Mini Review

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The Efficacy and Safety of Growth Hormone Therapy in Children with Noonan Syndrome: A Review of the Evidence

Jacqueline A. Noonan[a] Anne-Marie Kappelgaard[b]

[a]Kentucky Children's Heart Center, Division of Pediatric Cardiology, University of Kentucky, Lexington, Ky., USA;
[b]Novo Nordisk International Operations AG, Zurich, Switzerland

Key Words
Growth hormone · Noonan syndrome · Body height · Growth · Body composition

Abstract
Noonan syndrome is a genetic disorder associated with short stature. We reviewed 15 studies in which growth hormone (GH) therapy was used in children with Noonan syndrome. Data show consistent increases in mean height standard deviation score (SDS), with first-year changes of up to 1.26 SDS. Among studies reporting adult or near-adult height, GH therapy over 5–7 years resulted in adult height SDS from –0.6 to –2.1, with up to 60% of subjects in some studies achieving adult height within 1 SDS of mid-parental height. GH treatment results in an acceleration of bone age, likely reflecting normalization from the retarded bone age common in Noonan syndrome patients at the start of therapy. BMI is not affected by GH treatment, but favorable changes in fat mass and body composition are achievable. Longer-term studies and observational studies suggest a waning of the effect of GH therapy over time, as is seen in other GH-treated conditions, and early initiation of therapy and prepubertal status are important predictors of response. GH treatment does not appear to be associated with adverse cardiac or metabolic effects, and data on malignancy during GH treatment give no cause for concern, although they are limited.

Introduction

Noonan syndrome (NS) is a nonchromosomal genetic disorder observed in 1 in 1,000–2,500 live births [1] and is the most common cause of congenital heart disease after trisomy 21 [2]. NS may occur on a sporadic basis (de novo mutation) or in a pattern consistent with autosomal dominant inheritance [3]. The syndrome was originally identified on the basis of a set of common clinical features in children, including dysmorphic facial features and cardiac disorders, although diagnosis of NS can be made at any age and presentation of NS is highly variable. In general, features of NS are more prominent in early childhood and less so later in life.

Although birth weight and length are usually within normal ranges, up to 70% of NS individuals have short stature (with half of females and 40% of males below the 3rd centile) [4], accompanied by a variable delay in bone age [4, 5]. Reported estimates of adult height suggest that mean adult height is 154.4 cm (range 146.1–167.8) in females and 169.2 cm (range 153.0–188.7) in males [3, 6]. Delays in puberty are common [5], with an average delay of approximately 2 years [7]. Many individuals with NS display cardiovascular and electrocardiographic abnormalities [1, 8], and a variety of coagulation disorders have been reported [1]. Individuals with NS often display motor developmental delay with a higher incidence of clumsiness and poor coordination [1]. An estimated 10–40%

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E-Mail karger@karger.com
www.karger.com/hrp

Anne-Marie Kappelgaard
Novo Nordisk International Operations AG
Thurgauerstrasse 36/38
CH–8050 Zurich (Switzerland)
E-Mail amk@novonordisk.com

have special educational needs, and IQ scores in NS patients are lower than in unaffected family members [1].

Although genotyping is of value in the characterization of NS, and may provide useful information in the management of individual patients, the syndrome has a heterogeneous genetic basis and its cause remains unknown in 30–40% of patients [9–11]. Mutations in the *PTPN11* gene are present in up to 50% of NS individuals, with mutations in *SOS1* or *RAF1* in up to 20% [1]. Several of these mutations, which also include *KRAS, BRAF, MEK1* or *NRAS*, are thought to induce functional alterations of the Ras-MAPK signaling pathway, which is implicated in growth factor-mediated cell proliferation, differentiation and apoptosis.

It is unclear whether disturbances in growth hormone (GH) secretion or action are at work in the pathogenesis of NS. Short-term GH responsiveness appears to be reduced in at least some NS patients [12], data which are consistent with recent studies in animal models showing reduced growth and reduced sensitivity to GH in *PTPN11*-mutated NS mice [13]. Some investigators have found low nocturnal levels of GH in short-stature children with NS [14]; Noordam et al. [15] also found an unusual pulsatility of GH levels in some subjects. These findings suggest a role for GH therapy in the management of short-stature NS.

It may be expected that GH therapy in NS individuals with short stature would improve adult height, even though the effect on quality of life is undetermined. Furthermore, potential use of GH therapy in NS raises a number of questions. Firstly, what effect will changes in GH levels have on ventricular development in patients with the cardiac defects or abnormal cardiac function common in NS? Secondly, mutations in the Ras-MAPK pathway implicated in NS are also often involved in the pathogenesis of cancer, and germ-line mutations may represent constitutively hyperactive mitogen pathways. The most common cancers in NS are neuroblastoma, low-grade glioma, rhabdomyosarcoma and acute leukemia [16], while benign giant cell lesion of the jaw has also been associated with NS [17]. GH stimulates production of the mitogen insulin-like growth factor-I (IGF-I) and, hence, could potentially accelerate cancer growth in cells expressing IGF-I receptors.

Methodology

The current review evaluated data on the efficacy and safety of GH therapy in NS by reviewing all relevant published evidence. The medical literature was searched with PubMed for reports on NS patients treated with GH. The search strategy included two main issues: 'Noonan syndrome' and 'growth hormone replacement therapy'. We used all relevant keyword variations, including free text words. This resulted in the following search string: ('Noonan syndrome'[ti] OR 'Noonan syndrome'[Majr]) AND ('Growth Hormone/administration and dosage'[Mesh] OR 'Growth Hormone/therapeutic use'[Mesh] OR 'Growth Hormone/therapy'[Mesh] OR ((growth hormone OR growth hormones OR Somatotropin OR Somatotropins) AND (therapy OR therapeutic OR replacement))) AND (English [lang]). The search was limited to publications between January 1, 1990, and April 1, 2014. Furthermore, the references of relevant articles were checked for additional articles. No rhGH therapy was used as an exclusion criterion. Reports were accepted if they contained sufficient diagnostic clinical information and/or the patients had mutations in any of the genes associated with these syndromes. Duplicate reports were excluded.

Our initial search strategy led to the compilation of 42 suitable publications. Of these, 9 were review articles; these were screened for the inclusion of additional publications that were not identified in the initial search strategy. This strategy led to the identification of data from 15 clinical studies/case reports and 4 observational studies (tables 1, 2).

Height Gain with GH Therapy

Short-Term Growth Response to GH

All reviewed studies reported an increased mean height standard deviation score (SDS) and/or height velocity with GH treatment. Cotterill et al. [18] reported a significant increase in height SDS and height velocity in 24 of 27 patients receiving GH (0.045 mg/kg/day) for 1 year, with a mean (SD) increase in height velocity of +3.6 (0.3) cm/year. Similarly, de Schepper et al. [19] showed an increase in height SDS of 0.34 (1.5) after 1 year of GH (0.05 mg/kg/day) in 23 patients. Ahmed et al. [14] reported an increase in height velocity SDS after 1 year of treatment with GH in 6 patients (range at baseline 0.03–1.76, range posttreatment 1.48–3.75; p = 0.039). Changes in height velocity and SDS in NS are similar to those in Turner syndrome when similar doses of GH are used [19–21].

Studies of longer duration (up to 3 years) with treatment of GH at doses of 0.04–0.05 mg/kg/day have

Table 1. Published data from clinical trials of GH treatment in patients with NS

First author and year	At GH start						First year			Last observation			
	patients *(PTNP11)*, n	age at start, years	height SDS (normal ref.)[1]	height SDS (Noonan ref.)[2]	height velocity, cm/year	GH dose, mg/kg/day	Δ height SDS[1]	height SDS[1]	height velocity, cm/year	duration of treatment, years	height SDS (normal ref.)[1]	height SDS (Noonan ref.)[2]	height velocity, cm/year
Ahmed [14] (1991)	6	8.5–12.8[a]	−3.5 to −2.3[a]	–	−0.93 (0.67)[e]	0.03[b]	–	–	1.48 (1.40)[e] p = 0.039[c]	1	–	–	–
Thomas [46] (1993)	5	3.9 (2.5–6.5)[o]	−3.4 (−4.2 to −2.2)[o]	–	−2.1 (−4.1 to −0.3)[e, o]	0.05	–	−2.4 (−3.3 to −1.6)	3.1 (2.0–3.5)[e, o]	3	−2.1 (−3.1 to −1.4)[o]	–	−2.0 (−4.5 to 1.3)[e, o]
Nishi [31] (1995)	39	8.8 (2.6)	−3.4 (1.0)	–	−1.99 (1.67)[e]	0.17[f]	–	–	6.23 (0.87)	3	–	–	4.76 (1.25) p < 0.05[c]
Municchi [28] (1995)	4	12.3–15.1[a]		−1.9 to 0.2[a]	3.3–4.6[a]	0.028[b]	–	−1.4 to 1.0	3.5–9.0[a]	3	–	−0.9 to 0.9[a]	1.3–4.7[a]
Cotterill [18] (1996)	30	8.9 (0.5)	−3.01 (0.10)	–	4.9 (0.2)	0.047	0.6	−2.36 (0.1) p < 0.001[c]	8.1 (0.4) p < 0.0001[c]	1	–	–	–
de Schepper [19] (1997)	23	9.4 (3.0)		−2.28 (0.68)[p]	4.5 (1.0)	0.052	0.53 (0.46)	−1.8 (0.8)[1]	8.5 (1.5)	1	–	–	–
Soliman [35] (1998)	4	11.5 (1.8)	−2.2 (0.6)	–	−1.36 (0.3)[e]	0.04	–	1.45 (0.3) p < 0.05[c]	7.4 (0.6) p < 0.05[c]	1	–	–	–
MacFarlane [20] (2001)	23	9.3 (2.6)	−2.7 (4)	–	4.4 (1.7)	0.047	0.5	−2.2 (0.6)	8.4 (1.7)	3	−1.9 (0.3) p < 0.001[c]	–	5.8 (1.8) p = 0.01[c]
Ogawa [33] (2004)	15	7.5 (2.5)	−2.8 (0.7)	–	4.8 (1.0)	0.026	0.4	−2.4 (0.7)	7.0 (1.2)	2	−2.2 (0.5) p = 0.0039[c]	–	5.5 (0.6)
Ferreira [34] (2005)	7 (mut+)	12.9 (4.0)	−3.6 (1.0)	–	4.3 (1.0)	0.047	0.3 (0.41)	–	6.8 (1.5)	3	0.8 (0.41)[h]	–	5.7 (1.5)
	7 (mut−)	11.7 (3.0)	−3.4 (1.0)	–	3.9 (1.4)	0.047	0.42 (0.43)	–	7.6 (1.9)	3	1.74 (0.10)[h]	–	7.0 (3.8)
Binder [42] (2005)	11 (mut+)	7.4 (2.2)	−3.5 (0.7)	–	–	0.42	0.67 (0.21)	−2.4 (0.8)	–	1	–	–	–
	3 (mut−)	6.3 (1.9)	−3.8 (0.1)	–	–	0.05	1.26 (0.36)[i]	−2.5 (1.63)	–	1	–	–	–
Osio [23] (2005)	25	7.7 (2.1)[j] 8.6 (3.3)[k]	−2.9 (−4.0 to −2.0)[o]	−0.3 (−1.4 to 0.5)	–	0.033/ 0.067	0.8 (0.4)[l]	–	–	1–9	−1.2 (1.0)[l]	1.8 (1.1) males 1.0 (0.7) females	–
Limal [39] (2006)	15 (mut+)	10.4 (3.1)	−3.5 (0.9)[g]	–	4.3 (0.9)	0.043	–	−3.1 (1.4)	7.4 (1.6)	2	−3.1 (1.2)	–	5.8 (1.4)
	10 (mut−)	10.3 (3.3)	−3.0 (0.8)[g]	–	5.2 (1.4)	0.043	–	−2.4 (0.7)	8.5 (1.7)	2	−2.0 (0.9)	-	6.9 (1.6)
	10 (pubertal)	14.7 (1.7)	−3.4 (0.9)[g]	–	–	0.066	–	−2.8 (0.9) p = 0.002[c]	–	–	–	–	–
Noordam [24] (2008)	29	11.3 (5.8 to 17.5)[m]	−2.8 (−4.1 to −1.8)[m]	0.0 (−1.4 to 1.2)	–	0.050	0.5	−2.3 (0.7; −3.8 to −0.3)[n]	–	6.4 (3.0–10.3)[m]	−1.5 (0.8; −3.0 to 2.9)[n]	1.2 (0.8; −1.1 to 2.9)[n]	–
Choi [36] (2012)	18	8.3 (2.4)	−2.8 (0.8)[g]	–	5.0 (0.9)	0.066	–	−2.0 (0.9) p < 0.001[c]	8.9 (1.6) p < 0.001[c]	1	–	–	–

Data are mean values with SD in parentheses, unless otherwise stated.

[a] Range. [b] 6 days/week. [c] p versus baseline. [d] Median. [e] Height velocity SDS. [f] mg/kg/week. [g] Relative to normal population. [h] 3-Year cumulative change in height SDS. [i] p = 0.007 versus mut+ group. [j] 0.033-mg/kg/day group. [k] 0.067-mg/kg/day group. [l] Mean (SD) for the 18 patients who achieved final height. [m] Median (range). [n] Mean (SD; range). [o] Mean (range). [p] Versus Turner standards.

[1] Normal reference data: mean height SDS at ~13 years of age: −2.184 (range −6.968 to 0.940); mean height SDS at ~25 years of age −1.755 (range −6.209 to 1.395) relative to UK standard data [3].

[2] Height SDS relative to Noonan standards was calculated according to data published by Ranke et al. [7].

Table 2. Data from observational studies

	Romano [25] (1996)[c]	Kirk [29] (2001)	Raaijimakers [26] (2008)	Lee [22] (2012)
Database	NCGS	KIGS (UK)	KIGS	ANSWER
Patients, n	150	66	402	120
At start				
Age at start, years	10.6 (3.8)	10.2 (3.3)	9.73 (4.59–14.38)[a]	9.2 (3.8)
Height SDS (normal ref.)[1]	–3.5 (1.1)	–2.9 (2.7)	–2.86 (–3.24)[c]	–2.65 (0.73)
Height SDS (Noonan ref.)[2]	–1.35	–1.2 (0.8)	–1.04	–
Height velocity, cm/year	4.3 (2.3)	4.8 (1.1)	4.4 (2.9–6.5)[a]	–
GH dose, mg/kg/day	0.043	0.041 (0.013)	0.034 (0.023–0.051)[a]	0.047 (0.011) to 0.059 (0.016)
Duration of treatment, years	4	6	3	4
First year				
Height SDS (normal ref.)[1]	–2.8 (1.1)	–2.6 (0.8)	–2.32	–2.26
Δ height SDS (normal ref.)[1]	0.5	0.3	0.76	0.40
Height SDS (Noonan ref.)[2]	–	0.7 (0.9)	–	–
Δ height SDS (Noonan ref.)[2]	–	–	0.53	–
Height velocity SDS	–	1.9 (2.5); $p < 0.05$	–	–
Last observation				
Height SDS (normal ref.)[1]	–2.1 (1.2)	–2.3 (0.7)	–2.06	–1.32 (1.11)[b]
Δ height SDS (normal ref.)[1]	1.2	0.8	0.8 (0.61)[c]	1.07
Height SDS (Noonan ref.)[2]	–	–0.3 (0.9)	–	–
Δ height SDS (Noonan ref.)[2]	–	1.2	0.81 (0.97)[c]	–
Height velocity, cm/year	5.7 (1.9)	–	5.87	–

Data are mean values with SD in parentheses, unless otherwise stated. KIGS = Pfizer International Growth Database; NCGS = National Cooperative Growth Study; ANSWER = American Norditropin Studies: Web-Enabled Research Program® registry.

[a] Median (10th–90th percentile). [b] n = 17. [c] Data in parentheses are median values for 24 patients who achieved near-adult height.

[1] Normal reference data: mean height SDS at ~13 years of age: –2.184 (range –6.968 to 0.940); mean height SDS at ~25 years of age –1.755 (range –6.209 to 1.395) relative to UK standard data [3].

[2] Height SDS relative to Noonan standards was calculated according to data published by Ranke et al. [7].

shown an acceleration of growth velocity and increase in height SDS. MacFarlane et al. [20] reported significant improvement in height SDS after 3 years of GH treatment (1.3 mg/m^2/day) accompanied by an increase in height velocity, while in a further study conducted by Lee et al. [22], 12 of 17 patients receiving GH for 4 years achieved a normal height for their age and gender (height SDS >–2 SD). However, 30% of these patients remained short for their age and gender after 4 years of treatment, suggesting either resistance to GH or advanced chronological age or bone age at the start of treatment.

Adult Height/Near-Adult Height Outcomes with GH

Adult or near-adult height data have been reported from four large [23–27] and two small [28, 29] studies (table 3). The age at commencement and GH dose varied widely in these trials but mean height SDS at baseline was similar across the studies. The studies consistently showed a height gain in most patients, with gains to adult height SDS ranging from 0.6 to 1.7 when calculated according to Noonan standards [27, 29]. However, more recent data suggest that an additional spontaneous height gain of 1.00 SDS may occur in the second decade in girls and a further gain of 0.57 SDS may occur at the start of the third decade in boys [6]. This late pubertal growth spurt should therefore be incorporated into calculations of final height prediction for short children with NS. No significant correlation of GH dose to adult height has been shown in any study. Sixty percent of patients in the study by Osio et al. [23] reached mid-parental height ±1 SDS, with mean adult heights of 157.7 cm in females and 174.5 cm in males, representing height gains during GH treatment of 1.5 SDS (9.8 cm), and 1.8 SDS (13 cm), respectively. Somewhat smaller increases were reported by Shaw et al. [30], with gains of 5 cm (females) and 7 cm

Table 3. Published adult height data

	Kirk [29] (2001)	Osio [23] (2005)	Raaijimakers [26] (2008)	Noordam [24] (2008)	Romano [27] (2009)
Patients with adult height (female/male), n	10 (4/6)	18 (11/7)	24 (not specified)	29 (8/21)	65 (30/35)
Data source	KIGS UK (observational)	randomized, dose-response study	KIGS world (observational)	randomized study	NCGS (observational)
Patients with *PTNP11* mutations, n	–	–	–	22/27	–
Age at treatment start, years	12.1 (8–15)[a]	female: 7.7 male: 8.6	10.2[b]	11.0 (6–18)[a]	11.6 (3.0)
Height SDS (normal ref.)[1]	–3.1 (–4 to –2)[a]	–2.9 (–4.0 to –2.0)[a]	–3.24[b]	–2.8 (–4.1 to –1.8)[a]	–3.5 (1.0)
Difference in height SDS and mid-parental height SDS (normal ref)	–	–2.4	–	–	–
Height SDS (Noonan ref.)[2]	–1.2 (0.8)	–0.3 (–1.4 to 1.5) male: –0.2±0.4 female: –0.4±0.5	–	0.0 (–1.4 to 1.2)	male: –0.8 female: –1.1
GH dose, mg/kg/day	0.035	0.033[c] or 0.066[d]	0.035[b]	0.05	0.33 (0.05) scheduled at 6.2 (1.1) injections/week
Duration of therapy, years	5.3 (2–9)[a]	7.5 (4–12)[a]	7.6[b]	6.4 (3.0–10.3)[a]	5.6 (2.6)
Height SDS at adult height/near-adult height (normal ref.)	–2.3	–1.2±1.0	–	–1.5 (0.8; –3.0 to –0.3)[e]	–2.1 (1.0)
Mean gain in height SDS at adult height in boys (normal ref.)	1.16	1.8±1.0	–	–	1.2
Mean gain in height SDS at adult height in girls (normal ref.)	0.8	1.5±0.8	–	–	1.5
Δ height SDS (normal ref.)	0.8	1.7 (0.5–3.1)	0.6[b]	1.3 (–0.2 to 2.7)[a]	1.4 (0.7)
Height SDS (Noonan ref.)	0.6	male: 1.8±1.1 female: 1.0±0.7	–		male: 0.7 female: 0.3
Δ height SDS (Noonan ref.)	0.6	male: 2.0±1.1 female: 1.4±0.7	0.97	1.3 (–0.6 to 2.4)	male: 1.5 female: 1.4
Difference in height SDS and mid-parental height SDS (normal ref.)	–	–0.7	–	–	–

Data are mean values with SD in parentheses, unless stated otherwise. KIGS = Pfizer International Growth Database; NCGS = National Cooperative Growth Study.

[a] Median (range). [b] Median. [c] n = 10 (final height reported for 9 subjects), age at treatment start was 7.7 (2.1) years. [d] n = 15 (final height reported for 9 subjects), age at treatment start was 8.6 (3.3) years. [e] Mean (SD; range).

[1] Normal reference data: mean height SDS at ~13 years of age: –2.184 (range –6.968 to 0.940); mean height SDS at ~25 years of age –1.755 (range –6.209 to 1.395) relative to UK standard data [3].

[2] Height SDS relative to Noonan standards was calculated according to data published by Ranke et al. [7].

(males). These data are consistent with those recorded in the Kabi International Growth Study (KIGS) database, which showed an increase of 0.61 SDS according to Tanner standards and 0.97 SDS according to Noonan standards in children treated with GH to near-adult height [26]. After 3 years, 24 patients had reached near-adult height, of whom 54% had adult height below –2 SDS (Tanner standards) versus 95% at baseline. Romano et al. [27] reported data from 65 GH-treated NS patients reaching near-adult height in the NCGS database, with gains over the predicted height of 9.2 cm in females and 10.9 cm in males.

Effect of Treatment Duration on GH Response

A waning of treatment response to GH has been reported by most authors, an effect which is known in other indications. MacFarlane et al. [20] noted that 78% of patients showed an increased height velocity of ≥2 cm/year during the first year, falling to 52.2 and 30.4% in each of the subsequent 2 years. Other studies have shown similar results, with accelerated height velocity and SDS during the first year but with these declining progressively in subsequent years [26, 31]. As an approach to mitigating the waning effectiveness of GH therapy, Noordam et al. [21] studied the effect of temporary discontinuation of GH. This resulted in 'catch-down' growth with a decrease in height velocity and reduction in bone maturation; mean height velocity decreased from 7.2 to 3.8 cm/year ($p < 0.01$) and the mean change in height SDS was –0.2. Restarting GH treatment was associated with a greater change in height SDS (0.3 SDS) compared to patients who did not discontinue GH treatment (0.1 SDS), but a significantly slower rate of bone maturation (change in bone age relative to chronological age 0.4 and 1.2, respectively; $p < 0.05$). An alternative approach to counteract the waning effect of GH therapy in NS might be stepwise dose escalation, which has been shown to be effective in Turner syndrome [32].

Effect of GH Therapy on Bone and Body Composition

Most studies report retarded bone age at the start of treatment, with GH therapy associated with an acceleration in bone age; advancement of bone age of 1.1–1.2 years/year during GH therapy is typical [22, 25, 26, 33, 34]. Soliman et al. [35] reported a decrease in the mean (SD) difference between chronological age and bone age, from 2.8 (1.0) to 2.5 (0.9) years in 4 patients after GH treatment for 1 year. Cotterill et al. [18] reported a small but statistically significant decrease in mean (SD) difference between chronological age and bone age, from 1.2 (0.2) to 1.0 (0.5) years ($p = 0.03$) after 1 year of GH treatment; they also reported a significant change in the SDS for the bone maturity score (the sum of the scores attributed to the individual bones according to sex and bone age), from –1.11 (0.21) to –0.71 (0.21; $p = 0.02$). Data from the NS cohort of the KIGS registry showed that for the cohort of 73 prepubertal patients with 3-year longitudinal follow-up data (median age at treatment start 7.73 years), median bone age was 6.0 years at the start of GH treatment, advancing to a median of 9.3 years after 3 years of GH treatment, while those treated to near-adult height (n = 24) had a bone age delay of 3.17 years at a median chronological age of 7.0 years, advancing to a delay of 2.74 years at a median chronological age of 15.7 years after 7.59 years of GH treatment [26]. Romano et al. [25], reporting from the NCGS registry, noted that the advancement in bone age appeared faster in patients with more delayed bone age at the start of treatment. A negative correlation between 1-year height SDS and bone age at the start of treatment was noted by Choi et al. [36]. Since NS patients typically enter treatment with a delayed bone age, it is likely that the acceleration of bone age during GH therapy reflects normalization rather than an inordinate acceleration of bone age with potential consequences for final height.

Noordam et al. [37] assessed bone mineral density (BMD) and body composition before and during treatment with GH (0.05 mg/kg/day), finding that bone density at the proximal region of the phalanx, representing trabecular bone, had normal volumetric BMD at baseline, whereas mid-phalangeal (mostly cortical) bone had BMD in the lower normal range at baseline, each slightly increasing over 2 years of GH treatment. Although BMI did not change during GH treatment, there was a significant reduction in percentage fat mass from 17.3% (0.8) at baseline to 12.4% (1.1) after 2 years. Lee et al. [22] also reported a proportional increase in body weight with the increase in height associated with GH treatment, while BMI remained unchanged.

Effect of GH Treatment on Puberty

Although puberty occurs spontaneously in children with NS, it is typically delayed by an average of 2 years compared to healthy children. Furthermore, as adult height is generally achieved towards the end of the second decade, it is suggested that pubertal progression is slow and peak height velocity is below average [38]. The confounding effects of puberty on growth velocity in NS remain poorly characterized and optimal GH regimens during puberty have not been established. Noordam et al. [24] reported adult height data for 29 patients (21 boys and 8 girls) treated with GH (0.05 mg/kg/day) until adult height (growth velocity <1 cm/6 months). The mean age at the start of treatment was 11.0 years (range 5.8–17.5). Twenty-five of the children were prepubertal at the start of treatment and 4 were in early puberty (3 boys were in Tanner G:2, testis volume between 5 and

7 ml, and 1 girl was in Tanner B:2). The median duration of treatment was 6.4 years (range 3.0–10.3). The mean age at the start of puberty was 13.8 years for boys (range 11.2–17.5) and 13.5 years for girls (range 12–15.9). Linear regression analysis revealed that age at the start of puberty was a significant predictor of adult height (r^2 = 0.41; $p < 0.01$).

Predictors of Growth Response to GH Therapy in Children with NS

Effect of Age on GH Treatment Response

Age at treatment initiation and age and height SDS at the start of puberty all have an impact on the response to GH therapy. A later start of puberty also appears to have a positive effect on the treatment response [24].

Early initiation of GH treatment appears to be beneficial, with negative correlations between age at treatment commencement and the change in height SDS after 1 and 2 years of treatment [21, 23]. Pubertal status may be an important predictor of treatment response; MacFarlane et al. [20] found that increased height velocity was only significant during the first year of treatment in patients not advancing into puberty during that time. Analyses suggest that the older the child is at the start of puberty, the better their response to GH [24], while the duration of prepubertal GH treatment appears highly correlated with gain in prepubertal height SDS [24, 27]. Limal et al. [39], however, found the mean change in height SDS to be similar in prepubertal patients [from –3.3 (0.9) to –2.8 (1.1) after 2 years of GH treatment] and in pubertal patients [from –3.4 (0.9) to –2.8 (0.9)].

Studies documenting adult height [23, 24, 27] report improved outcomes with an early initiation and long duration of GH treatment, while height SDS at the start of puberty was positively correlated with near-adult height SDS [27].

Effect of Gender on the GH Treatment Response

There is little evidence for any gender difference in response to GH therapy in NS. Lee et al. [22] found no between-gender difference. Although a greater mean gain in height to adult height in boys versus girls was seen in one study, treatment durations were different, with boys receiving treatment between mean ages of 8.6 and 17.7 years, and girls between 7.7 and 15.2 years [23]. It is speculated that the reported gender differences may be attributed, at least in part, to an average 1.5-year longer pubertal growth period (totaling approximately 6.3 years compared with an average duration of 4 years in healthy males) in males compared to females [23].

GH Secretion and IGF-I Levels as Predictors of Response to GH Therapy

No correlation was found between pretreatment GH, IGF-I and IGF-binding protein-3 levels, and first-year response to GH therapy, supporting the hypothesis that these laboratory parameters do not generally predict first-year growth response to GH therapy [15]. In the report by Noordam et al. [24], mean IGF-I SDS increased from 0.3 (n = 29, range –1.5 to 0.7) to 0.9 (n = 29, range –0.8 to 1.8) during the first year of GH (0.05 mg/kg/day) treatment. There was a correlation, however, between the increment in height SDS and the increment in IGF-I and IGF-binding protein-3 levels during 1 year of GH treatment [15]. In general, children with the 'severe' NS phenotype had higher trough GH levels and secreted more GH than those with the moderate NS phenotype, as measured using spontaneous 12-hour overnight GH secretion. These data suggest that reduced sensitivity to GH may play a role in the short stature observed in NS [15].

Clinical Phenotype as a Predictor of Response to GH Therapy

Severe and moderate NS patients appear to respond similarly to GH treatment. Noordam et al. [40] scored 25 children with NS as severe phenotype (n = 13) or moderate phenotype (n = 12) based on the scoring system of van der Burgt et al. [41]. Both groups had similar height SDS at treatment initiation and no differences were observed in birth length, height at 1 year and height at 6 years of age. Treatment with GH (0.05 mg/kg/day) for 2 years was associated with a similar increase in height SDS in both groups despite a significantly higher mean GH level in the severe-phenotype group versus the moderate-phenotype group.

NS Genotype as a Predictor of Response to GH Therapy

Some studies have found an improved response to GH therapy in patients without the *PTNP11* mutation, which is consistent with the ability of this mutation to confer GH resistance [34, 39, 42]. However, a trend towards a better first-year growth rate in children without versus those with this mutation was statistically significant in only one study involving prepubertal children [12]. The observation of a correlation between the short-term

growth response and genotype (with a reduced growth response in the presence of a *PTPN11* mutation) has not been demonstrated when analyzing the data against adult height [24]. With a longer duration of treatment, Ferreira et al. [34] found that the greater gain in height SDS in patients without versus with the *PTPN11* mutation reached significant levels after 3 years, despite most patients entering puberty during the observation period. In contrast, Choi et al. [36] found no significant difference in GH effect between children with and without the *PTPN11* mutation. There is also no evidence that presence of the *PTNP11* mutation is associated with lower adult heights; Noordam et al. [24] found similar mean gains in height SDS of 1.3 in children with and without the mutation after a median 6.4 years of GH treatment.

Safety Data with GH Therapy in NS

Effect of GH Therapy on Cardiac Anatomy and Function in NS

Two prospective studies specifically evaluated the effects of GH therapy on cardiac anatomy and function in NS and did not indicate any cause for concern [18, 43]. In particular, long-term GH treatment does not appear to have clinically significant adverse effects on left ventricular dimensions in children with NS; there were no differences in cardiac dimensions between 27 children with NS receiving GH (0.05 mg/kg/day) and 16 NS controls [43]. Follow-up for 5.6 years in the children with cardiac defects at baseline showed no changes in ventricular wall thickness [24]. Two boys had mild progression of pulmonary valve stenosis considered unlikely to be related to GH therapy [24]. In another study, there were no signs of excess ventricular wall thickness with GH 0.05 mg/kg/day for 1 year [18]. One patient with mitral regurgitation at study entry developed left ventricular failure after 11 months of treatment with GH and was withdrawn. There were also no observed effects of GH therapy on the heart in a prospective Swedish study [23]. Similar conclusions have been drawn from registry data; Romano et al. [25] and Raaijimakers et al. [26] reported no cardiac adverse events during GH treatment in data from the NCGS (n = 150) and KIGS (n = 402) databases, respectively.

Effect of GH Therapy on Glucose Metabolism

Data from a number of studies show blood glucose readings remaining within normal limits during GH treatment [20, 23, 39] and hemoglobin A1c remained unchanged by GH therapy [18]. This was also the case in a further study where blood glucose levels increased to 'borderline' in 5 patients [33]. A temporary small increase in fasting insulin levels has been observed in some patients with NS receiving GH therapy [23].

Effect of GH on Tumor Risk/Malignancy

Patients with NS are predisposed to have a higher risk than the general population for leukemia and certain solid tumors. In patients with NS carrying the *PTPN11* mutation, the most common cause of NS, the cumulative risk of developing cancer was estimated as 3.5-fold higher (95% confidence interval 2.0–5.9) than the general population [44]. Data on GH and tumor risk give no cause for concern, but small patient numbers and few documented cases impede a robust risk assessment. Susceptibility to tumor growth should therefore be addressed when GH therapy is started and appropriate follow-up maintained. Among the reported cases, Moos et al. [45] reported a large subcutaneous infiltrating atypical granular cell tumor on the left forearm in a child with NS treated with GH. The authors note that although such tumors are rare in childhood, 5 cases have been reported in children with NS not treated with GH. Recurrence of a previously diagnosed maxillary gland giant cell granuloma has been reported in 1 GH-treated patient [27], while lymphoma was reported in another patient 3 years after starting GH treatment, in whom GH treatment was restarted without problems after remission [23].

Conclusions

GH treatment is effective in increasing growth velocity and, most probably, also adult height in NS (although either a controlled study in GH-treated and GH-untreated patients or a dose-response study would be needed to provide proof), and is effective in a wide range of NS pheno/genotypes. GH also accelerates bone age and has favorable effects on bone density and body composition. There is good evidence that GH therapy should be initiated early, preferably before puberty. Whenever started, a waning of effect is likely over time; it is possible that dose escalation may counteract this effect, as has been shown in Turner syndrome. Careful monitoring of IGF-I SDS during dose escalation is recommended.

Safety data with GH therapy in NS are broadly reassuring, with no indication of a propensity for adverse effects on cardiac geometry and function or glucose metabolism,

although monitoring of cardiac status is advisable in view of the prevalence of cardiac issues in the NS population. Data on malignancy during GH treatment give no cause for concern, but are limited by the small number of patients and cases.

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