Review article

https://doi.org/10.6065/apem.2018.23.4.176
Ann Pediatr Endocrinol Metab 2018;23:176-181

Annals of Pediatric Endocrinology & Metabolism
apem

Growth hormone therapy in patients with Noonan syndrome

Go Hun Seo, MD,
Han-Wook Yoo, MD, PhD

Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Noonan syndrome (NS) is an autosomal dominant disorder that involves multiple organ systems, with short stature as the most common presentation (>70%). Possible mechanisms of short stature in NS include growth hormone (GH) deficiency, neurosecretory dysfunction, and GH resistance. Accordingly, GH therapy has been carried out for NS patients over the last three decades, and multiple studies have reported acceleration of growth velocity (GV) and increase of height standard deviation score (SDS) in both prepubertal and pubertal NS patients upon GH therapy. One year of GH therapy resulted in almost doubling of GV compared with baseline; afterwards, the increase in GV gradually decreased in the following years, showing that the effect of GH therapy wanes over time. After four years of GH therapy, ~70% of NS patients reached normal height considering their age and sex. Early initiation, long duration of GH therapy, and higher height SDS at the onset of puberty were associated with improved final height, whereas gender, dosage of GH, and the clinical severity did not show significant association with final height. Studies have reported no significant adverse events of GH therapy regarding progression of hypertrophic cardiomyopathy, alteration of metabolism, and tumor development. Therefore, GH therapy is effective for improving height and GV of NS patients; nevertheless, concerns on possible malignancy remains, which necessitates continuous monitoring of NS patients receiving GH therapy.

Keywords: Noonan syndrome, Growth hormone

Introduction

Noonan syndrome (NS) is an autosomal dominant disorder that involving multiple organ systems, with an incidence of 1:1,000 to 1:2,500.[1] LEOPARD syndrome (OMIM 151100) (lentigines, electrocardiography conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensory neural deafness), cardiofaciocutaneous syndrome (CFC; OMIM 115150), and Costello syndrome (CS; OMIM 218040) exhibit overlapping phenotypes with NS and are thus categorized as NS-related disorders.[2,3] All aforementioned conditions share common clinical features such as short stature, dysmorphic facial features, congenital heart defects (most commonly pulmonary valve stenosis or hypertrophic cardiomyopathy), typical chest deformities (pectus carinatum superiorly, pectus excavatum inferiorly), increased bleeding tendency, cryptorchidism, and variable degrees of developmental delay/intellectual disability.[1,4-7]

Functional alterations of Ras/mitogen-activated protein kinase (MAPK) signaling pathway is implicated in growth factor-mediated cell proliferation, differentiation, survival and death.[8,9] Gain-of function germline mutations that affect the components of the Ras-MAPK pathway are involved in the development of NS and its related disorders.[4] Mutations in the *PTPN11* gene are present in up to 50% of NS cases, followed by mutations in *SOS1* and *RAF1* in up to 20%.[6,10] A small number of NS patients have been shown to carry mutations in *KRAS*, *BRAF*,

Received: 24 October, 2018
Revised: 28 November, 2018
Accepted: 9 December, 2018

Address for correspondence:
Han-Wook Yoo, MD, PhD
Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 88, Olympic-ro 43-Gil, Songpa-Gu, Seoul 05505 Korea
Tel: +82-2-3010-3374
Fax: +82-2-473-3725
E-mail: hwyoo@amc.seoul.kr
https://orcid.org/0000-0001-8615-186X

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

©2018 Annals of Pediatric Endocrinology & Metabolism

MEK1, and *NRAS* genes.[6,10] In addition, a mutation in the *SHOC2* gene was identified in patients with NS-like phenotypes and loose anagen hair.[11] Still, causative mutations are unknown in 30%–40% of NS cases.[4,6,10]

Short stature is a common presentation of NS that affects up to 70% of NS patients.[6] Birth weight and height of NS patients are generally within normal range, but NS patients undergo subsequent height loss of 1–1.5 standard deviation score (SDS) within the first year.[12] After 2 to 4 years, mean height begins to fall below the 3rd percentile until puberty due to delayed puberty and low peak height velocity.[12] Mean final height is 152.7–154.4 cm in females and 167.4–169.2 cm in males, which is less than 1.5 height SDS compared with normal population.[13,14] Thus, over the last three decades, GH therapy has been administered in NS patients, and U.S. Food and Drug Administration approved treatment with recombinant human growth hormone for NS patients in 2007.

This review describes a series of research in the field of GH therapy for NS patients as well as possible causes of short stature, short and long-term efficacy, factors affecting the response of GH therapy, and adverse events of GH therapy.

Possible mechanisms of short stature

Different views on the GH secretory dynamics in studies reflect the heterogeneity of the clinical and genetic condition of NS. Possible mechanisms for short stature include GH deficiency, neurosecretory dysfunction, and GH resistance. Approximately 40% of NS patients showed peak GH level of less than 10 ng/mL in pharmacological provocation tests.[15,16] Short children with NS showed disturbances in GH secretion such as low level of mean overnight GH concentration and unusual GH pulsatility with high trough GH concentration, suggesting neurosecretory dysfunction.[17] NS patients with *PTPN11* mutation had lower levels of insulin-like growth factor 1 (IGF-1) than those without *PTPN11* mutation.[16-19] These

Table 1. Short and long-term efficacy of GH therapy in NS patients

Study	No. of patients (M/F)	Age at start (yr)	Height SDS at start	GH dose (mg/kg/day)	Duration of GH therapy (yr)	GV (cm/yr), *P*-value	Change in height SDS	Height SDS at last follow-up, *P*-value
Cotterill et al.[20] 1996	30 (19/11)	8.9±0.5	-3.01±0.1	0.05	1	4.9±0.2 to 8.1±0.4, <0.001	N/A	-2.36±0.1, <0.001
Binder et al.[30] 2005	29 (19/10)							
	Mut +:16	7.4±2.2	-3.5±0.7	0.042±0.007	1		0.66±0.21	-2.4±0.8
	Mut -: 13	6.3±1.9	-3.8±0.1	0.050±0.008		N/A	1.26±0.36	-2.5±1.6
Choi et al. [21] 2012	18 (14/4)	8.3±2.4	-2.8±0.9	0.066			N/A	-2.0 ±0.9, <0.001
	Mut +:10				1	3.6±1.6		
	Mut -: 8					3.8±0.8		
Limal at al.[19] 2006	35 (19/16)	10.4±3.1	-3.3±0.9	0.030-0.046	2	Before: 4.7±1.1	N/A	
						1 yr after: 7.9±1.6		1 yr: -2.8±1.1, 0.1
						2 yr after: 6.3±1.5		2 yr: -2.7±1.3, 0.03
MacFarlane et al.[22] 2001	23 (16/7)	9.3±2.6	-2.7±0.4	0.05	3	before:4.4±1.7	N/A	-1.9±0.9, <0.001
						1 yr after: 8.4±1.7, <0.001		
						2 yr after: 6.2±1.7, <0.001		
						3 yr after: 5.8±1.8, <0.001		
Ferreira at al.[18] 2005	14 (10/4)		-					N/A
	Mut +:7	12.9±4	-3.6±0.1	0.048±0.005	3	N/A	0.76±0.41	
	Mut -: 7	11.7±3	3.4±0.1	0.046±0.07			1.74±0.10	
Raaijmakers et al.[28] 2008	402	9.7	-2.86	0.034	3	5.8	0.8±0.61	-2.06
Jeong et al.[23] 2016	15 (11/4)	7.9±1.8	- 2.6±0.6	0.050–0.075	3	Before: 4.6±0.8	N/A	-1.5±1.2, 0.001
						1 yr: 8.6±1.5		
						2 yr: 6.8±1.3		
						3 yr: 6.4±1.5, 0.003		
Noordam et al.[25] 2008	29 (21/8)	11.0	-2.8	0.035	6.4 (3 to 10)		1.3 (-0.6 to +2.4)	-1.5 (-3.0 to -0.3), <0.001
Romano et al.[26] 2009	65 (35/30)	11.6±3.0	-3.5±1.0	0.33±0.05	5.6±2.6		1.4±0.7	-2.1±1.0
Lee et al.[24] 2012	120	9.2±3.8	-2.7±0.7	0.047±0.011	4		N/A	-1.3± 1.1
Osio et al.[27] 2005	25 (12/13)	8.2±3.0	-2.9±0.4	0.33–0.66	1–9		1.7±0.9	-1.2±1.0

Values are presented as mean±standard deviation unless otherwise indicated.
Mut +, positive for mutation of *PTPN11*; Mut-, negative for mutation of *PTPN11*; GH, growth hormone; GV, growth velocity; SDS, standard deviation score; N/A, not available.

findings provide ground for the efficacy of GH therapy in the management of short stature in NS patients. Furthermore, NS patients with *PTPN11* mutation showed impaired production of IGF-1 and acid-labile subunit with normal insulin-like growth factor binding protein 3 (IGFBP-3) levels, which can result in GH post-receptor signaling defect.[19]

Efficacy of growth hormone therapy for the height

Table 1 describes the results of previous studies on GH therapy in NS patients. Several studies have reported acceleration of growth velocity (GV) and increase in height SDS within the first year of GH therapy. About 80% of patients treated with GH (0.045 mg/kg/day) for 1 year showed significant increases in mean height SDS (-3.01±0.1 to -2.36±0.1) and height velocity (4.9±0.2 to 8.1±0.4 cm/yr).[20] Another study reported that after 1 year of GH therapy (0.066 mg/kg/day), mean height SDS and GV increased from -2.8±0.9 to -2.0±0.9 and from 5.0±0.9 to 8.9±1.6 cm/yr, respectively.[21] Furthermore, in both prepubertal and pubertal patients, mean height SDS was improved after one year of GH therapy.[19]

After 3 years of GH therapy (0.05–0.075 mg/kg/day), significant increases in height SDS and GV were observed.[22,23] GV was the highest during the first year of treatment and gradually decreased every year thereafter, showing that GH therapy effectiveness wanes over time.[21,22] Approximately 78% of patients showed increased GV of more than 2 cm/yr during the first year, which decreased to 52.2% and 30.4% in the second and third years, respectively.[22] Similarly, another study reported a significant acceleration in GV, in which GV almost doubled after the first year of GH therapy compared with GV at baseline, followed by gradual decrease in the following years.[21] The decreasing trend of gain in height SDS for years 2 and three of GH therapy was not related to poor adherence to therapy, and persisted even upon yearly increases in the mean dosage of GH therapy.[22,24] The waning of GH therapy effect in NS patients may be due to age at the beginning of GH therapy, GH secretory status, GH resistance, and genetic factors.

Similarly, height SDS also increased from -2.6 to -1.3 upon 4 years of GH therapy, and about 70% of 17 patients reached normal height range considering age and sex (height SDS > −2).[24] Patients who were treated with GH for more than 3 years (median, 6.4 years) showed increase of 1.3 height SDS; consequently, 22 out of 29 patients achieved adult height within normal range.[25] However, even after 4 years of GH therapy, 29% of patients remained less than -2 height SDS.[24] Such differences in the effect of GH therapy might be due to resistance to GH or advanced bone age relative to chronologic age at the beginning of GH therapy.

Most patients given GH therapy (0.33 mg/kg/day) showed substantial gain in final height, with SDS ranging from 1.4 to 1.7.[26,27] Males showed 10.9±4.9 cm growth while females showed 9.2±4.0 cm by the age of 18 years.[26,27] In 60% of patients, mean adult height reached 157.7 cm in females and 174.5 cm in males.[27] Without GH therapy, all males or females with less than -2 height SDS did not show any noticeable catching up in growth after onset of puberty.[26] However, additional spontaneous height gains of 1.00 SDS and 0.57 SDS were observed in mid-to-late female teenagers and males in early 20s, respectively, which may be associated with delayed puberty.[14] In fact, mean final height of GH-untreated patients reached 154.4 cm (-1.73 SDS) for females and 169.2 cm (-1.27 SDS) for males.[14] Therefore, pubertal growth spurt that present much later than expected should be taken into consideration for assessment of the efficacy of GH therapy in terms of final height.

GH therapy was associated with advancement of bone age of 1.1–1.2 years/yr.[15,18,24,28] Mean difference between chronological age and bone age decreased and bone maturity score increased after one year of GH therapy.[20] As the bone age was more delayed at the start of GH therapy, the advancement of bone age underwent faster acceleration after GH therapy.[15] There was a negative correlation between bone age at the start of GH therapy and one-year height SDS.[21] Among NS patients who received GH therapy, those who showed significant increase in adult height did not have excessively advanced bone age.[22-25] Because NS patients typically begin GH therapy with markedly delayed bone age, the advancement of bone age during GH therapy may reflect normalization rather than excessive acceleration of bone age.

Factors affecting response of GH therapy

As the age at the onset of puberty is a predictive factor for adult height, delayed onset of puberty has a positive effect on treatment response.[25] Earlier initiation of GH therapy has an impact on the changes in height SDS after 1 and 2 years of treatment.[24,27] In particular, when using the age of 11 years in male and 10 years in female as a cutoff for younger versus older age, patients who started GH therapy at a younger age showed a trend of higher gain in change to height SDS after 1 year and 2 years of treatment.[24] Duration of GH therapy at prepubertal period and height SDS at the onset of puberty were also positively correlated with the increment in prepubertal height SDS and near-adult height SDS, respectively.[25,26] In summary, early initiation and long duration of GH therapy as well as higher height SDS at the onset of puberty are correlated with taller final height.

The mean gain in height SDS was similar for males and females during up to 2 years of GH therapy, suggesting that gender does not significantly affect the efficacy of GH therapy.[24] Additionally, there is no significant beneficial effect of higher dosage for final height, as demonstrated by previous studies that used different doses of GH (0.33–0.66 mg/kg/day).[25,27,28]

Basal IGF-I and IGFBP-3 before GH therapy were significantly related to height and GV, and subsequent improvements in IGF-I and IGFBP-3 level after one year of GH treatment were related to increases in height velocity.[17] Other studies showed also serum IGF-1 and IGFBP-3 level increased after 1 year of therapy.[21,25] However, basal IGF-1 and IGFBP-3 level could not

predict changes in height SDS.[21,24)]

Notably, NS patients showed similar response to GH therapy regardless of the severity of clinical phenotype.[29)] There was small difference in the increase of height SDS in both severe and moderate NS subgroups after 2 years of GH therapy (0.05 mg/kg/day) despite the higher GH secretion in the severe subgroup.[29)]

Studies on the severity of short stature and response to GH therapy according to the existence of mutation have shown conflicting results. Some studies reported a tendency to better response of height SDS from one to 3 years of GH therapy in patients without *PTPN11* mutations.[18,19,23,30)] However, others showed contradictory results in that response to GH therapy was not significantly different between patients with *PTPN11* mutations and those witihout.[21,25)] In addition, IGF-1 and IGFBP-3 levels at the start of GH therapy were significantly lower in patients with *PTPN11* mutation, which suggest mild GH resistance in mutation-positive patients.[30)] However, response to GH therapy represented by changes in serum IGF-1 and IGFBP-3 levels was not significantly different according to the presence of mutation.[21,23)]

Adverse events of growth hormone therapy

Several studies have shown that blood glucose levels remain within normal ranges during GH therapy.[22,25,27)] In addition, there were no abnormalities in metabolic profiles including HbA1c, triglyceride, and cholesterol over three years of GH therapy.[22)]

There was no evidence of excess ventricular wall thickness upon 1 year of GH therapy (0.05 mg/kg/day).[20)] Prospective GH trials of over 3 years showed that no children with NS experienced any serious complication of heart based on echocardiography.[27,31)] In particular, there were no significant thickening in left ventricular dimensions between 27 children with NS given GH (0.05 mg/kg/day) and 16 NS controls.[31)] For longer duration (mean, 5.6 years) of GH therapy, there was no significant change in ventricular wall thickness.[25)] Two patients showed mild progression of pulmonary valve stenosis, but it was not considered to be related to GH therapy.[25)] Two out of 65 patients presented biventricular hypertrophy and hypertrophic cardiomyopathy, which were manifestations of NS.[26)] Despite such positive outcomes, GH therapy in patients with *RAF1* mutation is controversial because ventricular hypertrophy may have progressive course. Thus, careful monitoring is recommended to detect any possible hypertrophic cardiomyopathy and progression of the underlying heart disease during GH therapy.

NS confers increased risk of benign and malignant proliferative conditions ranging from hematological abnormalities to solid tumors.[7,32)] Patients with *PTPN11* mutations had 3.5-times higher overall cancer risk by age of 55 years compared to general population.[32)] NS is often associated with dysembryoplastic neuroepithelial tumor of the brain, and GH therapy should be carried out with caution because it may promote tumor growth.[33)] In 1 patient with a previous diagnosis of maxillary germ cell granuloma, recurrence of the mandible was observed upon GH therapy,[26)] whereas another patient was able to start GH treatment again after lymphoma remission.[27)] There is a lack of follow-up studies on the risk of tumor development and its recurrence in large or small cohorts of NS patients treated with GH. Thus, all NS patients who undergo GH therapy should be evaluated for the association between malignancy risk and GH therapy.

This review suggested regular follow-up tests for prevention or early detection of adverse events of GH therapy based on the evaluation performed at this center (Table 2)

Conclusions

GH therapy in NS patients is effective for improving height and GV, enabling them to reach normal final height regardless of clinical severity and genotype. Early initiation (especially in the prepubertal period) and long duration of GH therapy

Table 2. Proposed regular follow-up tests for prevention or early detection of adverse events of GH therapy

Evaluation	Test	Comments
Initial evaluation	CBC, creatinine, LFT, fasting glucose, cholesterol, HbA_{1c}, TSH, free T4, IGF-1, IGFBP3, echocardiography, ECG	
Routine evaluation	CBC, creatinine, LFT, fasting glucose, cholesterol	Every 3 month If serum fasting blood glucose level is > 126 mg/dL in 2 consecutive tests, HbA1c is recommended
Endocrine evaluation	TSH, free T4, IGF-1, IGFBP3	Every 3 months
	Bone age	Every 6 months
Cardiac evaluation	Echocardiography, ECG	Not recommend regular follow-up If ventricular hypertrophy or congenital heart defect was presented in previous examination, recommend evaluate every 1–2 years
Tumor evaluation		Not recommend regular follow-up If symptom present, evaluate by each system

GH, growth hormone; CBC, complete blood count; LFT, liver function test; HbA_{1c}, hemoglobin $A1_c$; TSH, thyroid stimulating hormone; IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram.

show positive affect on final height. These results emphasize the importance of early diagnosis and initiation of GH therapy for optimal height outcomes. Furthermore, even though evidence on adverse events due to GH therapy in NS patients is scarce, careful monitoring of cardiac changes and malignancy is desired.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Mendez HM, Opitz JM. Noonan syndrome: a review. Am J Med Genet 1985;21:493-506.
2. Digilio MC, Conti E, Sarkozy A, Mingarelli R, Dottorini T, Marino B, et al. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet 2002;71:389-94.
3. Nava C, Hanna N, Michot C, Pereira S, Pouvreau N, Niihori T, et al. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet 2007;44:763-71.
4. Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y. The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. Hum Mutat 2008;29:992-1006.
5. Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. Horm Res 2009;71:185-93.
6. Lee BH, Kim JM, Jin HY, Kim GH, Choi JH, Yoo HW. Spectrum of mutations in Noonan syndrome and their correlation with phenotypes. J Pediatr 2011;159:1029-35.
7. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet 2013;381:333-42.
8. Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. Nat Rev Cancer 2003;3:459-65.
9. Giehl K. Oncogenic Ras in tumour progression and metastasis. Biol Chem 2005;386:193-205.
10. Ko JM, Kim JM, Kim GH, Yoo HW. PTPN11, SOS1, KRAS, and RAF1 gene analysis, and genotype-phenotype correlation in Korean patients with Noonan syndrome. J Hum Genet 2008;53:999-1006.
11. Cordeddu V, Di Schiavi E, Pennacchio LA, Ma'ayan A, Sarkozy A, Fodale V, et al. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. Nat Genet 2009;41:1022-6.
12. Ranke MB, Heidemann P, Knupfer C, Enders H, Schmaltz AA, Bierich JR. Noonan syndrome: growth and clinical manifestations in 144 cases. Eur J Pediatr 1988;148:220-7.
13. Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. Arch Dis Child 2007;92:128-32.
14. Binder G, Grathwol S, von Loeper K, Blumenstock G, Kaulitz R, Freiberg C, et al. Health and quality of life in adults with Noonan syndrome. J Pediatr 2012;161:501-5.e1.
15. Romano AA, Blethen SL, Dana K, Noto RA. Growth hormone treatment in Noonan syndrome: the National Cooperative Growth Study experience. J Pediatr 1996;128(5 Pt 2):S18-21.
16. Tamburrino F, Gibertoni D, Rossi C, Scarano E, Perri A, Montanari F, et al. Response to long-term growth hormone therapy in patients affected by RASopathies and growth hormone deficiency: patterns of growth, puberty and final height data. Am J Med Genet A 2015;167A:2786-94.
17. Noordam C, van der Burgt I, Sweep CG, Delemarre-van de Waal HA, Sengers RC, Otten BJ. Growth hormone (GH) secretion in children with Noonan syndrome: frequently abnormal without consequences for growth or response to GH treatment. Clin Endocrinol (Oxf) 2001;54:53-9.
18. Ferreira LV, Souza SA, Arnhold IJ, Mendonca BB, Jorge AA. PTPN11 (protein tyrosine phosphatase, nonreceptor type 11) mutations and response to growth hormone therapy in children with Noonan syndrome. J Clin Endocrinol Metab 2005;90:5156-60.
19. Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, Lyonnet S, et al. Noonan syndrome: relationships between genotype, growth, and growth factors. J Clin Endocrinol Metab 2006;91:300-6.
20. Cotterill AM, McKenna WJ, Brady AF, Sharland M, Elsawi M, Yamada M, et al. The short-term effects of growth hormone therapy on height velocity and cardiac ventricular wall thickness in children with Noonan's syndrome. J Clin Endocrinol Metab 1996;81:2291-7.
21. Choi JH, Lee BH, Jung CW, Kim YM, Jin HY, Kim JM, et al. Response to growth hormone therapy in children with Noonan syndrome: correlation with or without PTPN11 gene mutation. Horm Res Paediatr 2012;77:388-93.
22. MacFarlane CE, Brown DC, Johnston LB, Patton MA, Dunger DB, Savage MO, et al. Growth hormone therapy and growth in children with Noonan's syndrome: results of 3 years' follow-up. J Clin Endocrinol Metab 2001;86:1953-6.
23. Jeong I, Kang E, Cho JH, Kim GH, Lee BH, Choi JH, et al. Long-term efficacy of recombinant human growth hormone therapy in short-statured patients with Noonan syndrome. Ann Pediatr Endocrinol Metab 2016;21:26-30.
24. Lee PA, Ross J, Germak JA, Gut R. Effect of 4 years of growth hormone therapy in children with Noonan syndrome in the American Norditropin Studies: Web-Enabled Research (ANSWER) Program® registry. Int J Pediatr Endocrinol 2012;2012:15.
25. Noordam C, Peer PG, Francois I, De Schepper J, van den Burgt I, Otten BJ. Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-

receptor-type 11. Eur J Endocrinol 2008;159:203-8.
26. Romano AA, Dana K, Bakker B, Davis DA, Hunold JJ, Jacobs J, et al. Growth response, near-adult height, and patterns of growth and puberty in patients with noonan syndrome treated with growth hormone. J Clin Endocrinol Metab 2009;94:2338-44.
27. Osio D, Dahlgren J, Wikland KA, Westphal O. Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr 2005;94:1232-7.
28. Raaijmakers R, Noordam C, Karagiannis G, Gregory JW, Hertel NT, Sipilä I, et al. Response to growth hormone treatment and final height in Noonan syndrome in a large cohort of patients in the KIGS database. J Pediatr Endocrinol Metab 2008;21:267-73.
29. Noordam K, van der Burgt I, Brunner HG, Otten BJ. The relationship between clinical severity of Noonan's syndrome and growth, growth hormone (GH) secretion and response to GH treatment. J Pediatr Endocrinol Metab 2002;15:175-80.
30. Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab 2005;90:5377-81.
31. Noordam C, Draaisma JM, van den Nieuwenhof J, van der Burgt I, Otten BJ, Daniels O. Effects of growth hormone treatment on left ventricular dimensions in children with Noonan's syndrome. Horm Res 2001;56:110-3.
32. Jongmans MC, van der Burgt I, Hoogerbrugge PM, Noordam K, Yntema HG, Nillesen WM, et al. Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation. Eur J Hum Genet 2011;19:870-4.
33. McWilliams GD, SantaCruz K, Hart B, Clericuzio C. Occurrence of DNET and other brain tumors in Noonan syndrome warrants caution with growth hormone therapy. Am J Med Genet A 2016;170A:195-201.