The Impact of Growth Hormone Therapy on Adult Height in Noonan Syndrome: A Systematic Review

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Noonan syndrome · Growth hormone treatment · Adult height · Systematic review · Clinical trials

Abstract

Background: Recombinant human growth hormone (rhGH) is being used to promote linear growth in short children with Noonan syndrome. However, its efficacy is still controversial.

Aims: To systematically determine the impact of rhGH therapy on adult height in children with Noonan syndrome.

Methods: We searched the Cochrane Central Register of Controlled Trials, ISI Web of Science, MEDLINE, and the bibliographic references from all retrieved articles published until April 2014. Studies reporting adult/near-adult height in children with Noonan syndrome treated with rhGH or reporting at least a 3-year follow-up were analysed. Quality and strength of recommendation were assessed according to the Endocrine Society criteria.

Results: No controlled trials reporting adult height were available. Five studies were identified reporting adult height or near adult height. Data comparison showed inter-individual variability in the response to rhGH, mean height gain standard deviation score ranging between 0.6 and 1.4 according to national standards, and between 0.6 and 2 according to Noonan standards. Significant biases affected all the studies. Conclusions: High-quality controlled trials on the impact of rhGH therapy on adult height are lacking, and the robustness of available data is not sufficient to recommend such therapy in children with Noonan syndrome.

Introduction

Recombinant human growth hormone (rhGH) is prescribed in several conditions affecting stature [1, 2] to increase linear growth and adult height (AH), even in conditions not associated with impairment of growth hormone (GH) secretion [3, 4]. rhGH in Noonan syndrome (NS) was initially proposed in the 1980s [5–7]; however, the benefit of long-term therapy is still uncertain in this condition. Whilst rhGH in NS has been approved by the Food and Drug Administration in 2007, this indication has not been approved by the European Medicines Agency. This conflicting attitude may be confusing to physicians and specialists involved in the care of children with NS, resulting in a non-uniform care...
strategy in different countries and even within the same health care system.

NS is an autosomal dominantly inherited syndrome [8] with an incidence of 1:1,000–1:2,500 live births with an equal male to female ratio [9]. Most of the cases are due to de novo mutations of the PTPN11 gene (OMIM 176876) [10, 11]. Short stature is one of the main features with over 83% of patients affected. Phenotype is also characterised by dysmorphic facial features (ptosis, hypertelorism, webbed neck, down-slanting palpebral fissures), congenital cardiac defects (pulmonary stenosis, left ventricular hypertrophy), mild and variable developmental delay [9]. Growth retardation becomes evident in early infancy and is worse over the second decade of life. Half of the affected adults are below the 3rd centile for height [12]. Children with NS are mostly GH sufficient but may have a reduction in circulating insulin growth factor-1 [13], especially those with PTPN11 mutations [14]. PTPN11 encodes for the non-receptor-type protein tyrosine phosphatase, Src homology region 2-domain phosphatase-2 (SHP-2) [15]. Mutations result in a gain of function of SHP-2, which acts on the GH receptor (GHR) signalling pathway as a negative regulator [16].

To provide caregivers and policy makers with rigorous evidence-based information, we have performed a systematic review of the literature on rhGH efficacy in children with NS.

**Methods**

**Search Strategy and Inclusion Criteria**

We searched the Cochrane Central Register of Controlled Trials, ISI Web of Science, MEDLINE, and the bibliographic references from all retrieved articles describing such trials up to May 2014, using the search terms 'growth hormone' and 'Noonan syndrome' and 'adult height'. Only articles in English were considered. Height was expressed as standard deviation score (SDS) according to national references and specific Noonan standards [12]. Inclusion criteria were: (a) clinical diagnosis of NS; (b) height SDS below –2 according to national reference standards; (c) no other causes for short stature; (d) normal karyotype in females. Pubertal status and response to GH stimulation tests were not considered in the recruitment criteria. Puberty onset was defined as Tanner breast stage of at least 2 in females, and testicular volume of at least 4 ml in males. rhGH was administered as daily subcutaneous injections, and dosage was adjusted for changes in weight. AH was defined when the height velocity <2.5 cm/year. We decided to also include in the analysis the controlled trials (CTs) with long-term follow-up defined as a time duration of at least 3 years.

**Efficacy Outcome Measures and Quality Assessment**

Consistent with the results of our previous systematic review on the impact of rhGH on AH of children born small for gestational age (SGA) or with idiopathic short stature [3, 17], we considered a mean difference in AH between treated and untreated children of more than 0.9 SDS (about 6 cm) as a satisfactory response to rhGH therapy. This value was chosen as it represents the mean difference in AH between rhGH treated and untreated children born SGA [3].

In non-randomised trials, the only way to determine rhGH efficacy was to compare height gain (ΔH) SDS defined as the difference between the height at the end and at start of rhGH treatment. Most authors have considered Noonan-specific standards to assess the mean ΔH during treatment.

Lack of data or non-detailed reporting was considered as bias affecting the assessment of growth outcome and quality of the investigation. With regard to the controlled study reporting neither AH nor NAH, the efficacy outcome measures were 1st-year height velocity and ΔH from inclusion to the end of follow-up (at least ≥1 SDS).

Randomised CTs (RCTs) allow decision makers to draw causal inferences linking interventions and outcomes with protection against bias. Therefore, RCTs begin with a ‘high quality’ rating. The strength of a recommendation reflects the degree of confidence that the desirable effects of a recommendation outweigh the undesirable effects. Desirable effects can include beneficial health outcome, less patient burden, and cost savings. Undesirable effects can include harm, more patient burden, and expenses. According to the Endocrine Society [18] a scientific trial should be evaluated and classified into one of two grades (strong and weak) of recommendation, and the quality of the evidence into one of four categories (high, moderate, low, and very low). On this basis, grading was assigned to each study.

**Statistical Analysis**

All the parameters listed in table 1 were calculated and reported as means ± SDs, when available. When individual data were not available, the missing means were calculated by the weighted mean of the subgroups according to the following formula: mean = [(m m · n m ) + ( m f · n f )]/(n m + n f ), where m m and m f are the means reported for the male and female subgroups, respectively; n m and n f are the cohort sizes of the male and female subgroups, respectively. SD was calculated by the weighted mean of the SDs available, the missing means were calculated by the weighted mean of the subgroups according to the following formula: mean = [(m m · n m ) + ( m f · n f )]/(n m + n f ), where m m and m f are the means reported for the male and female subgroups, respectively; n m and n f are the cohort sizes of the male and female subgroups, respectively. SD was calculated by the weighted mean of the SDs reported for gender, according to the following formula: SD = [(sd m · (n m – 1)) + [sd f · (n f – 1)])/((n m + n f ) – 2), where sd m and sd f are the SDs of the male and female subgroups, respectively. The SPSS 17.0 computer program was used for all statistical calculations (SPSS Inc., Chicago, Ill., USA). Significance was assigned for p < 0.05.

**Results**

The search strategy identified 23 pertinent studies published between 1987 and 2009 (fig. 1). Seventeen studies were excluded; 3 were case reports, 9 reported a follow-up period <3 years, 5 reported a follow-up period >3 years but were not controlled. Only one study was con-
Table 1. Characteristics, results, and quality grading of non-randomised non-controlled trials and retrospective studies on final and near-final height after rhGH therapy in children with NS

<table>
<thead>
<tr>
<th>Rand Ctrls</th>
<th>Outcome</th>
<th>n</th>
<th>Age at start of therapy</th>
<th>Dose range, mg/kg/day</th>
<th>Duration of therapy</th>
<th>Height at start</th>
<th>FH or NH for national reference</th>
<th>Height gain for national standard</th>
<th>p</th>
<th>Height gain for Noonan standard</th>
<th>Grading</th>
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</thead>
<tbody>
<tr>
<td>Kirk et al. [23]</td>
<td>No No NAH</td>
<td>10</td>
<td>10.2±3.3</td>
<td>0.025–0.05</td>
<td>5.3±1.8</td>
<td>-3.1±0.6</td>
<td>-2.3±0.6</td>
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<td>0.6±0.4</td>
<td>Low quality</td>
</tr>
<tr>
<td>Males</td>
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<td>n.a.</td>
<td>0.03–0.06</td>
<td>7.5±1.3</td>
<td>-2.9±0.4</td>
<td>-0.7±0.6</td>
<td>0.8±0.3</td>
<td>0.001</td>
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</tr>
<tr>
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<td>-2.6±0.8</td>
<td>0.4±0.6</td>
<td>0.001</td>
<td>0.6±0.4</td>
<td>Very low quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-marketing study</td>
<td>n.a.</td>
<td>6.0±2.6</td>
<td>-3.8±0.5</td>
<td>-2.3±0.6</td>
<td>0.8±0.7</td>
<td>0.001</td>
<td>0.6±0.4</td>
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<td>Osio et al. [20]</td>
<td>No No AH</td>
<td>18</td>
<td>8.2±3.0</td>
<td>0.03–0.06</td>
<td>7.5±1.3</td>
<td>-2.9±0.4</td>
<td>-1.2±1.0</td>
<td>1.7±0.9</td>
<td>0.001</td>
<td>1.6±0.9</td>
<td>Low quality</td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
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<td>7.5±1.3</td>
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<td>-0.9±1.2</td>
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<td>1.6±0.9</td>
<td>Very low quality</td>
<td></td>
<td></td>
</tr>
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<td>1.6±0.9</td>
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<td></td>
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<tr>
<td>Noordam et al. [21]</td>
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<td>-2.8±0.7</td>
<td>-1.5±0.8</td>
<td>1.3±0.7</td>
<td>&lt;0.0001</td>
<td>1.3±0.7</td>
<td>Very low quality</td>
</tr>
<tr>
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<td>7.5±1.3</td>
<td>-2.8±0.7</td>
<td>-1.5±0.8</td>
<td>1.3±0.7</td>
<td>&lt;0.0001</td>
<td>1.3±0.7</td>
<td>Very low quality</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>9.7±2.9</td>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.001</td>
<td>1.3±0.7</td>
<td>Very low quality</td>
<td></td>
</tr>
<tr>
<td>Prospectve study</td>
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<td>7.5±1.3</td>
<td>-2.8±0.7</td>
<td>-1.5±0.8</td>
<td>1.3±0.7</td>
<td>&lt;0.0001</td>
<td>1.3±0.7</td>
<td>Very low quality</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Raaijmakers et al. [24]</td>
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<td>24</td>
<td>10.1±3.4</td>
<td>0.03–0.06</td>
<td>7.6±1.3</td>
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<td>0.6±0.4</td>
<td>0.97±0.4</td>
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<td>n.a.</td>
<td>n.a.</td>
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<td>0.97±0.4</td>
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<tr>
<td>Females</td>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.97±0.4</td>
<td>1.5±0.5</td>
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<td></td>
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<tr>
<td>Post-marketing study</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.97±0.4</td>
<td>1.5±0.5</td>
<td>Very low quality</td>
<td></td>
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<tr>
<td>Romano et al. [22]</td>
<td>No No NAH</td>
<td>65</td>
<td>11.6±3.0</td>
<td>0.03–0.06</td>
<td>6.6±2.6</td>
<td>-2.3±0.7</td>
<td>0.8±0.4</td>
<td>1.4±1.0</td>
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<td>Very low quality</td>
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<tr>
<td>Males</td>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.001</td>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.001</td>
<td>1.5±0.5</td>
<td>Very low quality</td>
<td></td>
</tr>
<tr>
<td>Post-marketing study</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.001</td>
<td>1.5±0.5</td>
<td>Very low quality</td>
<td></td>
</tr>
</tbody>
</table>

rhGH dose is presented as range according to doses showed in the original articles. Rand = Randomization; Ctrls = control group; n = number of patients suitable for the purpose of review; n.a. = not available because data not reported in original article. Age at start of therapy and duration of treatment are in years (decimals) and showed as mean ± SD, when available. Height at start, AH, NAH are showed as mean SDS ± SD, when available. Height gain for the national standard and the Noonan standard are presented as mean ± SD, when available. AH was defined as height velocity over last year of follow-up <1 cm/year. NAH was defined as an age at least over 14 years for females and 15 years for males with a height velocity <2.5 cm/year. In the study by Romano et al. [22], NAH was defined according to age and bone age of ≥14 years for females and 16 years for males. Data were considered statistically significant when p ≤ 0.05. * Data reported in original articles. † Data re-calculated and weighted means calculated from the original data.
trolled with a follow-up ≥3 years, but not randomised and without a placebo control group [19]. Neither AH nor NAH were reported. Finally, 5 studies reported AH or NAH [20–24], but none of them was an RCT: two were longitudinal prospective trials [20, 21] and 3 were longitudinal retrospective studies based on post-marketing studies [22–24]; 2 of these were from the same database [23, 24].

Controlled Trials

The study by MacFarlane et al. [19] was the only CT reporting data from 31 children (23 treated, 8 untreated), but no information was available on the method of randomisation. The mean chronological age at start of therapy was 7.4 ± 1.6 years (range 4.8–13.7) for treated children, and 9.0 ± 4.1 years (range 4.1–14.8) for untreated children. 5 boys (3 treated, 2 untreated) were in early puberty. The rhGH dose was the same for all treated children (0.047 mg/kg/day) and was adjusted according to changes in weight. Among the 23 treated patients, 19 completed a 3-year period of rhGH treatment. Pretreatment mean height SDS was −2.7 ± 0.4 for treated children and −2.7 ± 0.6 for untreated children. After 3 years of treatment, mean height SDS in the treated group was not significantly different from that of the untreated group: −1.9 ± 0.9 vs. −2.4 ± 0.7 (p = 0.25). Height velocity over the 1st year of treatment was significantly higher in the treated than in the untreated group (8.4 ± 1.7 vs. 5.6 ± 1.4 cm/year, p < 0.001), but not over the 2nd and 3rd years of treatment (6.2 ± 1.7 vs. 5.7 ± 0.9 cm/year, p = 0.4, and 5.8 ± 1.7 vs. 5.3 ± 1.1 cm/year, p = 0.5, respectively). After exclusion of pubertal children, the difference in height SDS at the end of therapy between treated (−1.9 ± 0.8) and untreated (−2.5 ± 0.8) patients remained not significant (p = 0.15). Mean height gain in SDS was 0.8 in the treated and 0.3 in the untreated group. Over the 3-year follow-up, the treated group gained an average of 3.3 cm more than the untreated group.

Uncontrolled Prospective Trials and Post-Marketing Studies

Adult Height

Two out of 5 studies without a control group reported AH [20, 21]. The inclusion criteria for these studies were similar, and 47 children (28 boys, 19 girls) were assessed for AH out of 62 enrolled. Results from each study are shown in table 1. Thorough individual anthropometric data were reported only in one study (table 2). The mean age at start of therapy was 9.9 ± 2.8 years. The mean duration of therapy was 6.8 years, but SD was not estimable due to lack of data. All but 4 patients were prepubertal. The dose of rhGH ranged from 0.033 to 0.066 mg/kg/day (mean ± SD not available). The mean height SDS at start of therapy was −2.8 ± 0.6, and the mean AH SDS was −1.4 ± 0.9. The mean AH SDS for gender was not calculable due to lack of data.

Near-Adult Height

Three out of 5 studies without a control group reported NAH [22–24]. Overall, 842 patients were enrolled, but NAH was only available in 99. Results from each study are listed in table 1. Criteria for defining the NAH was similar in all but one study, in which NAH was assessed according to bone age that was not available for all patients at the last visit, and was arbitrarily estimated adding to the last available measure the time passed up to the last visit, with an interval ranging from 1.1 up to 3 years. Detailed individual data were reported only in one study. In one study, rhGH dose was not reported in the patients who achieved NAH. The provided data were insufficient to
calculate NAH. From the 2 remaining studies, the mean rhGH dose was 0.045 ± 0.007 mg/kg/day. The mean age at start of treatment was 11.1 years, whilst the mean duration of treatment was 6.3 years.

In 1 out of 3 studies, the NAH was only showed in a graphic, not permitting a reliable interpretation. The mean NAH SDS from the remaining 2 studies was –2.1 ± 0.9. A reliable interpretation of the gender differences was not possible due to the lack of the SDs data.

Height Gain

Among the studies reporting AH, mean ΔH SDS was 1.4 ± 0.8, corresponding to 9.5 ± 5.4 cm. In particular, in the trial reported by Osio et al. [20], the mean ΔH SDS was 1.7 ± 0.9, corresponding to 11 ± 6 cm (13 ± 7.2 in males, 9.8 ± 5.2 cm in females), with a mean gain in height velocity of 1.4 cm per year of treatment. Noordam et al. [21] reported a mean ΔH SDS of 1.3 ± 0.7, corresponding to 8.6 ± 5 cm (gender difference not available), with a mean gain in height velocity of 1.3 cm per year of treatment.

In 1 out of the 3 studies reporting NAH, ΔH SDS was reported without SDs, both for national and Noonan standards [24]. The ΔH SDS, calculated from the 2 remaining studies, was 1.3 ± 0.9, corresponding to 8.6 ± 5.9 cm (range 5.3 ± 2.5 to 9.3 ± 6.6). The mean gain in height velocity was 1.5 cm per year of treatment. Analysis of the gender difference was affected by the lack of SDs in 2 out of the 3 studies. An ad hoc analysis for assessing significant difference in height gain was feasible in 1 study only and yielded a significant difference in height gain (p = 0.001). Any analysis regarding the ΔH according to Noonan reference standards was not feasible due to the lack of the SDs in 2 out of the 3 studies. The mean height gain in NAH above projected mean SDS was 1.4 (range 0.6–1.5 SDS, corresponding to 3.1–10.1 cm). In all studies, rhGH dose was never significantly correlated with the response to treatment, nor was genotyping in the studies in which it was performed.

AH Corrected for Mid-Parental Height

Among the studies assessing AH, the mean height SDS corrected for MPH before treatment improved from –2.2 ± 0.9 to –0.8 ± 0.9 in the study by Noordam et al. [21], and from –2.4 to –0.7 (SDs not available) in the study by Osio et al. [20].

Only 1 study from the 3 reporting NAH assessed ΔH and NAH corrected for MPH, and only 3 patients achieved their MPH.

Dropout Rate

With regard to the studies reporting AH, only 1 patient (5.3%) dropped out because of a lymphoma in the trial by Osio et al. [20], whilst 9 patients (23.7%) were lost to follow-up and not included in the final analysis in the study by Noordam et al. [21]. The mean ΔH in these patients was 0.42 ± 0.3 and 0.15 ± 0.3 SDS over the 1st and 2nd years of treatment, respectively.

Among the studies reporting NAH, 128 patients (31.8%) discontinued rhGH treatment before achieving NAH in the study by Raaijmakers et al. [24]. Height ve-
locity during the 1st year of treatment was lower in patients lost to follow-up than in patients who completed the treatment. In the study by Kirk et al. [23], 56 patients (84.8%) were lost to follow-up before achieving NAH, and the reasons were not entirely disclosed. Lost to follow-up rate was not reported by Romano et al. [22]. Voluntary withdrawal and poor response to the treatment were common reasons to stop treatment.

Finally, considering the whole NS population in which rhGH therapy was started, data on AH or NAH are available in only 146 out of the initially enrolled 907 patients (fig. 2).

Quality of Evidence and Strength of Recommendation

According to the Endocrine Society criteria, cohort studies without an RC group start with a low-quality level but may be upgraded in certain situations, e.g. when the magnitude of the treatment effect is very large. Several biases (table 2) in all uncontrolled studies affecting the quality of data and the wide variability in the response to the treatment do not allow to demonstrate a significant effect of rhGH therapy on AH in NS patients. Very low quality was assigned to 3 studies because of the incompleteness of data reporting and the consequent impossibility to implement data for carrying out a proper statistical analysis. Low quality was assigned to the remaining 2 studies, mainly due to a better data reporting accuracy that makes results replicable or suitable for comparison with a historical control group. A weak recommendation was assigned to all studies due to the low quality level and the high variability of results as variability reduces the degree of confidence in the estimate of efficacy.

Discussion

This systematic review of rhGH trials and retrospective studies in children with NS shows the lack of published RCTs providing data on the effect on AH or NAH. The only CT was the study of MacFarlane et al. [19] reporting a 3-year follow-up and not providing data on AH. An acceleration of height velocity was observed in the treated group only in the 1st year of treatment, with no significant difference in height gain after 3 years of therapy compared to the untreated group. The small cohort size and rhGH dose, similar to that used in GH-deficient patients, have been proposed as potential explanations. The uncontrolled studies, however, reported rhGH doses and patient cohorts similar to those described by MacFarlane et al. [19] (table 1). Due to the lack of high-quality RCTs, data from uncontrolled longitudinal and retrospective studies reporting AH or NAH were included in this review. However, the use of both national references and NS references represents a major bias affecting results in the absence of a matched control group. The comparison of height gain to national references may affect the results as delayed puberty frequently occurs in children with NS.

Previous studies have shown that catch-up growth may occur in late adolescence and that an AH greater than –2 SDS can spontaneously be achieved in 60% of males and 50% of females with NS [25], whilst short stature is present in the 83% of prepubertal children with NS. Indeed, the delayed pubertal growth spurt may account for at least part of the observed height gain.

With regard to the Noonan references, the most commonly used growth standards [12] were based on 20 males with mean AH 163.2 ± 5.4 cm, and 13 females with mean AH 152.3 ± 5.7 cm (fig. 3). Considering the first report on height gain from birth to adulthood in NS [26], the study cohort was even smaller and the SDs were different, although mean final heights were comparable (9 males, AH 161 ± 8.5 cm; 19 females, AH 150.5 ± 6.2 cm; fig. 3).

A re-assessment of AH in the same NS population studied 25 years later revealed an additional spontaneous late height gain leading to a higher AH, 6 cm in males (mean AH of 169.2 cm) and 2 cm in females (mean AH

Fig. 2. Whole population with NS initially enrolled in studies providing AH/NAH. Other reasons for dropping out included non-compliance, lost to follow-up, parent’s decision, other medical issues.
Males showed a catch-up growth still in the third decade of life, whilst females showed a spontaneous height gain of +1 SDS in the second decade of life (Fig. 3) [27]. This spontaneous height gain exceeds the value of 0.9 SDS that we set as a satisfactory response to rhGH therapy. It is noteworthy that rhGH therapy could be started a few years before the onset of the delayed puberty, especially in girls (Table 1).

The lack of robust data on growth trajectories in patients with NS may affect the interpretation of growth responses to rhGH therapy, especially in studies without untreated control group. In 2 studies, mean ΔH SDS was below 0.9 according to national references, whereas according to Noonan’s reference, mean ΔH was equal to or lower than the chosen cut-off value of 0.9 SDS (Table 1). In neither of the 2 studies were SDs from the mean reported. The 3 remaining studies reported a mean ΔH higher than 0.9 SDS according to either the national or the NS reference. However, a wide individual variability in height gain was observed (Table 1). Osio et al. [20] described the best outcome with half of the dose used by Raaijmakers et al. [24]. This finding suggests that, in case of unsatisfactory response to treatment, the increase in rhGH dose may be an unsuccessful strategy. In the study of Romano et al. [22], the duration of treatment has been positively associated with ΔH. Noordam et al. [21], however, reported a higher ΔH with a shorter therapy duration than those reported by Raaijmakers et al. [24].
The genetic heterogeneity of the study population may represent a further confounder for the individual variability of response to rhGH therapy. Although it was initially felt that the PTPN 11 marker might be a negative prognostic marker of growth response based on knowledge of the RAS/MAPK pathway and a 3-year trial [13], a subsequent long-term AH study demonstrated that there was no difference in response [21]. Indeed, in all studies providing genotyping and assessed in this review, children without PTPN11 mutation did not achieve a significantly higher AH than those with mutation.

It is noteworthy that among all the studies only 16% of enrolled patients were suitable for AH or NAH assessment. While it seems reasonable to assume that part of them were still on treatment when data were published, at the same time a considerable and significant proportion of patients dropped out of the studies, probably due to the poor response to treatment. Certainly, registry studies also have more study discontinuations due to uncontrollable things like patient’s moving and leaving the investigator. Nevertheless, the high dropout rate may substantially affect the interpretation of the results, limiting the analysis to the subgroup of patients with the greatest benefit from the rhGH treatment.

The efficacy of rhGH in NS was compared to that observed in other conditions where rhGH therapy is licensed. Romano et al. [22] reported a ΔH in Noonan children similar to that observed in girls with TS (1.4 vs. 1.2 SDS, respectively). However, the AH spontaneously achieved by patients with NS is higher than that observed in Turner syndrome, and pubertal spurt is not equally affected [28].

Safety of rhGH Therapy and Quality of Life

None of the published studies has reported serious adverse effects of rhGH therapy. In particular, no effects on the cardiovascular congenital abnormalities associated with NS were recorded, and no increase in the incidence of NS comorbidities was described.

The potential relationship between GH therapy and risk of neoplasms requires long-term surveillance even after treatment discontinuation, especially in children with intrinsic risk of malignancy due to their genetic disease such as NS [29, 30].

Information on quality of life in patients with NS is scarce. Untreated adults with NS have significantly lower education and graduation achievements than the general population. Mild intellectual impairment may explain the reported lower educational level. However, the perceived quality of life, as assessed by the SF-36 questionnaire, is comparable to that of the age-matched reference cohort [27]. These findings should be taken into account when considering rhGH therapy in patients with NS and PTPN11 mutations, who show an intrinsic 3.5-fold higher risk of cancer than the general population [31].

Implications for Caregivers and Policy Makers

Our review provides the caregivers with an accurate update on the available evidence supporting rhGH indication in NS. This current evidence suggests that rhGH therapy in patients with NS is safe, but the efficacy in increasing AH is still doubtful. We suggest that rhGH should be prescribed exclusively within a well-designed RCT protocol to avoid long, burdensome, expensive and even potentially harmful treatments in the long term.

Although an economic analysis is out of the scope of this review, treatments burdened by a high dropout rate involve a low benefit/cost ratio due to the unproductive investment of resources. Practitioners and policy makers need to address the clinical importance and value of the height gained in relation to the goals of treatment, including the impact of height on physical and psychosocial wellbeing, adverse effects, cost of therapy, and patients' expectations.

Limitations

A limitation to this systematic review is the extreme heterogeneity of available reports, which has not allowed a proper statistical analysis of the whole cohort of enrolled patients. This highlights the difficulty in achieving a definitive conclusion on rhGH efficacy in increasing AH in NS. As studies undertaken on rare genetic conditions are often biased by the small sizes of study cohorts, a complete and detailed description of all patients' data should be provided to compensate for the small cohort size. Unfortunately, the difficulties met by the authors in reporting patient characterisation and data led to a non-entirely unbiased pool of data, unsuitable for statistical cross-validation.

Assuming the patients described by Ranke et al. [12] and Witt et al. [26] as historical control groups to be considered for the statistical analysis, only the data by Osio et al. [20] on AH expressed in cm were suitable for comparison, thus making it impossible to perform a meta-analysis. Furthermore, we are aware that MacFarlane's study could be judged not consistent with the aim of the study; nevertheless, an accurate systematic review could not leave out data from the only RCT published.

A second potential limitation of any review is the 'file drawer' effect, in which studies with negative results...
might remain unpublished, thus biasing the literature towards positive findings.

Finally, we are aware of the existence of 2 previous reviews of the topic [32, 33]. However, they are descriptive rather than systematic reviews, not focusing on the detailed analysis of the quality of data.

Conclusions

Our systematic review clearly shows that, to date, no study has fulfilled the evidence-based medicine criteria for high quality of evidence and strong recommendation for the efficacy of rhGH therapy in increasing AH of children with NS. The impossibility to perform a meta-analysis on treatment efficacy due to the lack of data should discourage the clinician from routinely using rhGH in NS. More robust evidence-based data are needed to ascertain the efficacy, the cost/benefit ratio and, eventually, to identify the responders.

Finally, it seems reasonable to assume that the debate should include the impact of the long-term rhGH therapy and its magnitude on the quality of life of children with NS.

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