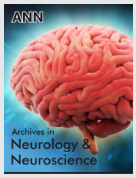

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Editorial

Advances in Molecular Biology of Pediatric Brain Tumors

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Editorial

Brain tumors are the most common solid tumors in children and the second most frequent childhood malignancy. The most common pediatric brain tumors are high-grade gliomas, medulloblastomas, low-grade gliomas, ependymomas, and brainstem/diffuse intrinsic pontine gliomas (DIPGs). Novel studies on the pathogenesis of pediatric brain tumors are still evolving, showing that over 8% of cases arise as germline predisposition syndromes, including neurofibromatosis de type 1, Li-Fraumeni syndrome, tuberous sclerosis, Turcot syndrome, and Gorlin syndrome. Advances in genomic sequencing technologies have allowed molecular profiling to change brain tumor classification. Groundbreaking methods including next-generation sequencing (NGS) have allowed the development of molecular-target therapies, precise diagnosis, and individualized treatment, thus improving prognosis, neurocognitive development, and quality of life. The medulloblastoma is the most common malignant pediatric brain tumor of the posterior fossa, comprising up to 20% of all pediatric tumors. Traditionally, medulloblastoma was classified into four histological variants, including classic, desmoplastic/nodular, anaplastic/large-cell, and extensive nodularity. Recently, the World Health Organization (WHO) reclassified medulloblastoma into four molecular subgroups: wingless-type (WNT), Sonic Hedgehog (SHH), group 3, and group 4. Each subgroup is further divided into several subsets. These molecular subgroups have distinct tumor biology, dissemination, patient outcome, and demographics. Mutations in the WNT subtype include mutations in WTN-α (70%), WTN-β (30%), DDX3X, SMARCA4, and TP53. The majority of patients with WNT medulloblastomas are disease-free 5 years post-diagnosis. In the SHH subtype, gene mutations include PTCH1, SUFU, SMO, and other less uncommon genes. Groups 3 and 4 represent approximately 55% of medulloblastoma cases. Group 3 accounts for approximately 25% of medulloblastomas and has the worst prognosis. Group 3 mutations include MYC-amplified tumors, conferring a short overall survival, in which only 20% of these patients survive up to 5 years. Group 4 is the most prevalent subgroup, representing 30% of all medulloblastomas, and is the least biologically characterized. Treatment of infants is more challenging because of radiation impact. Recently, DNA methylation and gene expression data combined with clustered clinical features revealed 12 different subtypes of medulloblastomas, which provide a means to improve treatment and reduce therapy morbidity. Ependymomas are the third most common brain tumor in children, accounting for approximately 10% of all childhood CNS lesions. In children, approximately two-thirds of ependymomas occur in the posterior fossa. Dissemination is observed in fewer than 10% of cases. Ependymomas are classified into four subtypes, including subependymoma and myxopapillary ependymoma (grade I), ependymoma (grade II), ependymoma RELA-fusion positive (grades II and III), and anaplastic ependymoma (grade III). DNA methylation profiling has been used to identify molecular subgroups within each anatomic compartment to predict prognosis. Patients with infratentorial posterior fossa ependymoma group A (PF-EPN-A) or supratentorial RELA-positive ependymoma have the worst prognosis and represent the largest molecular subgroups.

PF-EPN-A occurs mainly in infants and young children with a high recurrence rate. PF-EPN-B occurs more often in adolescents and young adults, having a better prognosis. The molecular subgroup of supratentorial ependymomas with the YAP1 fusion is often seen in children and has a good prognosis. Maximal safe surgical resection followed by adjuvant postoperative radiation therapy remains the standard of care for ependymomas. In children younger than 3 years, chemotherapy is used to delay irradiation, thus avoiding long-term morbidities, such as the increased risk of stroke, secondary neoplasms, and neurocognitive deficits. Low-grade gliomas (LGG) account for approximately 40% of all childhood brain tumors. LLGs include pilocytic astrocytomas, pilomyxoid astrocytomas, oligoastrocytoma, oligodendroglioma, and ganglioglioma. Pilocytic astrocytomas are often located in the cerebellum, but midline diencephalic lesions are common. Pilocytic astrocytoma mutations are primarily in the mitogen-activated protein kinase (MAPK) pathway. Complete surgical resection is curative for LLGs, however, when the tumors arise near vital structures, resection is difficult without causing morbidity or functional compromise. Several chemotherapeutic agents have been, including vinblastine and the combination of carboplatin and vincristine. Recent understanding of the genomic alterations in LGGs has provided a means to use molecular inhibitors to treat unresectable, refractory, or progressive lesions. Molecular alterations in the BRAF gene are common, including gene fusion between KIAA1549 and BRAF, which results in a fusion protein that lacks the BRAF regulatory domain. This fusion is often observed in posterior fossa pilocytic astrocytomas and approximately 40% of chiasmatic/hypothalamic tumors. In children with recurrent diseases, MEK inhibitors have been used. The BRAF V600E point mutation has been observed outside the posterior fossa and molecular inhibitors of BRAF point mutation have also been used, including vemurafenib and dabrafenib. Visual pathway gliomas are low-grade astrocytic tumors frequently associated with NF-1 and can involve the optic nerve, chiasm, tract, and optic radiations. Molecular alterations in BRAF are frequent in non-NF children, including BRAF fusions and BRAF point mutations in 40% of cases each. Tumor location makes complete surgical resection not feasible. The combination of carboplatin and vincristine has shown tumor shrinkage in 40% and disease stability in approximately 50% of children younger than 5 years. Several studies have shown dramatic recovery of vision with the incorporation of bevacizumab with irinotecan. Recent findings of the molecular pathways of LGGs have allowed the targeting of the BRAF pathway in several clinical trials. High-grade gliomas account for an incidence of 0,8 per 100,000 children per year. Despite therapy, children with high-grade gliomas have an overall poor prognosis with an estimated survival approaching 8 months. Novel research revealed mutations in histone H3 in pediatric high-grade gliomas, predominantly K27M mutations, in which lysine 27 is substituted by methionine. The majority of gliomas with histone mutations cluster with mutations in ATRX (α-thalassemia/mental retardation syndrome X-linked), DAXX (death-domain associated protein), and p53. Brainstem gliomas are currently classified as diffuse midline glioma H3K27M-mutant, representing up to 15% of all pediatric CNS tumors. Brainstem tumor biopsy is not risk-free, however stereotactic biopsy and frameless biopsy using neuronavigation systems can be safe with minimal morbidity and high diagnostic results. Novel findings of the molecular biology of midline lesions, including brainstem tumors, have led to trials targeting specific mutations. Approximately 80% of DIPGs harbor the H3K27M mutation. Other frequently found mutations include overexpression or amplification of the PDGFRA, somatic mutations in ACVR1, and mutation in PI3K (Phosphoinositide 3-kinase alpha), involved in cell proliferation and differentiation. Advances in imaging technology, genomics, and surgical techniques have provided a means to optimize treatment in children with CNS neoplasms, thus improving prognosis and overall survival. Groundbreaking research findings have revealed molecular and genetic changes in pediatric brain tumors necessary for the appropriate classification to improve diagnosis and to implement treatment modalities. Recent advances in molecular analysis have improved our understanding of the molecular profiles of pediatric brain tumors, allowing for novel epigenetic and immunotherapeutic treatment approaches currently being evaluated in clinical trials. Refinements in tumor classification and delineation of risk stratification have provided a means to implement target therapy with reduced morbidity and mortality, thus optimizing patient survival.

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Conflict of Interest

No Conflict of interest.