Noonan syndrome

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Noonan syndrome (NS) is a multisystem disorder characterized by abnormal facial features, developmental delay, and sporadically, also brain tumors, congenital heart defects, neurodevelopmental delay, and bleeding diathesis. Though rare, several neurosurgical manifestations have been associated with NS, such as Chiari malformation (CM-I), syringomyelia, brain tumors, moyamoya, and craniosynostosis.

A meticulous anesthetic, hematologic, and cardiac evaluation should be conducted. Neurosurgical interventions should then be planned accordingly [1)]

Exome-wide sequencing studies recently described PTPN11 as a novel brain somatic epilepsy gene. In contrast, germline mutations of PTPN11 are known to cause Noonan syndrome,

Ganglioglioma in Noonan syndrome

Hoffmann et al. performed a deep phenotype-genotype analysis of a comprehensive series of ganglioglioma (GG) with brain somatic alterations of the PTPN11/KRAS/NF1 genes compared to GG with common MAP-Kinase signaling pathway alterations, i.e., BRAFV600E. Seventy-two GG was submitted to whole exome sequencing and genotyping and 84 low-grade epilepsy-associated tumors (LEAT) were to DNA-methylation analysis. In 28 tumors, both analyses were available from the same sample. Clinical data were retrieved from hospital files including disease onset, age at surgery, brain localization, and seizure outcome. A comprehensive histopathology staining panel was available in all cases. We identified eight GG with PTPN11 alterations, copy number variant (CNV) gains of chromosome 12, and the commonality of additional CNV gains in NF1, KRAS, FGFR4 and RHEB, as well as BRAFV600E alterations. Histopathology revealed an atypical glial-neuronal phenotype with subarachnoidal tumor spread and large, pleomorphic, and multinuclear cellular features. Only three out of eight patients with GG and PTPN11/KRAS/NF1 alterations were free of disabling seizures 2 years

after surgery (38% had Engel I). This was remarkably different from our series of GG with only BRAFV600E mutations (85% had Engel I). Unsupervised cluster analysis of DNA methylation arrays separated these tumors from well-established LEAT categories. Data point to a subgroup of GG with cellular atypia in glial and neuronal cell components, adverse postsurgical outcome, and genetically characterized by complex alterations in PTPN11 and other RAS-/MAP-Kinase and/or mTOR signaling pathways. These findings need prospective validation in clinical practice as they argue for an adaptation of the WHO grading system in developmental, glial-neuronal tumors associated with early-onset focal epilepsy [2].

Case reports

A case of multifocal DNETs involving the cerebellum demonstrated delayed contrast enhancement. In addition, these occurred in a patient with Noonan syndrome (NS), a "RASopathy" disorder associated with low-grade glial and glioneuronal tumors. Tuohy et al present a summary of all previously reported cases of cerebellar DNETs.

The patient was successfully treated surgically and is doing well clinically, now one-year status post his last procedure, and is being closely monitored with serial MRIs for progression. Gross total resection is often curative without adjuvant therapy for most DNETs. Our case emphasizes the importance of radiographic surveillance, as multifocality and recurrence may necessitate more than one procedure. Lastly, clinicians should be suspicious for DNETs and other low-grade glial tumors when treating patients with NS, acknowledging their predisposition for multifocal involvement and atypical presentations [3]

The case of an adult patient with a history of Noonan syndrome (NS) presenting with slowly progressive right-sided hemiparesis and right-sided focal motor seizures. Despite initial imaging and histology suggesting a left frontal lobe high-grade intrinsic tumor typical of a glioblastoma, subsequent molecular analysis confirmed a diagnosis of Malignant intracerebral nerve sheath tumor (MINST). The patient's neurological condition improved after gross-total resection and adjuvant chemo-radiation; he remains on follow-up.

MINSTs are rare neoplasms with a poor prognosis; management options are limited, with surgery being the cornerstone of treatment. Reports on rare tumors such as this will increase awareness of this particular pathology and disclose clinical experience. In this case, the authors were unable to establish a definite cause-and-effect relation between NS and MINST. Nevertheless, it remains the first reported case in the literature [4]

A rare case of a 9-year-old NS patient with two IAPs presenting with episodes of intracerebral hemorrhage that were successfully managed with endovascular embolization.

This case represents a possible association between NS and the presence of ruptured IAPs [5].

A patient with concomitant Noonan Syndrome and Chiari I with 4th ventricular outflow obstruction.

The case highlights the importance of close clinical suspicion in this patient population. They utilize the case to delve into the intricacies of the known pathophysiology and encourage ongoing investigation [6].

A 10-year-old male patient with a heterozygous nonsense mutation, p.Arg183*, in ERF exhibited craniosynostosis with Noonan syndrome-like phenotypes. In consideration that loss-of-function variants in ERF would result in excessive RAS signaling and RASopathy phenotypes, we propose that ERF may represent a causative gene for Noonan syndrome. Since preceding studies on ERF mutations dealt with patients who were ascertained because of craniosynostosis, further studies are needed to evaluate whether patients with variants in ERF can present with Noonan syndrome-like features without craniosynostosis [7].

A 12-year-old girl with Noonan syndrome presented with back pain and new onset neurological deficits and was found to have a spinal cord lesion. T10-L1 laminoplasty with safe maximal resection was done. The postoperative pathological analysis identified this lesion as a high-grade astrocytoma consistent with glioblastoma multiforme.

Spinal cord glioblastoma multiforme is a rare occurrence in the general population, particularly in a patient with an underlying diagnosis of Noonan syndrome. Patients with spinal cord tumors can present with a multitude of clinical signs and symptoms and treatment should not be delayed [8]

A 13-year-old girl with NS associated with a recurrent mutation in PTPN11 developed three different types of brain tumors, i.e., an optic pathway glioma, a glioneuronal neoplasm of the left temporal lobe, and a cerebellar pilocytic astrocytoma. Molecular characterization of the glioneuronal tumor allowed to detect high levels of phosphorylated mTOR (pMTOR); therefore, a therapeutic approach based on an mTOR inhibitor (everolimus) was elected. The treatment was well tolerated and proved to be effective, leading to a stabilization of the tumor, which was surgically removed. The positive outcome of the present case suggests considering this approach for patients with RASopathies and brain tumors with hyperactivated MTOR signaling [9]

Case report from the HGUA

53-year-old female, during the investigation for an episode of dizziness with instability and right parieto-occipital headache, a posterior fossa lesion was identified.

In the MRI a large cystic lesion with a solid component in the right cerebellar hemisphere intra-axially, measuring 5 x 4 x 2.8 cm in transverse, anteroposterior, and craniocaudal dimensions. The solid component within the lesion is markedly heterogeneous, measuring approximately 2.7 cm, with abundant hypointense signal and magnetic susceptibility artifact on gradient echo sequences, appearing as calcification on CT at the solid component's location. The cystic area appears hyperintense on FLAIR and T2-weighted images and hypointense on T1-weighted images. There is heterogeneous contrast enhancement at the solid component but not at the cystic capsule.

It is challenging to determine whether the lesion is intra- or extra-axial due to its size and proximity to the dura mater. In terms of morphology and signal intensity, it is similar to a hemangioblastoma; however, calcification is very rare in hemangioblastomas. Another diagnostic possibility, if the lesion is extra-axial (unlikely but not ruled out), is a partially calcified meningioma with cystic degeneration. It causes mild surrounding vasogenic edema and a significant mass effect on the fourth ventricle, leading to near-complete collapse and triventricular hydrocephalus with signs of transependymal edema.

The patient was scheduled for excision of the lesion. Low-grade glioma WITH ABUNDANT CALCIFICATIONS KI67: 1% IDH (IHC): NEGATIVE Glial fibrillary acidic protein (GFAP) positive EMA: NEGATIVE

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