CLINICAL REPORT

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Noonan Syndrome, *PTPN11* Mutations, and Brain Tumors. A Clinical Report and Review of the Literature

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Noonan syndrome (NS), an autosomal dominant disorder, is characterized by short stature, congenital heart defects, developmental delay, and facial dysmorphism. *PTPN11* mutations are the most common cause of NS. *PTPN11* encodes a non-receptor protein tyrosine phosphatase, SHP2. Hematopoietic malignancies and solid tumors are associated with NS. Among solid tumors, brain tumors have been described in children and young adults but remain rather rare. We report a 16-year-old boy with *PTPN11*-related NS who, at the age of 12, was incidentally found to have a left temporal lobe brain tumor and a cystic lesion in the right thalamus. He developed epilepsy 2 years later. The temporal tumor was surgically resected because of increasing crises and worsening radiological signs. Microscopy showed nodules with specific glioneuronal elements or glial nodules, leading to the diagnosis of dysembryoplastic neuroepithelial tumor (DNT). Immunohistochemistry revealed positive nuclear staining with Olig2 and pERK in small cells. SHP2 plays a key role in RAS/MAPK pathway signaling which controls several developmental cell processes and oncogenesis. An amino-acid substitution in the N-terminal SHP2 domain disrupts the self-locking conformation and leads to ERK activation. Glioneuronal tumors including DNTs and pilocytic astrocytomas have been described in NS. This report provides further support for the relation of DNTs with RASopathies and for the implication of RAS/MAPK pathways in sporadic low-grade glial tumors including DNTs.

Key words: Nooonan syndrome; *PTPN11* mutations; dysembryoplastic neuroepithelial tumor; low-grade glial tumors; glioneuronal tumors

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INTRODUCTION

Noonan syndrome (NS, OMIM 163950) an autosomal dominant disorder, first described in 1968, has an estimated prevalence between 1/1,000 and 1/2,500 live births [Roberts et al., 2013]. NS is related to various genes. Mutations in the *PTPN11* gene are the most frequent. *PTPN11* encodes SHP2, a protein tyrosine phosphatase (PTP). NS-associated mutations of

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PTPN11 induce hyperactivation of ERK1/2 both in vitro and in vivo, in different cell types, in a basal state or under stimulation by agonists [Tajan et al., 2015]. Other genes (*RAS*, *SOS1*, *NRAS*, *RAF1*, *BRAF*, *A2ML1*, *RASA2*, *RRAS2*, *LZTR1*, *SOS2*, *RIT2*, *SHOC2*, *CBL*, and *PPP1CB)* are implicated in the MAPK/ERK pathways and are associated with NS and closely related conditions [Cavé et al., 2016; Gripp et al., 2016]. These autosomal dominant disorders with RAS pathway overactivation are now collectively named RASopathies [Roberts et al., 2013; Cavé et al., 2016]. These RASopathies are associated with germline alteration of the Ras signaling pathway and present phenotypical overlap with common clinical features resembling NS. Other signaling pathways, notably the PI3K/AKT cascade, may be involved in some of these conditions [Tajan et al., 2015].

NS is associated with a possible increase in risk of tumor development, including hematologic proliferations and, less frequently, solid tumors. Juvenile myelomonocytic leukemia (JMML) has been described in *PTPN11*-associated NS [Tartaglia et al., 2003]. Somatic point mutations of *PTPN11* have been identified as the main cause (35% of cases) of JMML, a rare and aggressive myeloid malignancy of early childhood [Tartaglia et al., 2010]. Similarly, *PTPN11* somatic mutations may occur, albeit rarely, in solid tumors [Grossmann et al., 2010]. They have been observed in pilocytic astrocytoma, admittedly always together with *FGFR1* mutations [Collins et al., 2015]. Brain tumors described in NS and other RASopathies are mainly low-grade glial or glioneuronal tumors.

We report a patient with *PTPN11*-associated NS who developed a dysembryoplastic neuroepithelial tumor (DNT). We review the features of previously reported DNTs tumors associated with NS to better define this association and further analyze these tumors considering the role of RAS pathways in sporadic low-grade glial or glioneuronal tumors.

CLINICAL REPORT

The male patient born at term, with no abnormality at birth, presented slight developmental delay (language), cryptorchidism, short stature, and dysmorphic facial features in infancy. He did not receive GH treatment. When he was 11 years old, a holosystolic heart murmur was diagnosed. Echocardiography revealed idiopathic arterial pulmonary hypertension which was successfully medically treated.

At age 12, during evaluation after head injury, magnetic resonance imaging (MRI) revealed a multicystic lesion in the left temporal lobe extending into the insula and basal ganglia. This was a cortical lesion without peritumoral edema or mass effect, hypointense on T1-weighted and hyperintense on T2-weighted sequences. No contrast enhancement was noted. These features suggested a DNT corresponding to type 1 b MRI (polycystic-like) [Chassoux et al., 2012]. MRI also showed a few cysts in the left frontal lobe and a small round cystic lesion in the right thalamus.

At age 14, the patient presented atypical malaise. Video-electroencephalography was in favor of complex partial epilepsy. The clinical signs, which associated several dysmorphic facial features (hypertelorism, down-slanting palpebral fissures, low-set posteriorly rotated ears with fleshy helix), short stature, pubertal development delay, moderate language deficit, cryptorchidism, and cardiac defect, suggested NS.

At age 16, in spite of medical treatment, seizures increased, with sustained drug resistance. MRI showed an increase of lesion size. The left temporal lobe tumor was partially resected. No further seizures

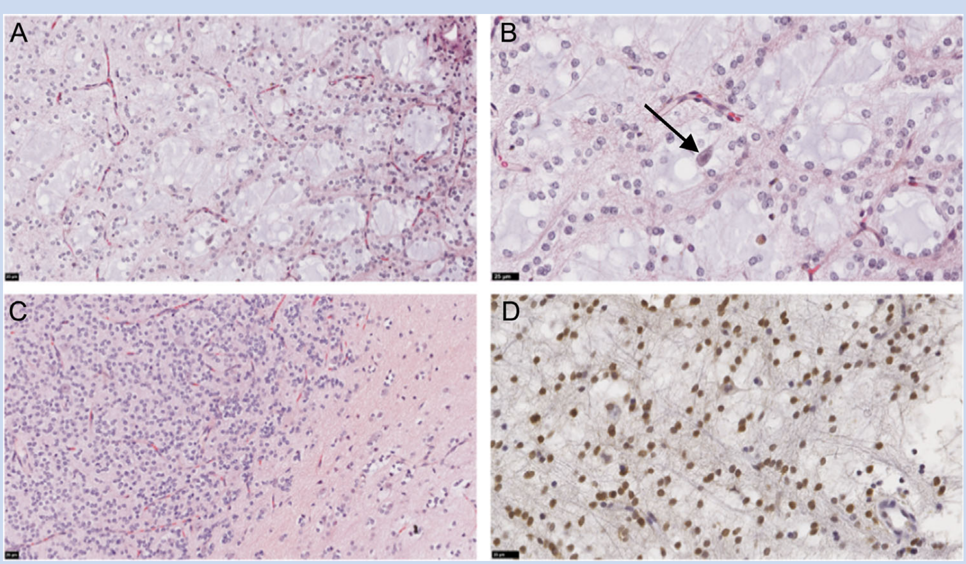

FIG. 1. First resected lesion. (A) Typical glioneuronal component. (B) A neuron floating in the mucoid matrix (↘) and oligo-like small round cells. (C) Oligodendroglial nodule. (D) Significant staining of nuclei with anti-ERK1/2 antibody in some areas. [Color figure can be viewed at wileyonlinelibrary.com]

occurred for 6 months, but then complex partial epilepsy again appeared and the rate, severity and duration of seizures increased. A second surgical procedure (left anterior temporal lobectomy) was carried out 22 months later, but treatment-resistant epilepsy with learning disabilities nevertheless persisted.

Microscopy and immunohistochemistry were performed on both surgical specimens. Microscopically, multifocal lesions were seen (Fig. 1A–C). Poorly-demarcated nodules were composed of mucoid sheets surrounded by small round cells, often arranged in columns. Rarer nodules were composed of oligodendroglial-like cells. On immunohistochemical staining, these cells were positive for Olig2. Neurofilament and synaptophysin antibodies highlighted columnar formations. A few cells expressed GFAP but not Olig2. CD34 stained vascular structures. MIB1 index was low (<3%) as well as P53 nuclear index. There was no staining with IDH1-R132H and BRAF V600E antibodies but a strong positivity in small round cells nuclei with anti-phospho-ERK1/2 antibody (Fig.1D). The diagnosis of DNT (complex form) was established.

METHODS AND RESULTS

Mutation screening of *PTPN11* was performed on genomic DNA by bi-directional Sanger sequencing of exons and their flanking intron-exon boundaries [Keren et al., 2004]. It revealed a germline heterozygote mutation of *PTPN11:* c.922A>G leading to a p. Asn308Asp substitution.

DISCUSSION

Malignancies have been described in NS and in related syndromes such as Costello syndrome (CS), cardiofaciocutaneous syndrome (CFCS), and NS with multiple lentigines (NSML; previously referred to as LEOPARD syndrome). Several hematologic cancers occur in NS, particularly during childhood, at a slightly higher proportion than in the general population. These cancers include JMML, acute myelogenous leukemia, and B-cell acute lymphoblastic leukemia [Tartaglia et al., 2003; Roberts et al., 2013]. Solid tumors are also cited: rhabdomyosarcoma, granular cell tumor, Sertoli cell tumor, neuroblastoma, and glial tumors. In mutation-positive individuals with NS or related syndromes, compared with the general population, a significant excess risk for all childhood cancers combined was observed (10.5-fold increased risk) [Kratz et al., 2015]. In a cohort study of 297 Dutch NS patients with a *PTPN11* mutation, a 3.5–fold increase in the overall cancer risk up to age 55 years was found, compared with the general population [Jongmans et al., 2011]. In a review of the literature of brain tumors in *PTPN11*-driven NS patient, 9 DNTs, and 13 other primary brain tumors were identified [McWilliams et al., 2016]. Our update identified 25 tumors. Beside one medulloblastoma [Rankin et al., 2013], all were glial or glioneuronal tumors [Sanford et al., 1999; Takagi et al., 2000; Jongmans et al., 2005; Martinelli et al., 2006; Fryssira et al., 2008; Schuettpelz et al., 2009; Sherman et al., 2009; De Jong et al., 2011; Karafin et al., 2011; Bendel and Pond, 2014; Rush et al., 2014; Kratz et al., 2015; Nair et al., 2015]. There were nine DNTs which characteristics are summarized in Table I. While pilocytic astrocytomas are the commonest pediatric brain tumors (brain and spinal tumors 25%) glioneuronal tumors and DNTs are rare (<1%) [Rickert and Paulus, 2001]. With regard to cases with epilepsy, the incidence of DNT is 17.8% of brain tumors in adults and 23.4% in children [Louis et al., 2016]. Our report reinforces the suggestion that DNTs appear as a non-coincidental tumor in NS [Kratz et al., 2015; McWilliams et al., 2016].

The *PTPN11* gene encodes SHP2, a growth factor-regulated cytoplasmic phosphatase that controls cell growth, differentiation, and

TABLE I. Dysembryoplastic Neuroepithelial Tumor (DNTs) Related to Noonan Syndrome (NS) With *PTPN11* Mutations

Reference	Sex	Age (y) at diagnosis	Location of the tumor	PTPN11 Mutation	Clinical event
Jongmans et al. [2011] (patient 3)	N/A	10	Temporal lobe	c.179G > C p.Gly60Ala	N/A
Bendel et al. [2012]	M	17	Left temporal lobe	c.174C > G p.Asn58Lys	Seizure
Bendel et al. [2012]	M	37	N/A	Maternal uncle of patient above	Seizure
Krishna et al. [2014]	M	11	Right temporal lobe and right cerebellum	p.Asp61Gly	Lethargy and altered mental status
Pellegrin et al. [2014]	M	13	Left parietal lobe	Exon 3	Paresthesia
Pellegrin et al. [2014]	M	13	Right parieto-occipital lobe	N/A	Asymptomatic
Kratz et al. [2015] (patient 7)	F	6	N/A	p.Asn308Asp	N/A
McWilliams et al. [2016]	M	8	Temporal lobe, left and right cerebellum	p.Glu139Asp	Headache vomiting
Our case	M	16	Left temporal and frontal lobe, right thalamus	c.922A > G p.Asn308Asp	Seizure

N/A: not available

migration through activation of the RAS-MAPK cascade. The physiological functions of SHP2 are complex. The mutations observed in NS induce a gain of function of SHP2 [Tajan et al., 2015; Cavé et al., 2016]. The mutations lead to a change of conformation, locking the enzyme in a more favorable position for catalysis inducing ERK hyperactivation. SHP2 is involved in central nervous system development, where it can promote ERK-dependent neurogenesis while inhibiting STAT3-dependent gliogenesis [Gauthier et al., 2007]. The signification of DNT remains unsettled. Multiple locations as well as stable evolution of DNTs in NS, similarities of pathological aspects of DNTs with developmental abnormalities in NS may suggest a hamartomatous nature of this tumor, at least in some cases.

Our report described a patient harboring a *PTPN11* mutation, a gene frequently affected in NS (50%). No predominant mutation of *PTPN11* associated with DNTs seems to emerge (Table I). Another case presented the mutation in *PTPN11*, p. Asn308Asp observed in our patient. In JMML, *PTPN11* p. Thr73Ile appears to play a key role [Tartaglia et al., 2010; Strullu et al., 2014]. The association between a specific amino-acid change in *PTPN11* and DNTs has to be further explored; the number of reported cases with germline or somatic mutations remaining low.

The spectrum of brain tumors described in NS reflects the different low-grade tumors which, when occurring sporadically, are related to dysregulated RAS/MAPK pathways and present some pathological overlaps. Other genes implicated in RASopathies have been described in sporadic low-grade gliomas, including DNTs. Some are related to NS, such as *NF1*. Neurofibromatosis is a RASopathy and *NF1* mutations may produce a NS phenotype, while mixed syndromes have been described [Thiel et al., 2009]. *NF1* mutations induce loss of the neurofibromin activity that triggers aberrant MAPK/ERK activation. The link between pilocytic astrocytoma and neurofibromatosis type 1 is well known [Rodriguez et al., 2008; Louis et al., 2016]. A germline *NF1* mutation was found in four epileptic patients presenting with DNT, suggesting a non-fortuitous association between DNTs and RASopathies [Barba et al., 2013]. *FGFR1* mutations have been described in pilocytic astrocytoma and recently in rosette forming glioneuronal tumor (RGNT). In the latter, this anomaly could be related to a specific subtype. *FGFR1* mutations were recently reported in sporadic DNTs and in familial cases. Constitutional and somatic *FGFR1* alterations and MAPK pathway activation are key events in the pathogenesis of DNT [Rivera et al., 2016]. They were not identified in a series of periventricular and intraventricular DNTs, suggesting that *FGFR1* could be a candidate for defining a subtype of glioneuronal tumors including certain DNTS and RGNTs [Gessi et al., 2016].

Activation of RAS/MAPK pathways through *BRAF* alterations has been well established in low-grade pediatric glioma. MAPK activation by gene fusions involving *BRAF* defined pilocytic astrocytoma [Jones et al., 2012]. *BRAF V600E* mutations known in pilocytic astrocytoma have been described in DNT [Chappé et al., 2013], and are considered the most common molecular alteration in cortical DNTs.

These data shed light on the relationship between alterations in MAPK pathways in particular via *PTPN11*.

CONCLUSION

DNT may be part of the tumor spectrum associated with *PTPN11*-driven NS. It needs to be sought and recognized. Further studies are needed to precisely evaluate the incidence of DNT and the necessity of an increased surveillance in children with NS. DNT, RGNT, and pilocytic astrocytoma have close similarities in histology and in oncogenetic pathways. They may be part of a spectrum of tumors which will soon be better defined thanks to new molecular findings. This report provides further support for the relation of glioneuronal tumors with RASopathies, even if these tumors are heterogeneous at the genomic level with *BRAF*, *NF1*, or *PTPN11* mutations.

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