REVIEW

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Noonan Syndrome, Cancer Risk, and Growth Hormone Treatment

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Abstract

Cancer may occur in patients with Noonan syndrome (NS). Review of English literature revealed that myeloproliferative diseases are the most prevalent, followed by intracranial tumours. There is no genotype-phenotype relationship between germline pathogenic variants so it not possible to precisely predict cancer risk in NS, however some *PTPN11* variants are exclusively detected in juvenile myelomonocytic leukemia and are not observed in other types of cancer. Among patients on growth hormone, cancer development was reported in seven patients with genetically confirmed NS, and five patients with clinically diagnosed NS. However, information on growth hormone dose, timing, and follow-up characteristics in these cases is heterogeneous. In the light of current data, especially in cases for whom growth hormone therapy is considered, the diagnosis should be genetically confirmed, and the results of genetic analysis should be compared with the cases reported in the literature. Families should be informed about possible cancer risk and in cases predisposing to juvenile myelomonocytic leukemia, early initiation of growth hormone therapy should be avoided.

Keywords: Rasopathy, growth retardation, somatotropin, oncogenesis, malignancy

Introduction

Noonan syndrome (NS) is the most common type of RASopathy. Related main overlapping disorders are NS and multiple lentigines, cardiofaciocutaneous syndrome, Costello syndrome (CS), neurofibromatosis type 1 (NF1), Legius syndrome, and NS-like disorder with loose anagen hair (1,2,3). In this review, we focused on NS in order to ensure the accuracy of diagnosis and strengthen the reliability of the findings by minimizing potential misclassification of overlapping conditions.

Somatic mutations in the genes of the RAS/MAPK pathway, including *PTPN11*, *KRAS*, *HRAS*, *NRAS*, *NF1*, and *CBL*, which are involved in regulating cell growth, division, and differentiation in response to growth factors, have been shown to play an important role in the development of some cancers. For instance, *PTPN11* encodes SHP-2, a tyrosine phosphatase enzyme that modulates intracellular signaling. Some mutations in *PTPN11* lead to abnormal activity of this enzyme and disrupt normal signaling processes. Furthermore, somatic mutations in *PTPN11* enhancing phosphatase activity of mutant SHP-2 have been detected in childhood leukemia (4). Mutations in *KRAS* and *NRAS* may lead to hyperactive RAS/MAPK pathway due to defective intrinsic GTPase activity (5). Given this evidence, there have been concerns regarding the potential genetic predisposition to cancer in individuals with NS, which occurs with germline and mostly heterozygous changes of some genes in this pathway. The use of growth hormone (GH) therapy for short stature in NS further increases the concerns (6,7). However, GH therapy has been approved by the US Food and Drug Administration in 2007 for cases of NS with short stature, and there is still no global consensus on routine cancer screening in NS (8,9,10).

Considering that NS had an average prevalence of 1 in 2000 in the overall population, the number of reported cancer cases is relatively low. On one hand, this might be explained by the fact that certain cases of NS exhibit subtle symptoms,

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possibly resulting in underdiagnosis. On the other hand, NS-related variants might not be directly associated with cancer and various additional genetic changes may have indeed contributed to the development of oncogenic processes in cases of NS. Studies have recently shown the presence of hyperdiploid karyotype in the leukemic cells of a significant portion of acute lymphoblastic leukemia (ALL) cases (36-73%) carrying a germline *PTPN11* variant. It has been proposed that additional factors, such as chromosome breaks or certain epigenetic influences, may contribute to an increased susceptibility to cancer in patients with NS (11,12). Some studies observed a relationship between uniparental disomy in several genes and oncogenesis (13). Interestingly, in a NS patient with ALL, the germline *PTPN11* variant was not present in the leukemic cells, suggesting other mechanisms (14).

Methods

A literature review was conducted using web search tools including PubMed, OMIM, and Google Scholar (1987 to present; last access date September 23rd, 2024) using the search terms "Noonan" or "Noonan Syndrome" to identify all relevant case reports or cohorts. The reference list of all articles was also searched to identify further relevant publications. We included only patients clinically and genetically diagnosed with NS. All cases with NS-like syndromes, such as NF-1 with NS features, were excluded. We should point out that clinical and genetic data in the published reports were heterogenous; most articles presented insufficient clinical details about the cases, and there was a notable absence of comprehensive analyses of other conditions that might contribute to cancer predisposition. It was assumed that the cases did not receive GH treatment if it was not mentioned.

Cancer in Patients with NS Who did not Receive GH

There are various data regarding the general cancer frequency in NS. The first comprehensive report on this topic reviewing the literature from 1937 to 2010 found 46 cancer events in 45 cases (3.9%) among 1151 subjects with either a clinical or genetic diagnosis of NS (15). It was reported that the age at cancer diagnosis was similar to that seen in the general population. In this cohort, 73% of the cases were 20 years of age or younger, with the predominant cancers being neuroblastoma (n=8), ALL (n=8), glioma (n=6), and rhabdomyosarcoma (n=6). This article, which has frequently been cited in reviews, has important limitations, including a lack of genetic investigation in many cases and the exclusion of myeloproliferative disorders.

Table 1 presents the list of histopathologically confirmed malignant tumors reported in the literature among pediatric cases with NS, whose diagnoses were confirmed through genetic analysis. For the small number of cases with multiple cancers, we recorded the first one. Myeloproliferative diseases are the most common, followed by intracranial

Table 1. List of histologically confirmed malignant tumors reported in patients with a diagnosis of NS(the number is shown within parantheses when a mutation is reported in many patients)

Tumor	Gene	Germline variant at protein level	References
Juvenile myelomonocytic leukemia (n=40)	*PTPN11*	G60A D61G (2) D61H (2) D61N Y62D F71L A72G (3) T73I (11) E139D (3) F285L (2) N308D N308S G503A G503R (4) Q506P R65Q Y63C 179-181delGTG	(4,16,17,25,34,38,40,47,51,58)
	KRAS	T58I	(20)
	NRAS	G13D G12S	(28,43)
	RIT1	M90I	(56)
	RAF	S257L	(60)

Table 1. Continued

Tumor	Gene	Germline variant at protein level	References
Acute lymphoblastic leukemia (n = 19)	*PTPN11*	N58S G60A Q79R E139D (2) Y279C N308D (5) G503R M504V (3) R501K[a]	(11,14,21,35,40,54,58)
	SOS1	M269R M269T	(12)
	RIT1	D81G	(36)
	LZTR	R210*&c.2220-17C > A E563Q	(46)
Acute myeloid leukemia (n = 1)	*PTPN11*	G268S	(61)
Non-Hodgkin lymphoma (n = 1)	*PTPN11*	P491L	(18)
Dysembryoplastic neuroepithelial tumor (n = 6)	*PTPN11*	G60A D61G[a] E139D[a] N308D (2) N58K	(34,40,42,44,45)
Low-grade glial tumor (n = 1)	*RAF1*	G361A	(53)
High-grade glial tumor (n = 2)	*PTPN11*	T2I N308D	(48)
Glioneuronal tumor (n = 2)	*PTPN11*	N58D N308D	(29,49)
Pilocytic astrocytoma (n = 4)	*PTPN11*	G60A N308D[a] F491P	(30,40,45)
	KRAS	D153V	(40)
Pilomyxoid astrocytoma (n = 1)	*PTPN11*	E139D	(41)
Oligoastrocytoma (n = 1)	*LZTR1*	R284C[a,b]	(50)
Oligodendroglioma (n = 2)	*PTPN11*	E139N	(34)
		T22A	(22)
Hypothalamic glioma (n = 1)	*PTPN11*	E139D	(19)
Medulloblastoma (n = 1)	*PTPN11*	T468M	(37)
Neuroblastoma (n = 4)	*PTPN11*	G60A I282M I282V N308D(2) D61G	(11,23,26,34,58)
Rhabdomyosarcoma (n = 5)	*SOS1*	P102R[a] S548R L728I	(31,32,33)
	RRAS2	G23C	(52)
		G12R	(55)
Sertoli cell tumor (n = 1)	*SOS1*	M269T[a]	(33)
Hepatoblastoma (n = 1)	*PTPN11*	N308D	(27)
Giant cell tumour (n = 1)	*RIT*	A57G	(39)
Wilms tumor (n = 1)	*ERF*	I46N	(59)

[a]Treated with growth hormone, [b]Cancer was diagnosed at 22 years old

tumors among solid tumors. The cancers were generally linked to variants in *PTPN11*, a prevalent cause of NS. The T73I variant in *PTPN11* has only been found in cases with juvenile myelomonocytic leukemia (JMML), the other variants were present in various tumor types. Since many of the variants listed are also found in NS cases who did not develop cancer, no clear correlation can be established between the *PTPN11* variants and the occurrence of cancer (4,11,12,14,16-61).

Myeloproliferative diseases in NS may present in two different clinical situations. While most of the cases have a benign course, the remaining cases progress aggressively; this type is called JMML and it is rarely seen in children without NS. The association between this form of leukemia and NS was initially reported by Tartaglia et al. (16) in 2003. Nevertheless, comprehensive details regarding the clinical characteristics of the patients were not provided at that time. In a study covering a 10-year period from a reference hospital from France, JMML was present in 20 (3.12%) of 641 cases with NS with a *PTPN11* variant (Table 1). JMML-related findings had appeared in the first three months of life in all cases and, interestingly, a history of polyhydramnios may be a warning sign for development of JMML since its incidence was significantly higher in such cases (50%) compared to the NS cases who did not develop JMML (11.7%). In addition, the majority of the *PTPN11* variants detected in NS cases with JMML were also found in NS patients without myeloproliferative diseases (38). A study published later from the same center reported that ALL occurred in 4 out of 778 cases (0.5%) with a *PTPN11* variant and in 2 out of 94 cases (2.1%) with a variant in the *SOS1* gene (Table 1) (12).

In a study including data of NS patients collected from 25 molecular genetic laboratories in Germany, 8 out of 632 (1.27%) children had cancer. Importantly, all these cases had a *PTPN11* variant (Table 1) (40). Based on these findings, the risk of developing childhood cancer in NS was estimated to be 8.1-fold increased; however, the risk of developing ALL and neuroblastoma appeared to be similar with that of the general population. In the same study, the risk of developing cancer in those with CS and those with a *KRAS* variant was 42.4-fold and 75.8-fold increased, respectively.

In a study from the Netherlands, among 297 subjects with NS with a *PTPN11* variant, 12 (4.04%; 4 children, 8 adults) developed cancer during a median follow-up duration of 13 years. It was concluded that the risk of developing cancer until the age of 55 was 3.5 times higher compared to the general population (Table 1) (62).

In a study from Italy, among the 35 NS cases with a clinical and/or genetic diagnosis, 2 (5.7%) patients with a *PTPN11* variant had developed a cancer. Unfortunately, specific variants were not mentioned (63). A study from China reviewed 102 patients with NS, five of whom carried *PTPN11* variants and were found to have tumors. Among these, two were diagnosed with JMML, two with neuroblastoma, and one with ALL (58).

Among the 107 patients with NS and a *RAF* mutation reported in the Italian cohort, 20 were newly identified cases. Two cancer cases were noted, but the specific types of cancer were not provided (60). Genetic findings of subjects with NS and cancer reported as case reports have been given in Table 1, however, we could not include a 14-year-old boy with T-cell ALL and glioblastoma since the variant in *PTPN11* was not specified (64).

There are also a few case reports of rabdomyosarcoma in patients with a clinical diagnosis of NS (65,66). On the contrary, no cancer was reported among some studies from various countries which included over 1000 cases (67-78).

Cancer in Patients with NS Treated with GH

The relationship between GH therapy and cancer has been an ongoing debate for several years since elevated levels of insulin-like growth factor 1 (IGF1) have been identified as a potential risk factor for the development of certain tumors and congenital 1 deficiency appears to provide a protective effect against cancer (79). Based on data obtained from case series, the treatment of GH for idiopathic GH deficiency, idiopathic short stature, and short stature in infants born small for gestational age is generally not associated with an increased risk of cancer. Notably, cases with a history of cancer, those with predisposing conditions like neurofibromatosis, Down syndrome, chromosomal breakage, or DNA repair abnormalities have a natural vulnerability to developing cancer (80). In terms of NS, while various animal models with RASopathies exist, the effects of the relevant gene mutations in response to GH therapy have not been studied in these models (1). The outcomes of GH treatment in humans with NS have been reported in the medical literature since it was first used in 1987 (81). We categorized the reported cancer cases into two subheadings based on the type of diagnosis (clinical diagnosis only vs clinical and/or genetic diagnosis) given that NF 1, which is well known to have a predisposition to cancer, was reported to be the underlying condition in some patients with a clinical diagnosis of NS, even in the absence of café-au-lait spots (82). Furthermore, eight cases reported in congresses were not included (42). However,

the data exhibited heterogeneity in dose and timing of GH treatment, IGF1 levels, duration of follow-up, and genetic analysis information. We have summarized the relevant data as far as possible.

Cases with a Clinical Diagnosis of NS

In a single center study from Sweden, the outcomes of GH treatment in 25 children with NS were reported. Ten of the cases were initially treated with a dose of 0.23 mg/kg/week, while the remaining 15 were treated with a dose of 0.46 mg/kg/week. According to the study protocol, dose adjustments were made two years later, and after three years of GH treatment, one patient out of 25 (4%) developed lymphoma (83).

Data from the US registry of a GH manufacturing company revealed that a possible left parietal lobe tumor developed in one of 65 cases (1.5%). The reported average dose of the GH was 0.33 mg/kg/week, and the patient achieved adult height (84).

An atypical granular cell tumor, of which the histological features could not definitively distinguish between benign or malignant, was reported in a 10-year-old girl. The girl was treated with GH for three years; after surgical excision, no recurrence developed during three years of follow-up (85).

In a study performed on cases who received GH for a duration exceeding four years using an international registry of another GH manufacturing company, two cases, aged 9.5 and 10 years, developed glioneuronal tumor and a brain tumor (for which no clear information is available) after GH therapy for 1.2 and 2.5 years, respectively (7).

NS Cases with Genetic Data

In an international study published in 2010, *SOS1* analysis was performed in 102 cases without *PTPN11* or *KRAS* mutations. The study reported that a 4-year-old patient with the P102R variant in the *SOS1* gene developed rhabdomyosarcoma, while another 4-year-old patient with the M269T variant was diagnosed with a Sertoli cell tumor. Although GH therapy was noted in both cases, no further details regarding the timing, dosage, or follow-up of the treatment were provided (86).

In 2016, it was reported that an 8-year-old patient with NS who had been receiving GH therapy for the past 4 years and had an E139D variant in *PTPN11* was diagnosed with a dysembryoplastic neuroepithelial tumor. Upon reviewing the cranial magnetic resonance imaging (MRI) images taken for another reason when the patient was 1.5 years old, smaller lesions, previously described as "nonspecific", were identified in the same regions where the current lesions were found. However, no detailed information regarding endocrine follow-up was provided (42).

In 2017, an 8-year-old patient with a D61G variant in *PTPN11* was reported to have developed a low-grade dysembryoplastic neuroepithelial tumor in the 15th month of GH therapy. The dose was 0.3 mg/kg/week and an IGF-1 level 115 ng/mL during the first six months of treatment. A subtotal resection was performed, and the GH was stopped. At the end of the first year, due to a low growth rate, GH therapy was restarted without a stimulation test. The IGF-1 level was maintained between 1 and 2 SDS according to the patient's age and pubertal stage, and MRI follow-up showed no growth in the residual mass. In a second patient reported by the same center, with an N308D variant in *PTPN11*, no pathology was found in a cranial MRI taken for migraines at the age of 9.5 years. At 13.5 years of age, GH therapy was started without a stimulation test at a dose of 0.35 mg/kg/week. During follow-up, the maximum dose was 0.4 mg/kg/week and IGF-1 levels were in the normal range. In the 18th month of treatment, the patient presented to the emergency department with confusion and was diagnosed with pilocytic astrocytoma, leading to the discontinuation of GH therapy (45).

Recently, *LZTR1* mutations have been found to cause NS through either autosomal dominant or recessive inheritance. In 2020, it was reported that a patient with a heterozygous R284C variant in this gene, who had been using GH at a dose of 0.23-0.25 mg/kg/week between the ages of 15 and 17 years, developed an oligoastrocytoma at the age of 22 years (50).

In a study evaluating cases from an international database of a GH manufacturing company, including patients who had received treatment for more than four years, an adolescent with an unspecified *PTPN11* mutation was reported to have developed a pilocytic astrocytoma and spinal metastases after 2.5 years of GH treatment (79). A few years later, the same company reported another case, who was a 9-year-old male with an unspecified *PTPN11* variant and a brain neoplasm (dysembryoplastic neuroepithelial tumor) 14 months after initiation of GH treatment (82).

In another case report, the nine-year-old patient, who had been diagnosed with NS in infancy and carried a R501K variant in *PTPN11*, was diagnosed with medium-risk T-ALL after receiving GH treatment for a 3-year period. Unfortunately, no more information on GH treatment was given (54).

Conclusion

An article published by the Pediatric Endocrine Society (PES) in 2015 in the United States discussed the cancer risk in patients treated with GH, and NS was assessed as one of the conditions that predispose individuals to tumor development in these patients (80). Moreover, a report in 2017 published by a group primarily consisting of oncology specialists from the USA, Germany, Japan, and Canada stressed the importance of performing physical examinations, blood counts, and blood smear tests during the initial five years of life for cases with a genetic variant that may be associated with JMML. This report recommended using a blood smear as a screening method for this group. However, it was not recommended for cases with genetic variants that were not linked to developing JMML, as there was a minimal risk of developing cancer in this group. Therefore, routine screening was considered unnecessary, and it was suggested that cases should be warned to attend for further evaluation if they experienced any symptoms that may be a sign of a tumor (87).

As a general approach by the PES, if GH treatment is started in cases with a predisposition to cancer, such as a genetic disease, although there is no evidence to support or contradict it, the cautious approach is to keep blood IGF1 at age-appropriate levels and to perform routine cancer screening according to disease specific guidelines. However there are no generally accepted cancer screening guidelines for NS (84).

Based on the current literature and recommendations, particularly in cases of NS when GH treatment is being considered, it is advisable to: (i) confirm the diagnosis through genetic analysis; (ii) compare the identified genetic changes with cases documented in the literature; (iii) avoid early initiation of GH treatment in individuals who are at risk for JMML; and (iv) appropriately communicate potential risks with families and establish a comprehensive follow-up plan.

Footnotes

Authorship Contributions

Concept: Korcan Demir, Design: Korcan Demir, Data Collection or Processing: Korcan Demir, Kübra Yüksek Acınıklı, Literature Search: Korcan Demir, Kübra Yüksek Acınıklı, Writing: Korcan Demir, Kübra Yüksek Acınıklı.

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