF-36 questionnaires. The majority of the subjects had a score of zero (no complaints) on the various dimensions of the NHP. Therefore, the scores were dichotomized. In a logistic regression analysis with adjustment for age and gender, no differences between the treated and the control group were found for any of the dimensions. Comparison of the ISS subjects with the norm group yielded similar results (data not shown). The mean scores of two dimensions of the SF-36 (Bodily Pain and Health Change) were significantly different between the groups (with adjustment for age and gender; p < 0.05). However, these mean scores, like the mean scores for the remaining dimensions of the SF-36, were similar to those of the norm group. The scores for the Health Change dimension of the rhGH-treated subjects did not correlate with the duration between the end of the treatment and time of interview (data not shown).

Uni-dimensional quality of life

In Table 2 the results of the impact of short stature on the quality of life are presented. The percentage of the subjects who described their actual height as shorter than average was lower in the treated group than in the control group (p = 0.02). The large majority of the subjects stated that
they were satisfied with their present height. The degree of satisfaction with their height was not significantly related to the subject group, actual height, gender, and age in a logistic or linear regression model (data not shown).

The majority of the subjects, however, would like to be taller, if this was possible (Table 2). Of these subjects, 69% would like to be 1–10 cm taller, whereas 31% would like to be at least 10 cm taller. This did not differ significantly between the groups. Despite this wish, only a minority of both the treated and control subjects was willing to make any trade-off. Thirty-nine percent of the subjects preferred to attain an average height by taking medication (TTO) without any loss of life-years rather than keeping their actual height. Thirty-eight percent preferred an operation (SG) without any risk rather than keeping their actual height. If they would live shorter by taking medication, 22% of the subjects would still choose the medication. The median number of life-years they were willing to give up was 5 y, ranging from 1 to 24 y. If there was a risk to die during the operation, 11% of the subjects still wanted an operation. The median risk to die they would accept was 1:1000, ranging from 1:2000 to 1:5. If the subjects assumed that their actual height was at the 3rd percentile for Dutch standards, similar results were obtained (data not shown).

Both rhGH-treated and control subjects reported that as a child they were less satisfied with their height than at present (p = 0.005 and p < 0.001, respectively) (Table 2). Forty percent of the subjects said that at that time they would have made a higher trade-off in TTO or SG than at present. The responses of the rhGH-treated and control subjects were similar.

### Problems related to short stature and personality

Seventy-four percent of the subjects were able to come up with one or more negative events. In the extensive interview detailed questions concerning problems related to short stature were asked. Because of their short stature, subjects were often teased at school (25%), or often heard teasing remarks at present (19%). During childhood, 38% of the subjects were often treated as a younger person. As an adult, this hardly happens, as only 5% of the subjects reported that they were often treated as younger than they were. Professional help because of psychological problems with their height was asked by 6% of the subjects. Seventeen percent of the subjects stated that their stature restrained them from having the occupation they preferred, and 16% stated that a job that they wanted was refused because of their short stature. No significant difference between the treated and the control subjects with ISS was observed in any of these problems.

In Table 3 various aspects of the personality of the treated and control subjects with ISS and a norm group are shown. The personality of the treated and control subjects was similar, and did not differ from the norm group in any of the measured aspects.

### Table 2. Impact of short stature on the quality of life of rhGH-treated and control children with ISS. The percentage of subjects is presented.

<table>
<thead>
<tr>
<th></th>
<th>Treated (n = 24)</th>
<th>Controls (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As an adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height is smaller than average</td>
<td>54*</td>
<td>79</td>
</tr>
<tr>
<td>Satisfied with height</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>Would like to be taller</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Willing to take medication if risk is 0% in Time Trade-Off</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>Willing to take medication if risk is &gt; 0% in Time Trade-Off</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Willing to be operated if risk is 0% in Standard Gamble</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Willing to be operated if risk is &gt; 0% in Standard Gamble</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>As a child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfied with height</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Take more risk with medication in Time Trade-Off than as an adult</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Take more risk at operation in Standard Gamble than as an adult</td>
<td>42</td>
<td>40</td>
</tr>
</tbody>
</table>

Treated vs control subjects: *p < 0.05.

### Table 3. The mean (SD) values for dimensions of the Dutch restricted version of the Minnesota Multiphasic Personality Inventory (NVM) for rhGH-treated and control children with ISS.

<table>
<thead>
<tr>
<th>Dimensions of the NVM</th>
<th>Treated ISS (n = 17)</th>
<th>Controls ISS (n = 47)</th>
<th>Standard population (n = 809)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negativism</td>
<td>17.9 (10.3)</td>
<td>15.7 (9.7)</td>
<td>14.7 (7.7)</td>
</tr>
<tr>
<td>Somatization</td>
<td>5.9 (6.6)</td>
<td>4.7 (4.4)</td>
<td>5.3 (5.3)</td>
</tr>
<tr>
<td>Shyness</td>
<td>8.6 (7.5)</td>
<td>9.6 (7.6)</td>
<td>8.0 (6.4)</td>
</tr>
<tr>
<td>Severe psychopathology</td>
<td>3.1 (2.4)</td>
<td>2.7 (3.5)</td>
<td>2.7 (2.7)</td>
</tr>
<tr>
<td>Extraversion</td>
<td>20.4 (5.1)</td>
<td>19.7 (4.8)</td>
<td>17.1 (5.3)</td>
</tr>
</tbody>
</table>
Experiences and expectation of the rhGH treatment

The subjects reported that they had seldom (41%), or never (53%) problems with the rhGH injections. Twenty-five percent of the subjects stated that they omitted the rhGH injection sometimes (≥1 times a month). Overall, rhGH treatment was well tolerated. Three subjects reported side effects like acne, hirsutism and uncontrolled growth of scar tissue. The parents gave similar answers to these questions.

The large majority of the subjects and their parents (both 88%) was satisfied with the rhGH treatment, because they thought that rhGH had resulted in a substantial final height gain. At the start of treatment, the parents expected that rhGH would increase the adult height of their child by an average of 16 (7) cm, ranging from 7 to 30 cm. According to them, the actual final height gain was on average 13 (7) cm, ranging from 0 to 28 cm. According to the subjects, the actual final height gain was 12 (8) cm, ranging from 0 to 35 cm.

Discussion

In this paper we demonstrate that the quality of life of rhGH-treated and untreated young adults with ISS was similar, and equal to the general population. The only remarkable difference between both groups was that rhGH-treated subjects were less likely to have a partner. Three quarters of the ISS subjects reported a negative event in relation to their stature. Their personality was not different from the general population. Almost all rhGH-treated subjects were satisfied with the treatment, because they believed that it had resulted in a substantial final height gain. This was in contrast to height gain calculations based on the initial predicted adult height.

The influence of the retrospective nature of the control group on the results of our study is probably limited. These subjects fulfilled the same inclusion and exclusion criteria as the treated subjects. As the control subjects were older, and nobody was asked to participate in a study on rhGH treatment, the difference between the groups seems to be only a matter of time. Thus, it is reasonable to believe that the control group is appropriate for comparison with the treated group.

The validity of the measurement of height at home has been reported in another study of our group (14). In a sample of 30 subjects we showed that the validity is good. The mean difference between reported and measured final height was only 0.5 cm.

With regard to partnership we found that the proportion with a partner in the rhGH-treated group was less than in the control group, although no difference with the Dutch general population could be demonstrated. An explanation might be that long-term rhGH treatment might delay the development of independence in adolescence. Our results concerning level of education in young adults with ISS are in line with those reported by Rikken et al. (24), who found no differences in partnership and level of education between subjects with untreated ISS and subjects with an average stature. Busschbach et al. (11) reported no difference in level of education between adults with short stature of several diagnostic groups. In both studies no comparison with the Dutch general population was made.

Quality of life measured by the NHP or SF-36 has the advantage that various diseases can easily be compared. Their disadvantage is that sensitivity to detect small differences between two health states is limited. Although the SF-36 is more sensitive than the NHP in measuring a health state that is expected to be quite similar to health state of the general population (25), we could not demonstrate that the general health state of both treated and control ISS subjects is different from the norm group. Our observations supplement those of Busschbach et al. (11), who demonstrated that the scores for the NHP dimensions of untreated ISS subjects were not different from subjects with growth hormone deficiency, Turner syndrome, renal failure or normal short persons sampled from the general population.

Although the large majority of the subjects stated to be satisfied with their present height, almost all subjects would like to be taller, if this was possible. This indicated a silent wish of the subjects, while they reconciled themselves to the situation. The wish to be taller appeared to be weak. This can be deduced from the small proportion of subjects who were willing to make a trade-off in TTO or SG to obtain an average height. During childhood or adolescence, their short stature was a bigger problem than it is at adulthood. Our results correspond with those of Crowne et al. (26, 27).

The results of the TTO and SG indicated that the quality of life of ISS subjects was hardly different from that of the general population. In particular, the maximum risk of dying during the operation (SG) appeared to be difficult to establish in ISS subjects, because the risks hardly differed from zero. As small probabilities are difficult for subjects to use (28), the validity of this method in our study population is limited. Therefore comparing the TTO and SG scores of our study population, with that of other health disorders, should be performed with caution.

Although about three quarters of the subjects reported at least one negative event in relation to their short stature, in about one fifth this was rated as an important negative event. These proportions were similar to those observed by Crowne et al. (26, 27). The ISS subjects are apparently able to manage these experiences well, since no reduction in quality of life compared to the norm group could be demonstrated. Our findings in young adults with ISS are compatible with findings in children with ISS. Twenty percent of the ISS children were teased at school and 27% were treated as being younger than their age (29).

No differences in peer acceptance, self perception and social competence between short-statured children and their classmates were found (1). Downie et al. (8) also demonstrated that self esteem, self-perception and behaviour of ISS children were similar to children of average stature. These studies indicate that also during childhood...
most of the ISS children are able to cope with the negative events well. The satisfaction with the treatment of the subjects and their parents was high. The final height gain caused by rhGH treatment according to the opinion of the subjects and their parents was remarkably higher than if the final height gain was based on the initial predicted adult height. Besides, the rhGH-treated subjects perceived their stature as significantly taller than the control subjects did. Downie et al. (8) showed that after 5 y follow-up, both rhGH-treated and untreated ISS children had unrealistically high expectations about their final height. They also found that the perceived height of the treated children was higher than that of the untreated children. During treatment, the level of satisfaction with the treatment was also high (30). To what extent this is influenced by coping, and by the opinion of their paediatrician remains unclear.

In conclusion, three-quarters of ISS subjects have had a negative experience because of their short stature. This did not result in a reduced quality of life in comparison to the norm group. Treatment with rhGH did not improve the quality of life. In spite of this, rhGH-treated subjects reported feeling very satisfied with the treatment.

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References

17. Latten JJ, Cuyvers PF. Relatie- en gezinsvorming in de jaren negentig, Voorburg: Centraal Bureau voor de Statistiek, 1994

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