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Management strategies for optimal linear growth in Noonan syndrome (NS) children: minireview and case series of three patients with NS due to *PTPN11* mutation and confirmed growth hormone deficiency

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Abstract

Noonan syndrome (NS) is a disease in which molecular genetic tests reveal mutations in the genes responsible for the RAS/MAPK signalling pathway, most often *PTPN11*. Short stature leading to unsatisfactory final height (FH) is one of the components of NS. It is an established worldwide practice to treat NS children with recombinant human growth hormone (rhGH), but in Poland it remains a controversial issue and typically is only recommended in cases of concomitant growth hormone deficiency (GHD), in which the therapy is considered as substitutive. In this paper, therefore, we present the most recent available knowledge on the principles of rhGH treatment in children with NS, as well as an analysis of the course of treatment in 3 of our own cases, which were challenging for the clinicians treating them. rhGH therapy improves linear growth and FH in NS patients; however, not all children achieve satisfactory results. The aim of the article is to summarise the results of long-term rhGH treatment used as monotherapy or — in cases of deteriorating growth prognosis during monotherapy — combined with pharmacological inhibition of puberty [with gonadotropin-releasing hormone analogues (GnRHa)] or of epiphyseal ossification [with aromatase inhibitors (AI)] in 3 NS children due to *PTPN11* mutation. Height standard deviation score (hSDS) during treatment improved in all children by 1.6 ± 0.67. We observed a positive correlation between height velocity (HV) and the insulin-like growth factor 1/insulin-like growth factor binding protein 3 (IGF-1/IGFBP-3) molar ratio SDS (r = 0.41). We discuss our results with data from the literature, presenting a mini review.

Conclusions:

1. IGF-1/IGFBP-3 molar ratio SDS assessment helps to optimise the rhGH doses in NS children.
2. Although rhGH therapy generally improves HV and FH in short NS children, if the growth prognosis during therapy worsens, it is worth considering additional treatment with GnRHa or AI. **(Endokrynol Pol 2024; 75 (6): 592–603)**

Key words: *growth; growth hormone deficiency; growth hormone therapy; short stature; Noonan syndrome; PTPN11; molecular diagnostics; IGF-1; IGFBP-3; letrozole; GnRH agonist*

Introduction

The main function of growth hormone (GH) in childhood is to promote linear growth until bone epiphyses are closed. Thus, GH substitution is a standard treatment in children with growth hormone deficiency (GHD). The beneficial effects of using GH administrations in some diseases not related to GHD have also been documented, and GH therapy has been approved for indications other than GHD. An example of genetically determined disorders, in which GH therapy is approved for growth promotion, is Noonan syndrome (NS). Currently, there is an ongoing discussion about the principles of recombinant human GH (rhGH) treatment in short children with NS, including the optimal time to start therapy, rhGH dosage, monitoring of the therapy, as well as the safety of rhGH treatment. However, no cases of children with NS additionally treated with gonadotropin-releasing hormone (GnRH) analogues (GnRHa) or aromatase inhibitors (AI) to improve final height (FH) have been reported so far.

In Poland, to date, children with NS have only been treated with rhGH if they had concomitant GHD, whereas worldwide, treatment of children with NS with rhGH is a recognised clinical practice, regardless of the GH status in the stimulation tests.

We present the most recent data on rhGH treatment in patients with the most common mutation causing this disorder and 3 cases of patients with NS and GHD who were treated with rhGH long-term to demonstrate the management and outcome of our efforts.

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NS (OMIM 163950) is an autosomal, dominant, relatively frequent genetic disorder, which occurs in approximately 1 in 1000-2500 individuals [1]. It is caused by germline mutations in genes encoding components of the Ras/mitogen-activated protein kinases (MAPK) pathway (Ras/MAPK). This signal transduction cascade controls the most important cellular processes (e.g. proliferation, differentiation, migration, and metabolism) in response to many growth factors, hormones, and cytokines [2]. Genes encoding this pathway, whose mutations are responsible for the symptoms of NS, include *PTPN11* (50% of cases), SOS1 (10–13%), RAF1 (3–17%), KRAS (< 4%), RIT1 (4–9%), MAP2K1 (< 2%), BRAF (< 2%), and NRAS (< 1%) [1].

Regardless of the type of mutation, the features that characterise NS are as follows: facial dysmorphia (90%), congenital heart defects (50–90%), and short stature (50–70%) [1]. The diagnostic criteria were first developed by van der Burgt in 1994 and revised in 2007 [3].

As mentioned above, a mutation in the *PTPN11* gene is the most common cause of NS. The *PTPN11* gene is located in the chromosome 12q24.13 region and comprises 16 exons. It encodes Src homology region 2 domain-containing phosphatase-2 (SHP-2) 3, also known as a protein tyrosine phosphatase cytoplasmic enzyme that positively regulates Ras signalling. SHP-2 binds to its phosphotyrosyl-containing signalling partners through the SH2 domain for controlling its subcellular localisation and functional regulation [1, 2].

Regarding the growth processes in children with NS, the birth length and birth weight are usually normal, but in the postnatal period the height velocity (HV) is slow, and an attenuated pubertal growth spurt is observed during puberty [4, 5]. For this reason, the FH of patients with NS is shorter than in the population and amounts to approximately 161–162.5 cm for men and 150–153 cm for women [2, 6]. Possible mechanisms for short stature in NS are suspected to include GHD, neurosecretory dysfunction, or GH resistance [6]. The rhGH therapy was approved for children with NS in the USA in 2007, and subsequently in Brazil, Israel, Japan, South Korea, and in Europe in 2020 [5]. Since then, many studies have reported that this treatment results in significant improvement in HV and increase in standard deviation score (SDS) of height (hSDS) during the growing process in children and adolescents [7–14]. These studies most often concern the first 4 years of treatment, but long-term observations are rarely presented. They showed that children with NS generally achieved a good growth response to rhGH therapy, although those with a *PTPN11* gene mutation had worse results compared to other NS-causing gene mutations, due to their surmised mild insensitivity to GH [15, 16].

Recently, there have been reports on the effect of combined treatment with rhGH and GnRHa or with rhGH and AI on improving FH in short stature children with poor growth prognosis [17–21]. However, no data have yet been presented regarding the use of GnRH analogues or AI therapy in addition to rhGH treatment for FH improvement in short stature children with NS.

The aim of the study was to describe the clinical characteristics and results of rhGH therapy in children with NS caused by *PTPN11* gene mutation and with comorbid GHD based on 3 cases with long-term follow-up, treated at our clinical centre.

In the discussion, the authors presented a mini review of the current knowledge on the principles of rhGH treatment in short children with NS, including the optimal time to start therapy, rhGH dosage, and effectiveness and safety of rhGH treatment. Moreover, it was discussed whether children with NS treated with rhGH can improve their growth prognosis by inhibition of the process of puberty as a result of the use of GnRH analogues (GnRHa) or by inhibiting the ossification of bone epiphyses using AI.

Case reports

We collected 3 cases of NS patients with concomitant GHD, who were treated with rhGH in the Department of Endocrinology and Metabolic Diseases of the Polish Mother's Memorial Hospital - Research Institute in Lodz (Poland) over a period of 4.5 to 11 years, from 2013 to 2024. In each case, the diagnosis of GHD was made based on the results of 2 stimulating tests (using clonidine and glucagon) with a cut-off point: max GH secretion during tests < 10 ng/mL for the diagnosis of GHD. Therefore, all children received fully reimbursed rhGH therapy, which is provided to short stature children with GHD in our country as a part of government therapeutic programs. The patients were assessed at the visit initiating rhGH treatment and then during follow-up visits: the first one 3 months after the start of treatment, and subsequent visits every 6 months. Based on the available medical records and the results of laboratory and imaging tests, the following data were collected for each control point (if available): anthropometric data (height and weight), stage of puberty according to Tanner scale (I–V), recommended dose of rhGH, laboratory test results, and bone age (BA).

Anthropometric data were converted: height into hSDS and body mass index (BMI) into BMISDS, according to local data [22]. Target height (TH) was calculated according to the formula: [(paternal height + maternal height)/2] +6.5 cm for boys

and –6.5 cm for girls, and TH SDS was calculated. BA was determined based on the results of X-ray examinations of the non-dominant wrist and hand (according to the Greulich-Pyle method), which were performed for the first time before the initiation of rhGH therapy and then repeated once a year during the treatment. A BA/chronological age (CA) ratio was calculated for each available BA result. Once rhGH therapy was initiated, serum laboratory tests were performed, including assessment of such molecules concentrations as insulin-like growth factor 1 (IGF-1) and insulin like growth factor binding protein 3 (IGFBP-3), as well as free thyroxin (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH), and HbA_{1c} — assessed to ensure euthyreosis and normal glucose level, depict the metabolic effect, and adjust the rhGH dosage. None of the children had hypothyroidism at baseline or required treatment with L-thyroxine during therapy. No elevated HbA1c levels were observed in any child. The dose of rhGH was modified based on the IGF-1 result. IGF-1 concentrations were expressed in terms of SDS for sex and age (IGF-1 SDS), according to reference data [23].

IGF-1 and IGFBP-3 concentration were assessed using Immulite DPC assays. For IGF-1, the World Health Organisation (WHO) National Institute for Biological Standards and Control (NIBSC) First International reference reagent (IRR) 87/518 standard was used, with an analytical sensitivity of 20 ng/mL, a calibration range up to 1600 ng/mL, an intra-assay coefficient of variation of 3.1–4.3%, and inter-assay coefficient of variation CV of 5.8–8.4%. Furthermore, the IGF-1/IGFBP-3 molar ratio was calculated and assessed according to reference data [24, 25].

The concentrations of TSH, FT4, and FT3 were measured using the electrochemiluminescent immunoassay (ECLIA) method with commercially available appropriate kits (Roche Diagnostic, Mannheim, Germany). Normal range values were as follows: for TSH: 0.51–4.3 mIU/l, with inter-assay coefficients of variation (CVs) 1.3–1.8%, for FT4: 0.98-1.63 ng/dl; and for FT3: 2.56–5.01 pg/mL with CVs 2.0–2.4%.

Case 1

An 8.5-year-old prepubertal girl with short stature, congenital heart disease — ASDII (ostium secundum atrial septal defect), and typical features of NS was admitted to our department for diagnostics of short stature. The girl was born to unrelated parents in the 37th week of pregnancy, appropriate for gestational age (AGA), with normal body weight — 3430 g (0.92 SD) and normal body length — 54 cm (2.93 SD). The girl did not have any chronic diseases (beside ASDII), did not take any medications, or report any complaints. The parents' heights were as follows: for the mother — 156 cm, and the father — 173 cm. Thus, her TH is 158 cm (–1.1 SD). Finally, GHD was confirmed (maximal GH concentration in stimulation tests was: 7.73 ng/mL) with low IGF-1 concentration (< 25 ng/mL; reference range: 74–388 ng/mL), but genetic analysis revealed a mutation 1510 A>G in exon 13 of the *PTPN11* gene, and NS was diagnosed. NS is familial in this girl; the girl's mother was diagnosed with the same genetic mutation. The thyroid serum profile as well as the results of magnetic resonance imaging (MRI) of the hypothalamic-pituitary region were normal.

Before starting rhGH treatment, her height was 114 cm (hSDS: –3.43, Fig. 1) and her BA was assessed as 5 years and 9 months. The girl was treated with rhGH for 8 years. At the age of 16.5 years, her present height is 157.8 cm (hSDS: –1.17, Fig. 1), BA: 14 years, reaching her near final height (NFH). Menarche occurred at the age of 15 years. No additional treatment was applied. The girl's height is reaching TH. The treatment was uncomplicated and considered successful because there was a significant improvement in hSDS (+2.27).

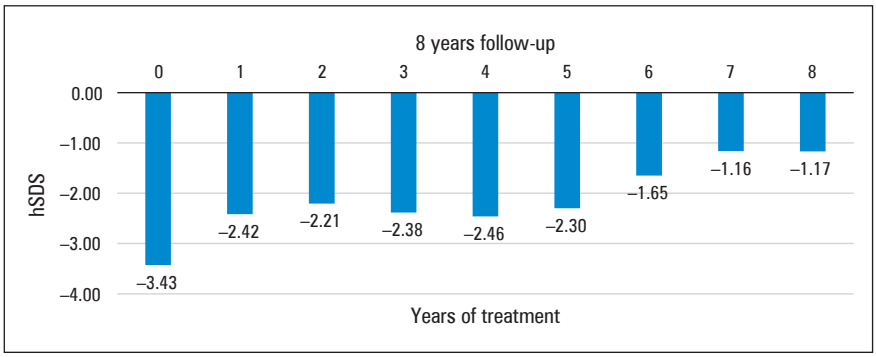

Figure 1. *Height standard deviation score (hSDS) changes (–3.43 to –1.17) during 8 years of recombinant human growth hormone (rhGH) treatment of a girl with Noonan syndrome (NS) (case 1), who is reaching her near final height (NFH)*

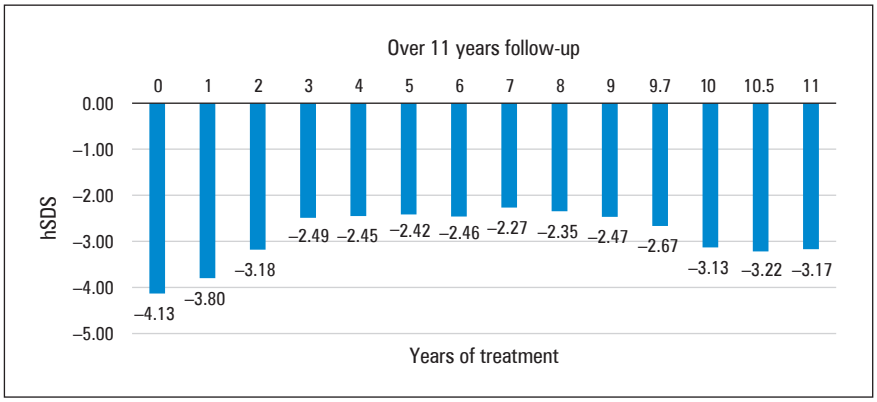

Figure 2. *Height standard deviation score (hSDS) changes (–4.13 to –3.17) during 11 years of recombinant human growth hormone (rhGH) treatment of a boy with Noonan syndrome (NS) (case 2), who is treated with rhGH and — for 12 months — with letrozole*

Case 2

A 5.9-year-old prepubertal boy with short stature and typical features of NS was admitted to our department for diagnostics of short stature. The boy was born to unrelated parents in the 39th gestational week, appropriate for gestational age (AGA), with normal body weight of 3880 g (0.78 SD) and normal body length of 52 cm (0.77 SD). The boy did not have any chronic diseases, take any medications, or report any complaints. There were no chronic diseases in the family. The parents' heights were as follows: for the mother — 156 cm, and the father — 175 cm. His TH is 172 cm (–1.12 SD). Finally, GHD was confirmed (max GH in stimulation tests was: 9.32 ng/mL) with low IGF-1 concentration (40 ng/mL; reference value: 52–297 ng/mL), but genetic analysis revealed a M504V mutation in exon 13 of the *PTPN11* gene, and NS was diagnosed. The thyroid serum profile as well as the results of MRI of the hypothalamic-pituitary region were normal.

Before starting rhGH treatment, his height was 98.4 cm (hSDS: –4.13, Fig. 2), and BA was 2.5 years. The boy was treated with rhGH for 11 years. At the age of 15.5 years, his height was 155.5 cm (hSDS: –2.67, Fig. 2), BA — 14–15 years, sexual maturity was assessed as Tanner stage IV, and annual HV was low (below 3 cm/year), so there was a concern that the boy will not achieve TH-like growth. After discussing the seriousness of the situation with the parents and patient, written consent was obtained to start additional off-label treatment with letrozole (third-generation aromatase inhibitor) together with normal doses of rhGH. After half a year of mutual treatment, his BA remained at 14–15 years and his HV was not satisfactory - his height was 157.0 cm (hSDS: –3.22, Fig. 2) and HV = 3.0 cm/year. We decided to continue this additional treatment for another 6 months, but with increased rhGH doses to elevate IGF-1 concentration and IGF-1/IGFBP-3 molar ratio. The boy is currently 159.3 cm (SD: –3.17, Fig. 2), thus his HV improved once again to 4.6 cm/year, and with BA 15 years he is still growing, giving hope for further enhancement in FH.

Case 3

A 10.5-year-old prepubertal girl with short stature and typical features of NS was admitted to our department for diagnostics of short stature. The girl was born to unrelated parents, with normal body weight of 3400 g (0.36 SD) and normal body length of 55 cm (3.16 SD) in the 38th gestational week. The girl did not have any chronic diseases, take any medications, or report any complaints. There were no chronic diseases in the family. The parents' heights were as follows: for the mother — 174 cm, and the father — 176 cm. Her TH is 168.5 cm (0.42 SD). Finally, GHD was confirmed (max GH in stimulation tests was: 7.12 ng/mL) with low IGF-1 (116.8 ng/mL; reference range: 123–427 ng/mL). Genetic analysis also revealed a c.922A>G mutation in exon 8 of the *PTPN11* gene, thus NS was diagnosed. The thyroid serum profile as well as the results of MRI of the hypothalamic-pituitary region were normal.

Before starting rhGH treatment, her height was 122 cm (hSDS: –3.38, Fig. 3), BA was 7 years and 10 months. The girl was treated with rhGH for 4.5 years. At the age of 13 y 9 m, BA was 11 y, but at the age of 13 y 11 m, 2 months later, her BA was 13 years. Over that time, rapidly progressive puberty occurred. Without a pubertal growth spurt, her height was 147.7 cm (hSDS: –2.30, Fig. 3), and puberty was assessed as stage III/IV according to the Tanner scale. There was a concern that the girl would not achieve TH-like growth and after discussing the situation with the parents and the child, so consent was obtained to start additional treatment with triptorelin (GnRHa). The reimbursable treatment

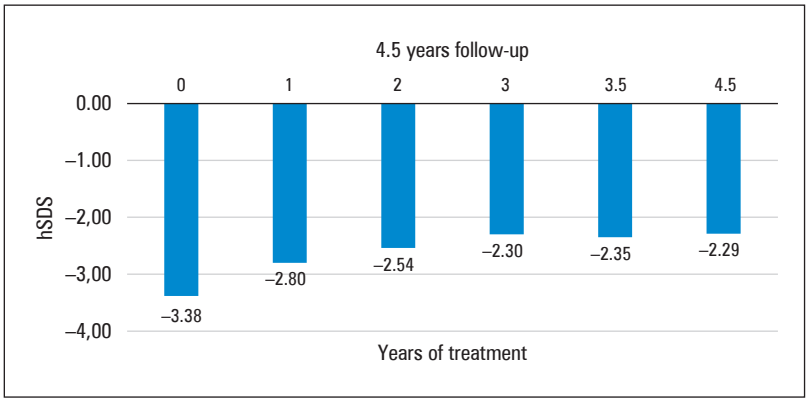

Figure 3. *Height standard deviation score (hSDS) changes (–3.38 to –2.29) during 4.5 years of recombinant human growth hormone (rhGH) treatment of a girl with Noonan syndrome (NS) (case 3), treated with rhGH and — for the last 10 months – additionally with triptorelin*

in Poland requires drug intramuscular administration in an outpatient clinic, which requires the patient to visit the hospital every 28 days. After the first dose of GnRHa, menarche occurred; subsequent menarches were not observed. She continues the growing process, but slowly – her BA does not accelerate. Thus, after 3.7 years of rhGH therapy and 10 months of mutual treatment (both GnRHa + rhGH), she is 14.9 years old, her height is 149.8 cm (hSDS: –2.29, Fig. 3), and her BA is still 13 years. Further GnRHa treatment was discontinued due to the patient's fatigue with monthly visits to the outpatient clinic, and rhGH treatment was maintained while further growth was observed.

Results

In all our patients with NS, a mutation in the *PTPN11* gene and simultaneous occurrence of GHD were confirmed. rhGH treatment was initiated at 5.9, 8.5 and 10.5 years of age, respectively, at an average age of 8.3 ± 2.7 SD years (Tab. 1). The rhGH dose in all cases was within the range 0.48-0.89 IU/kg/week. Mean hSDS at baseline was –3.65 ± 0.48 SD. In all cases, hSDS during treatment improved by about 1.08 to 2.27 (hSDS mean ± SD: 1.6 ± 0.67, Tab. 1.). We observed a strong positive correlation between HV and IGF-1/IGFBP-3 molar ratio SDS (r = 0.41) (Fig. 4). In one patient (case 1), near FH (NFH) was obtained, consistent with the TH calculated based on parental height. In the remaining 2 patients (case 2 and case 3), rapid progression of BA and puberty process were observed, which resulted in worse growth prognosis. Therefore, to prolong the growth process and allow for improvement in FH, additional treatment with GnRHa or AI was used, which ultimately resulted in further improvement in HV and further height gains in these patients. We did not observe any adverse events due to the used therapies.

Mini-review

The influence of the time of initiation of rhGH therapy in children with NS on the effectiveness of treatment

As mentioned in the introduction, rhGH is recommended for the treatment of short stature in children with NS; however, the analysis of the results obtained in published studies is difficult due to the usually small groups of patients presented, different types of mutations determining NS in them, different ages at the start of therapy, differences in the used doses, and finally often unavailable state of GH secretion and lack of long-term follow-up [5]. However, based on the available data, it appears that the most effective increase in HV occurs in the first year of treatment [21, 26], but its significant improvement is achieved by using rhGH therapy for at least 4 years [8]. Furthermore, it has been shown that the earlier the treatment is started and the longer it lasts until the child's puberty, the greater the improvement in final hSDS [10, 12, 13, 16, 26, 27]. However, these conclusions are often based on the results of studies on short-term observation, most often lasting for 4 years of rhGH treatment, where FH or even near FH have not yet been obtained. Long-term follow-up studies showing the FH of patients with NS after completion of rhGH treatment are less frequently published, and their results indicate very large discrepancies (from 130 cm to 162 cm in females and from 133 cm to 180 cm in males) [12]. According to Libraro A. et al., based on a group of 41 NS patients with GHD and available FH results, the hSDS increased from −3.10 ± 0.84 to −2.31 ± 0.99 during rhGH treatment, with a total height gain of 0.79 ± 0.74, and no significant difference between untreated and treated NS at FH [38].

In our analysis, we presented cases of children who were treated in our centre for more than 4 years, dur-

Table 1. *Anthropometric and laboratory data in the presented children*

	CA (years)	Treatment time (years)	Height (cm)	HV (cm/year)	hSDS	BA (years)	rhGH (IU/kg/week)	IGF-1 (ng/mL)	IGF-1 SDS	IGF-1 within range	IGF BP3	IGF-1/IGF BP3 molar ratio	IGF-1/IGF BP3 molar ratio SDS	Tanner stage
Case 1 – Female TH 158 cm, delta hSDS = +2.26	8y6m	0	114	3.90	–3.43	5y9m	0.65	< 25	–3.77	<	1.56	0.09	–2.23	T1 P1
	9y5m	1	123	9.82	–2.42	7y10m	0.7	117	–1.44	n	4.93	0.1329	–0.56	T1 P1
	10y7m	2	130.1	6.09	–2.21	ND	0.85	149	–1.39	n	5.54	0.1506	–0.51	T1 P1
	11y7m	3	135	4.90	–2.38	9.5y	0.89	156.7	–1.64	n	4.19	0.2093	0.85	T1 P1
	12y9m	4	142	6.00	–2.46	12y	0.62	138.1	–2.37	<	4.11	0.1882	–1.45	T1 P2
	13y7m	5	147.2	6.24	–2.30	ND	0.69	211.6	–1.64	n	4.63	0.2562	–0.87	T1/2 P2
	14y6m	6	153.1	6.44	–1.65	13y	0.66	226.7	–1.72	n	4.05	0.3135	–0.22	T2 P2
	15y5m	7	157.2	4.47	–1.16	13.5y	0.48	352.8	–0.59	n	5.39	0.3663	1.18	T3 P4 M
	16y	7.5	157.8	1.03	–1.17	14–15y	0.49	224.8	–1.99	n	4.95	0.2545	–1.02	T4 P4
	16y6m	8	158.5	0.64	–1.08	16y	End	352.6	–0.18	n	6.30	0.314	0.31	End
Case 2 – Male TH 172 cm, delta hSDS = +1.0 SD	5y10m	0	98.4	3.40	–4.13	2.5y	0.56	40	–1.99	<	–	–	–	P1
	6y9m	1	106.8	9.16	–3.80	3.5y	0.58	118	–0.11	n	–	–	–	P1
	7y10m	2	113.1	5.82	–3.18	4y	0.74	245	1.04	n	4.98	0.2755	5.37	P1
	9y	3	121.3	7.03	–2.49	5.5y	0.73	171	–0.15	n	4.67	0.2051	2.01	P1
	9y10m	4	125.3	4.80	–2.45	ND	0.75	181	–0.34	n	5.75	0.1763	0.49	P1
	11y	5	131.5	5.31	–2.42	ND	0.76	179	–0.82	n	6.39	0.1569	–2.09	P1
	12y	6	136	4.50	–2.46	8y	0.83	290	–0.05	n	5.44	0.2987	1.65	P2
	13y	7	142	6.00	–2.27	11y	0.77	316.8	–0.15	n	6.03	0.2942	–0.50	P2
	13y10m	8	147.4	6.48	–2.35	13y	0.6	486.7	0.72	n	6.64	0.4107	3.20	P2
	14y10m	9	153.5	6.10	–2.47	13.5y	0.6	511.7	0.67	>	6.3	0.4548	2.73	P2
	15y5m	10	155.5	3.43	–2.67	14–15y	0.59	321.5	–0.68	n	6.49	0.2776	–3.27	P3 +L
	15y11m	10	157	3.50	–3.12	14–15y	0.81	323.5	–0.73	n	–	-	–	P3 +L
	16y7m	11	159.3	3.26	–3.17	14–15y	0.74	573.4	0.88	>	621	0.517	4.94	P4 +L

Table 1. *Anthropometric and laboratory data in the presented children*

	CA (years)	Treatment time (years)	Height (cm)	HV (cm/year)	hSDS	BA (years)	rhGH (IU/kg/week)	IGF-1 (ng/mL)	IGF-1 SDS	IGF-1 within range	IGF BP3	IGF-1/IGF BP3 molar ratio	IGF-1/IGF BP3 molar ratio SDS	Tanner stage
Case 3 - Female TH 168.5 cm, delta hSDS = +1.16	10y6m	0	122	3.50	–3.38	7y10m	0.69	116.8	–1.82	<	3.43	0.1910	1.94	T1 P1
	11y6m	1	130.4	8.40	–2.80	10y	0.75	325.6	–0.11	n	5.79	0.3152	4.7	T1 P1
	12y7m	2	140.5	9.32	–2.54	10y	0.66	562.6	0.87	>	6.71	0.4698	7.64	T2 P2
	13y9m	3.5	147.7	6.17	–2.30	11y	0.69	531.6	0.63	>	6.24	0.4333	4.12	T3 P3
	13y11m	3.7	147.7	5.60	–2.35	13y	0.45	482.8	–	n	–	-	–	T3/4 P3/4 M + GnRHa
	14y3m	4.1	149.2	3.50	–2.35	13y	0.45	452	0.20	n	5.78	0.4385	2.69	T3/4 P3/4 + GnRHa
	14y9m	4.3	149.8	2.52	–2.29	13y	0.43	435	–	n	5.61	0.434	2.59	T4 P4 without GnRHa

CA — chronological age; BA — bone age; HV — height velocity; P — pubarche; T — thelarche; M — menarche; End — end of treatment; L — letrozole additional treatment; GnRHa — GnRH analogue additional treatment; ND — no data; < — below the range; > — above the range).

ing which we could observe long-term effects of rhGH therapy. Although rhGH treatment began at different ages (8.5, almost 6.0, and 10.5 years of age), in each of those cases, it took place before the onset of puberty, which occurred in the first case — at 3 years, in the second — at 5 years, and in the third — at 2 years after the start of rhGH therapy.

In the second case, despite the very early initiation of treatment (5 years and 10 months of age), we did not achieve a spectacular final effect regarding the height SDS, and the child ultimately required additional treatment that inhibited the ossification of the epiphyses to prolong the growth process. In turn, in the first case — in whom rhGH treatment was implemented relatively late (at 8.5 years of age) — the best final effect was achieved, i.e. the girl's FH was consistent with TH, without the need for additional therapies. Therefore, the cases we present do not confirm the principle that starting treatment as early as possible guarantees success in terms of FH.

In turn, the results of published studies suggest that in children with NS treated with rhGH, the growth rate increases during the first 4 years of therapy and then slows down [8]. In our cases, the growth rate also increased significantly in the first 3 years of therapy to over 6 cm/year but slowed down in the fourth year. However, at further follow-up, we observed another acceleration in growth rate, probably related to the pubertal growth spurt. Unfortunately, in 2 cases it was significantly lower (about 6 cm/year) than observed in the healthy population. In the following years of treatment, we observed further reduction of HV. In the third case, the growth acceleration was greater (approximately 8.4 cm in the first year of rhGH therapy, 9.3 cm in the second, and 6.7 cm in the third); however, the onset of puberty coincided with the second/third year of rhGH treatment. Perhaps this is why the growth rate was so high. Regrettably, due to the advancement of BA before the girl reached the desired height for the onset of puberty, the prediction of TH turned out to be unfavourable. This observation, in turn, indicates that if puberty begins quite early and is accompanied by rapid acceleration of BA, it is worth considering inhibiting puberty through treatment with GnRH analogues.

Research results indicate also that in children with NS caused by a *PTPN11* mutation, the response to rhGH may be worse, probably due to mild GH insensitivity [15, 16, 28, 29]. It is also suggested that in the case of poor growth response despite the use of high doses of rhGH, treatment should be discontinued [8]. In our cases of children with NS as a result of *PTPN11* mutation, we found the possibility of further improvement of height SDS by using additional therapies to extend

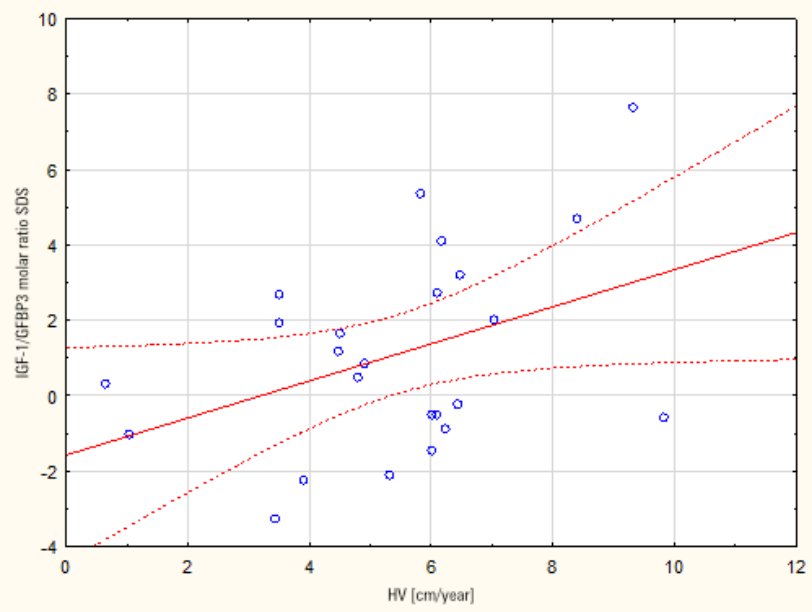

Figure 4. *Correlation between insulin-like growth factor 1/insulin-like growth factor binding protein 3 (IGF-1/IGFBP-3) molar ratio standard deviation score (SDS) and height velocity (HV) in the analysed children (r = 0.41, p < 0.05).*

the duration of the growth process, still using doses of rhGH that ensure normal IGF-1 levels. Perhaps our results will be used to consider the suppression of puberty using GnRH analogues in girls and boys or AI in boys with NS who have not achieved sufficient growth before puberty.

The influence of the dose of rhGH used and the improvement achieved in the concentration of IGF-1 and IGF-1/IGFBP-3 molar ratio in children with NS on the effectiveness of treatment

Studies on rhGH dosage in NS remain inconclusive. There are no solid beliefs concerning ideal dosage, and the decision is generally personalised to the patient, with attention paid to comorbidities and potential side effects. The initial doses of rhGH in short children with NS range from 0.69 IU/kg/week (0.23 mg/kg/week) to 1.39 IU/kg/week (0.46 mg/kg/week), and those used during further rhGH treatment usually range from 0.42 IU/kg/week (0.14 mg/kg/week) to 1.39 IU/kg/week (0.46 mg/kg/week) [8, 12, 13, 15]. In our study, the rhGH doses used remained within the ranges of 0.48–0.88 IU/kg/week, corrected by IGF-1 concentration and IGF-1/IGFBP-3 molar ratio. Thus, we used quite low doses of rhGH both at the beginning of treatment and in the following years of therapy. It should be mentioned that all presented patients were diagnosed with GHD; therefore, rhGH therapy was a replacement treatment and did not involve overcoming GH resistance. In all our cases, the initial level of IGF-1 was reduced, and due to the doses of rhGH we proposed, the IGF-1 levels at least tripled in the first year of treatment. Moreover, in case 1, in which the IGF-1 level increased by up to 400% in the first year of treatment compared to the baseline values, during the entire therapy period the rhGH doses never exceeded 0.89 IU/kg/week, and the level of IGF-1 remained within normal range. In this girl, the improvement in height SDS throughout the treatment period was 2.27 SD (from –3.43 to –1.17 SD), and the girl achieved NFH (157.8 cm) consistent with TH (158 cm). It is also worth mentioning that the patient's mother suffered from the same disease. Although she had never been treated with rhGH, she also gained a height of 158 cm. Therefore, the TH calculated for this girl was relatively low. As a child, the girl's mother was not as short as her daughter. In fact, this was the reason why the mother admitted her daughter to the endocrinology department and, finally, an additional diagnosis of GHD was confirmed. Although we did not use very high doses of rhGH in this girl, we managed to obtain satisfactory FH.

We believe that one of the important factors to improve and maintain her HV was the normal level of the IGF-1/IGFBP-3 molar ratio. In our case, this is what we observed. The IGF-1/IGFBP-3 molar ratio systematically increased from 0.09 (–2.23 SD) before treatment to 0.13 (–0.56 SD) after the first year of therapy, and in subsequent years to 0.2 (–0.87 SD) and 0.3 (1.18 SD), which is consistent with the reference values for healthy children [24, 25].

It should be noted that although short-term use of high doses of rhGH has been reported to improve

growth velocity, safety data for long-term high-dose therapy are unknown [15].

It seems that calculating the IGF-1/IGFBP-3 molar ratio SDS helps to decide whether to reduce or increase the rhGH dose [24].

In turn, in the boy (case 2) using relatively low doses of rhGH (0.6 IU/kg/week), an increased IGF-1 concentration was observed, but this did not result in further improvement in growth rate. However, in the fourth and fifth years of therapy, the IGF-1/IGFBP-3 molar ratio decreased below –0.2 (–2.09 SD). It can be assumed that the doses in this case were too low. In the girl, case 3, treatment was started quite late, and using doses of 0.66–0.75 IU/kg/week normal IGF-1 concentrations with a normal IGF-1/IGFBP-3 molar ratio were obtained. Thus, very accurate treatment results could be expected. Meanwhile, the puberty period occurred quite early, and the BA began to advance; thus, a good final result was unsure. Therefore, additional treatment to inhibit puberty was implemented. One should perhaps consider whether it was not applied too late.

As mentioned, long-term effects are not often reported, but in the available publications, the range of FH varies greatly, from very low to normal, and it is difficult to determine the cause of failures. The cases we describe are homogeneous in that they concern children with the *PTPN11* mutation and are characterised by GHD. It seems that the dose of rhGH should be selected individually, under the control of not only IGF-1, but also the IGF-1/IGFBP-3 molar ratio, which should be within the normal ranges. Calculating the IGF-1/IGFBP-3 molar ratio SDS leads to additional benefits [24].

On the other hand, in our cases, only one of the children reached a height close to their TH, and the rest required additional treatment. It is difficult to determine the exact reasons for this, but it seems that the dosage of rhGH is not the only factor; thus, ensuring the appropriate level of IGF-1 and maintaining the safety principles of therapy are of key importance.

Safety of the rhGH treatment in children with NS

In the literature, the most frequently reported adverse events during rhGH treatment in NS children include non-severe symptoms, such as headaches, pain at the injection site, and arthralgia. In patients treated with rhGH and diagnosed with NS, 2 aspects are of greatest concern: cardiovascular complications and the risk of developing cancer.

The side effects related to the circulatory system analysed in many studies are reassuring and indicate that treatment with rhGH in children with NS is safe. There is no clear evidence that rhGH treatment increases the possibility of heart disease. However, due to the elevated risk of cardiac anomalies in NS itself, close cardiac monitoring both before and during the treatment is recommended.

Some gene mutations responsible for NS predispose to cardiac anomalies, such as cardiac arrhythmias and inborn defects - mainly pulmonary stenosis or hypertrophic cardiomyopathy (HCM). HCM risk is reported to be elevated in the case of RIT1 and RAF mutations. In these patients, rhGH treatment initiation is recommended after the age of 4 years to avoid deterioration of the pre-existing condition, because most of the HCM cases develop before that age [30].

According to the multicentre study on heart defects in NS patients (n = 274), by Sznajer et al. [31], the *PTPN11* gene mutation was observed in 38% of subjects, among whom 85% were diagnosed with congenital heart conditions. Pulmonary valve stenosis is most prevalent in individuals with *PTPN11* mutation whereas HCM is more common in individuals with other gene mutations [32].

So far, there has been one reported case of the development of HCM during rhGH treatment, while in another case, worsening of HCM was observed [15, 33]. There was also one case of atrial fibrillation reported during rhGH therapy [14, 27].

Concluding, it seems that cardiac complications are rare in NS patients treated with rhGH, but close cardiac follow-up should be carried out. All our patients remained under cardiac care (including cardiac echocardiographic examination and regular electrocardiography), we did not observe any adverse events, ASDII (in case 1) was stable, and no HCM was observed.

On the other hand, molecular analysis indicates that RAS/MAPK signalling pathway dysfunction may raise neoplastic risk and induce oncogenesis. NS itself is associated with a higher risk (about 3.5-fold) for benign and malignant proliferative disorders. In comparison to the healthy population, there are more cases of juvenile myelomonocytic leukaemia (JMML), haematological cancers, and solid tumours, such as neuroblastoma, brain tumours, and embryonal rhabdomyosarcoma [5].

The observed genotype-phenotype relationships suggest that activating mutations in the *PTPN11* gene predisposes to JMML, and NS has distinct effects on the course of the disease. Specific mutations in the *PTPN11* gene associated with isolated JMML occur as somatic changes and have never been observed as congenital defects, suggesting that these molecular damages are stronger and may lead to embryonic lethality. On the other hand, the observation that most mutations in the *PTPN11* gene associated with NS, which sufficiently disrupt developmental processes, do not result in full leukemogenesis, suggests a milder activating effect. In this concept, mutations in NS/JMML

are predicted to have intermediate effects, potentially explaining the milder course of JMML when it occurs in the context of NS [34].

Treatment with rhGH does not appear to increase the incidence of JMML, although regular morphology check-ups should be performed. In our case, complete blood counts were performed systematically, and no abnormal findings were observed in our patients.

In the literature review, the authors noted that the most severe adverse effects were uncommon and included new-onset spinal or intracranial tumours in 4 cases in children with NS treated with rhGH [12, 16, 33]. There was also one case of bone tumour recurrence, and 2 other cases of neoplasms. However, none of them have been proven to be caused by rhGH treatment [14, 16]. According to the review by Stagi et al. in a cohort of 297 individuals with *PTPN11* variant of NS, the incidence of tumours in the group treated with rhGH for known GHD is low, reporting 2 cases of primary tumours including cerebellum and intraventricular mass [5].

While the studies on rhGH and cancer in NS are negative, it is important to consider the patient's inherent propensity for tumour growth before beginning rhGH therapy. Clinical symptoms, routine physical exams, and laboratory blood testing (i.e. IGF-1 should remain within the normal range to reduce the oncogenic risk) must all form the basis for follow-up care. The relationship between NS genotype and oncological risk should be taken into consideration both before and during rhGH treatment. For this reason, radiological surveillance was conducted in our patients (including MRI of the pituitary gland and ultrasound examination of the abdomen, pelvis, testes, and thyroid gland), but no abnormalities were observed.

Puberty in children with NS and the possibility of supporting the improvement of FH through the additional use of GnRH analogues or AI in addition to rhGH treatment

NS is characterised by delayed puberty, with mean age at onset of 13.4 years in boys and 13 years in girls with no growth spurt [11]. A small number of studies revealed that girls were more likely than boys to experience a delayed onset of puberty (49% in girls *vs*. 28% in boys [35]). Some authors suggest induction of puberty, especially in boys [27], for psychological reasons.

In our study, the beginning of puberty was typical and spontaneous (between the ages of 12 and 12.9 years) during rhGH treatment; however, the advancement of puberty was rapid with acceleration of BA. Thus, in 2 children, we decided to cease the process of maturation, hoping to prolong the growing phase.

Triptorelin — gonadotropin-releasing hormone analogue

In the study on patients with central precocious puberty [20], it was proven that the combination of GnRHa with rhGH treatment results in better height gains. The gonadal axis was suppressed, and progression of BA was delayed, with good safety and efficacy [20].

The adverse events regarding combined treatment using rhGH and GnRHa noticed in studies included decreased bone mineral density after years of treatment [21]. There are no data on treatment with rhGH and GnRHa in NS patients; however, we believe this combination may be beneficial in girls and boys at the early stages of puberty, reaching higher FH.

Letrozole — third-generation aromatase inhibitor

Effective bone longitudinal growth is possible prior to epiphyseal fusion. To reduce the synthesis and action of oestrogens, an AI is used, suppressing testosterone transformation into oestrogen, thereby delaying epiphyseal fusion. The mode of action of letrozole covers the reduction of serum oestrogen by the inhibition of P450 aromatase [19]. Several studies have revealed that AI delays the rate of bone maturation with an improved predicted adult height [17, 19].

In clinical studies, in boys with idiopathic short stature (ISS), long-term letrozole therapy started during puberty reveals retardation of bone maturation without a significant decrease of linear growth, and thus improvement of the final adult height. No severe adverse events were found in the studies of ISS children [36].

In the ANSWER study, GHD children were treated with letrozole for 2 years. Comparing BA prior to and after 2 years of letrozole treatment, a significant decrease in the BA/CA ratio was observed, proving cessation of the BA progress [37].

No studies on letrozole combined with rhGH treatment including NS patients have been conducted. Studies on GHD and ISS children imply that delaying epiphyseal fusion increases height gain, thus improving FH. It provided no adverse effects during the treatment, including spinal deformities [18].

Thus, we present our patient as the first in whom we applied this treatment for over a year in a case of a very low final growth prognosis, reaching an additional 4.3 cm in height during that period. We believe that we will be able to improve his FH.

Conclusions

In patients with NS simultaneously diagnosed with GHD, the rhGH increases HV not only in the first 3 years of treatment, but also in subsequent years, significantly improving hSDS. However, obtaining satisfactory FH

is not certain during rhGH treatment and depends on many factors, including the onset of puberty and its course in NS, as well as — undoubtedly — the dosage of rhGH. Special attention should be paid to IGF-1 levels and IGF-1/IGFBP-3 molar ratio for optimisation of treatment. It appears that in patients with an unfavourable growing prognosis, the introduction of puberty or ossification of bone epiphyses inhibiting treatment may result in additional improvement; however, further research related to interfering puberty in NS children needs to be done because the growth prognosis may be improved in some uncertain cases.

In addition, both cardiovascular and oncological complications should be monitored, although — according to the literature — adverse events appear to be infrequent and, in most cases, difficult to prove as being related to the rhGH therapy.

Note that in Poland the treatment of short stature children with NS is only reimbursed in the case of concomitant GHD, and therefore the data are only available for these cases. However, because, worldwide, these children are treated with rhGH regardless of comorbidities, it seems significant to present experiences in this field.

REVIEW

Authors' contributions

Conceptualisation: D.K. and R.S.; methodology: D.K. and R.S., software: R.S.; data curation, D.K. and R.S.; writing — original draft preparation: D.K. and R.S.; writing — review and editing: R.S. and A.L.; visualisation: D.K.; supervision: A.L., and R.S. All authors have read and agreed to the published version of the manuscript.

Ethics statement

The research was conducted in accordance with the principles of ethics of the World Medical Association Declaration of Helsinki. Data were collected retrospectively. Written informed consent was obtained from the patient for the publication of this case report (including all laboratory data and images).

Conflict of interest

The authors declare that they have no conflict of interest.

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