Characteristics of Patients with Noonan Syndrome Carrying a PTPN11 Mutation: A Long-Term Follow-up

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INTRODUCTION

Noonan Syndrome (NS) is a heterogeneous group of diseases with a genetic etiology affecting the RAS/MAPK signaling pathway known as RASopathy (1). Genes known to cause NS are PTPN11, KRAS, SOS1, RAF1, BRAF, SHOC2 and RIT1. There are sufficient studies indicating that recombinant growth hormone (rhGH) therapy can be given without increasing risk of developing cancer in NS cases with PTPN11 mutations from different centers (2).

AIM

We aimed to evaluate the genotypic and phenotypic characteristics, the experience of the rhGH therapy and long-term follow-up of the patients with NS in single center.

METHOD

The cases who were admitted to our pediatric endocrinology clinic between 01.01.2010 and 31.12.2020 due to short stature were considered to be diagnosed with NS with van der Burgt criteria and who underwent genetic analysis were included. Genetic, clinical and follow-up data of patients were obtained from the patient files.

RESULTS

Of the 29 cases whose PTPN11 gene mutation analysis was performed, 11 were heterozygous mutation and one polymorphism was found (12/29, 41%). rhGH therapy was given to 11 patients with heterozygous mutations. On admission, the mean chronological age of patients was 9.35±3.35 (3.5-14.5) years, average height standard deviation score (SDS) was -3.11±1.10 [-5.33-(-1.98)], average target height was 162.7±7.2 (154.5-174) cm, average target height SDS was -1.40±1.12 [-3.44-(-0.36)], duration of rhGH therapy was 3.01±1.96 (0.25-7.1) years and the average follow-up time was 7.56± 2.91 (3.1-11.5) years. In 9 patients who reached final height with rhGH therapy, the mean Δheight SDS was 0.16± 0.54 [(-0.73- (1.08)]. No side effects were observed in the cases.

Table-1: Characteristics of PTPN11 mutation cases

Cases	1	2	3	4	5	6	7	8	9	10*	11*	12
Age (at admission) (years)	11,5	9	9,5	9	14,5	10,2	13,9	8	9,3	3,5	4,5	10,5
Gender	M	M	F	F	M	M	M	F	M	M	M	M
Height (cm)(SDS)	127 (-3)	107,4 (-4,68)	114,1 (-3)	121,7 (-1,9)	140,7 (-2,98)	118 (-4)	123 (-5,33)	116 (-2)	121,7 (-2,36)	91,3 (-2,26)	95 (-2,8)	120,5 (-3,25)
Weight (kg) (SDS)	24,9 (-2,46)	17,3 (-3,64)	22,2 (-1,75)	21,1 (-1,8)	36,75 (-2,65)	18 (-3,77)	27,7 (-3,56)	19 (-2,3)	24,95 (-1,19)	13 (-1,62)	13 (-2,5)	21,25 (-2,77)
BMI (kg/m^2) (SDS)	15,44 (-1,36)	15 (-0,87)	17.05 (0.13)	14.25 (-1.17)	18.56 (-0.84)	12.93 (-2.61)	18.31 (-0.77)	14.12 (-1.07)	16.85 (0.09)	15.6 (0.37)	14.4 (-0.94)	14.63 (-1.47)
Target height (cm) /(SDS)	155 (-3.44)	165.7 (-1.7)	154.5 (-1.46)	158.8 (-0.72)	168.7 (-0.71)	162.9 (-2.16)	-	159.4 (-0.63)	174 (-0.36)	155.95 (-2.86)	173 (-0.03)	171.5 (-0.76)
Bone age	8	5	8.8	7.8	12.5	7	11	8.8	7	1.5	2,6	7.5
Genetic mutation	PTPN11 het.	G503R (c.1507G>C)	N308D (c.922A>G)	E139D (c.417G>T)	N308D (c.922A>G)	F285L (c.853T>C)	D61G (c.182A>G)	N58D (c.172A>G)	F285L (c.853T>C)	D106A (c.317A>C)	N308S (c.923A>G)	(c.854-21C>T)
GH replacement	+	+	+	+	+	+	+	+	+	+	+	-
GH replacement time (years)	3	7,1	4	4	2	1	0,25	1,6	4,2	3	4,7	
Final height (cm) (SDS)	156,3 (-2,67)	147,7 (-4,5)	143,9 (-3)	155,5 (-1,29)	162,6 (-1,9)	131,8 (-3,62)	126,1 (-5,84)	141,4 (-2,73)	155,1 (-2,25)	129 (-2,03)	125,5 (-1,78)	126,6 (-3,11)
Final BMI kg/m^2 (SDS)	19,18 (-1,4)	17,4 (-2,36)	21,25 (-0,26)	22,3 (0,26)	19,9 (-1,29)	13,47 (-2,96)	17,92 (-1,2)	20,9 (0,36)	18,62 (-1,05)	15,02 (-1,3)	16,06 (-0,41)	-

*Cases on rhGH therapy

CONCLUSIONS

We think that our experiences in a genetically homogeneous group are new data to reduce the variability between examination and follow-up data.

Similar to the literature, in our cases it was found that body composition improved, body mass index did not change, and serious side effects were not observed with rhGH therapy.

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