REVIEW

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Update in pediatric primary brain tumors – from histology to genetically defined tumors

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Abstract

In childhood and in adolescence, primary tumors of the central nervous system (CNS) are the second most common malignancy after leukemia. The most common entities are gliomas, craniopharyngiomas and embryonal tumors, including primitive neuroectodermal tumors of the CNS, such as medulloblastoma. Proper management of malignancies requires a histological diagnosis, especially in childhood, since diagnostic errors have a significant negative influence on the treatment and subsequently on the patient's care. Experimental research conducted in the last years regarding the genomic and epigenetic landscape of pediatric brain tumors has provided considerable help in understanding their pathogenesis. New mutations and new signaling pathways have been associated with pediatric neoplasia, according to recent studies. Current therapeutic protocols recommend triple therapy, consisting in the surgical resection of the tumor, radiotherapy and chemotherapy. However, the success of the therapy depends on the precociousness of establishing the diagnosis and initiating the treatment, age of the child, type of surgery (total/partial), result of the histological examination, chemotherapy protocols and type of radiotherapy. Although immunotherapy and gene therapy continue to be a challenge, extensive studies are needed in order to confirm their promising role in the management of pediatric brain tumors.

Keywords: brain tumors, histology, genetic alterations, children.

Introduction

In childhood and in adolescence, primary tumors of the central nervous system (CNS) are the second most common malignancy. This heterogeneous group of diseases requires a multimodal therapeutic approach. When possible, surgery, with complete excision of the lesion is being associated with radiotherapy and chemotherapy. Before initiating the systemic antineoplastic therapy, various factors, such as patient age, histological diagnosis, tumor localization, etc., must be taken into consideration [1, 2].

The causes of CNS tumors are still unidentified. As other neoplastic processes, the accumulation of multiple genetic alterations, affecting cell cycle progression, is involved in the dynamic of tumor growth. Carcinogenic agents that alter cellular deoxyribonucleic acid (DNA) are chemicals, radiant energy and microbial agents. Various epidemiological studies have shown that only 5% of the patients with brain tumor have a genetic predisposition, linked to familial syndromes, such as tuberous sclerosis, neurofibromatosis type I and II, hereditary retinoblastoma, Li-Fraumeni, and Rubinstein–Taybi syndromes [2].

Epidemiological characteristics

Epidemiological studies of CNS tumors in the pediatric population are difficult to perform due to the small number of cases, tumors heterogeneity, unknown latency period and also due to brain's vulnerability to external factors. When studying the incidence of CNS tumors among the young population, is extremely important to pay attention to the environment where the children are raised (urban areas, industrialized countries, race, culture, etc.) [3].

Into what concerns the etiological environmental factors, the role of ionizing radiation has been demonstrated. In 2013, a second evaluation was carried out, to assess the carcinogenic risk of radiofrequency electromagnetic fields, being published by the *International Agency for Research on Cancer* (IARC) [4].

Numerous studies regarding the role of viruses and infections have been conducted during recent years, but clear evidence of their contribution has not been obtained yet. The researchers' attention was also directed towards harmful chemicals, such as metals, nitroderivatives, polycyclic aromatic hydrocarbons, and their role in the children onocogenesis of CNS tumors, but conclusive evidence has not been established [3].

Clinical manifestations generally occur as a consequence of the direct compression of the brain tissue, which may result in increased intracranial pressure, displacement of

brain parenchyma, or focal cerebral ischemia. These occurrences vary with the location, size and extent of the tumor. Often the symptoms may be nonspecific, with headache, nausea, vomiting, ataxia, asthenia, seizures, walking disorders, and speech or visual disorders. Acute onset may happen due to the blockage of the cerebrospinal fluid outflow or to stroke [5].

Histological features

The histological classification of brain tumors comprises phenotypic features obtained with the help of optical and electron microscopy and also immunohistochemical aspects, all aiming to identify the cell-of-origin of the tumor and its degree of differentiation. Recent studies have shown that tumors with similar microscopic and histological features that could be classified as astrocytoma, for example, may behave differently depending on their molecular characteristics and genetic individuality [1, 6].

Following the 2007 *World Health Organization* (WHO) Classification of CNS tumors, molecular studies have clarified the oncogenesis of CNS embryonal tumors. Genomic studies and biological characterizations of tumors have led to a new classification, with recognition of subclasses and new entities [1, 7].

The 2016 *WHO* Classification of CNS tumors includes more than 100 entities, some of them being very rare. This categorization brought important changes in the taxonomy of glial and embryonal tumors of CNS and only minor modifications in all the other categories, including: peripheral tumors of the tegument, meningiomas, CNS mesenchymal non-meningothelial tumors, melanocytic tumors, germ cell tumors and non-neuroendocrine tumors of the pituitary gland [1, 8].

In children, the most frequent brain tumors are gliomas, craniopharyngiomas and embryonal tumors, including medulloblastoma and primitive neuroectodermal tumors of the CNS. Histological classifying features of brain tumors includes for grades. Grade I comprises tumors with low proliferative index, which generally cure after surgical excision. Grade II tumors are usually infiltrative and frequently recur, even though they show low proliferative rate. Grade III involves lesions with clear histological mark of malignancy, which requires radiation and/or chemotherapy. Grade IV consists of cytologically malignant tumors with high mitotic activity, areas of necrosis, having rapid evolution and fatal outcome (Table 1) [1, 9].

From a histopathological (HP) and implicitly a therapeutic perspective, gliomas represent a heterogeneous group, comprising low-grade gliomas, such as pilocytic astrocytoma, which are generally of favorable prognosis, and high-grade gliomas, tumors of fatal evolution, such as intrinsic pontine glioma.

Pilocytic astrocytoma

Pilocytic astrocytoma (grade I *WHO*) accounts for 85% of all low-grade gliomas (Figures 1–3) located mainly in the cerebellum and in the hypothalamic/chiasmatic region, being followed by the diffuse astrocytoma and the pleomorphic xantoastrocytoma. The astrocytic tumors having low to moderate cellularity often show a biphasic pattern, comprising condensed bipolar cells with Rosenthal fibers and multipolar cells with microcysts, best seen in tumors of the cerebellum. Diffuse oligoastrocytoma and oligodendroglioma are rare in children. Low-grade diffuse gliomas are located mainly in the cerebral hemispheres, thalamus, and brainstem and have an infiltrative growth pattern as well as high-grade pediatric gliomas, glioblastomas, and anaplastic astrocytomas [10]. They are composed of well-differentiated fibrillary astrocytes disposed in a loose tumor matrix, often with microcystic features [1].

Table 1 – ***Features of the most frequent brain tumors in children***

Type	Histological grade	*WHO* grade	Age of presentation
Gliomas			
Pilocytic astrocytoma	Low-grade	I	0–14 years
Diffuse astrocytoma	Low-grade	II	<20 years
Pleomorphic xanthoastrocytoma	Low-grade	II	Children, young adults
Craniopharyngioma	Low-grade	I	Children
Medulloblastomas, histologically defined	High-grade	IV	
Medulloblastoma, classic			Childhood
Desmoplastic/nodular medulloblastoma			Children aged <3 years
Medulloblastoma with extensive nodularity			Children aged <3 years
Large cell/anaplastic medulloblastoma			Any age
Atypical teratoid/rhabdoid tumors	High-grade	IV	Children aged <3 years
PNETs of the central nervous system	High-grade	IV	Children

WHO: World Health Organization; PNETs: Primitive neuroectodermal tumors.

Craniopharyngioma

In the pediatric population, craniopharyngioma is a rare embryonal tumor (Figures 4–6), developed from Rathke's pouch remnants, having two clinicopathological variants: adamantinomatous and papillary, with different phenotypes and distinctive mutations. Usually is a low-grade tumor (grade I *WHO*), of low mortality, but of considerable morbidity [11]. Adamantinomatous craniopharyngiomas are composed by well-differentiated epithelium, with different architectural patterns: cords, lobules, nodular whorls, and irregular trabeculae surrounded by palisading columnar epithelium. Papillary craniopharyngiomas include solid, monomorphic areas of well-differentiated squamous epithelium lacking surface keratinization [1].

Medulloblastoma

CNS embryonal tumors make up about 20% of pediatric brain tumors. This category includes medulloblastoma (Figures 7–9), atypical teratoid/rhabdoid tumors, and primitive neuroectodermal tumors (PNETs) of the CNS, which are the most common types of malignancies, biologically and molecularly different [12, 13]. Medulloblastomas include as a common feature a major population

of small round undifferentiated cells with mild to moderate nuclear pleomorphism and high mitotic figures. These tumors are now classified into molecular and morphological variants, with utility in clinical practice [1].

Proper management of malignancies requires a histological diagnosis, especially in childhood, since diagnostic errors have a significant negative influence on the treatment and subsequently on the patient's care [14].

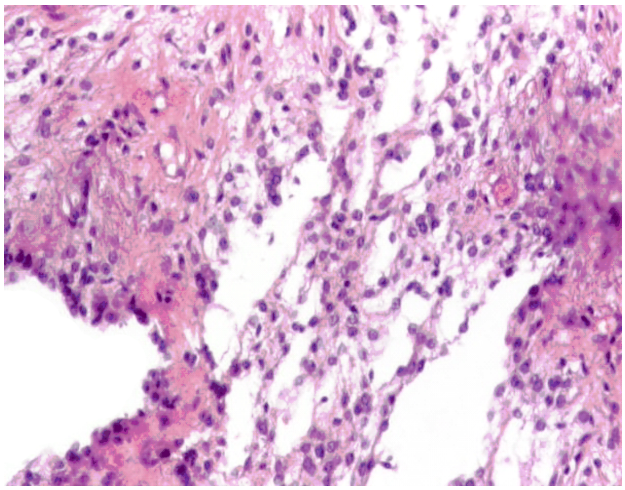

Figure 1 – ***Pilocytic astrocytoma with cystic areas (HE staining, ×100). HE: Hematoxylin–Eosin.***

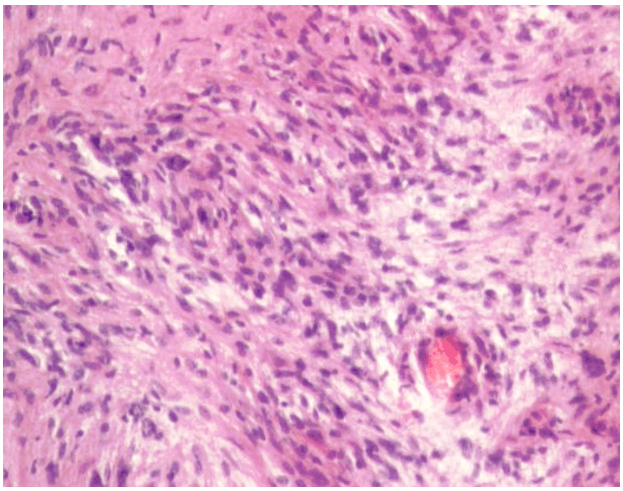

Figure 2 – ***Pilocytic astrocytoma: bipolar cells with Rosenthal fibers (HE staining, ×100).***

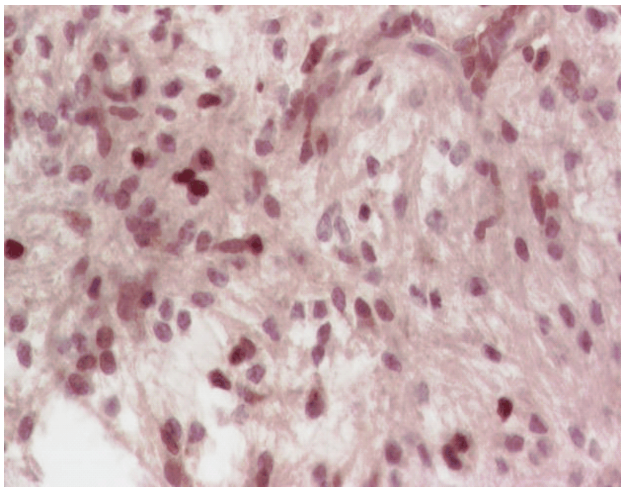

Figure 3 – ***Pilocytic astrocytoma: low Ki67 immunostaining (Anti-Ki67 antibody immunomarking, ×200).***

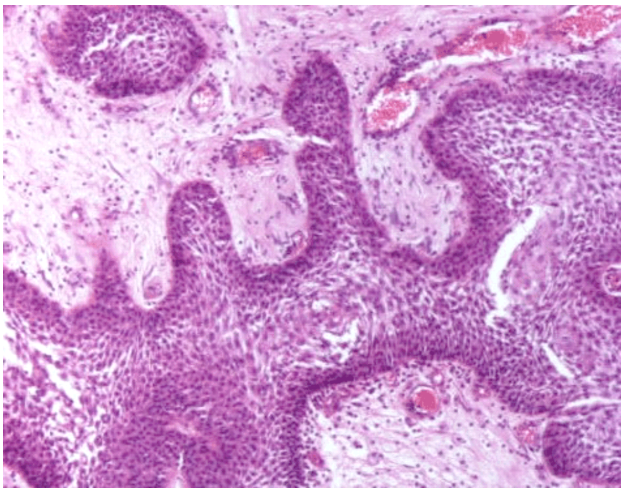

Figure 4 – ***Craniopharyngioma: sheets, nodules and trabeculae of squamous epithelium (HE staining, ×40).***

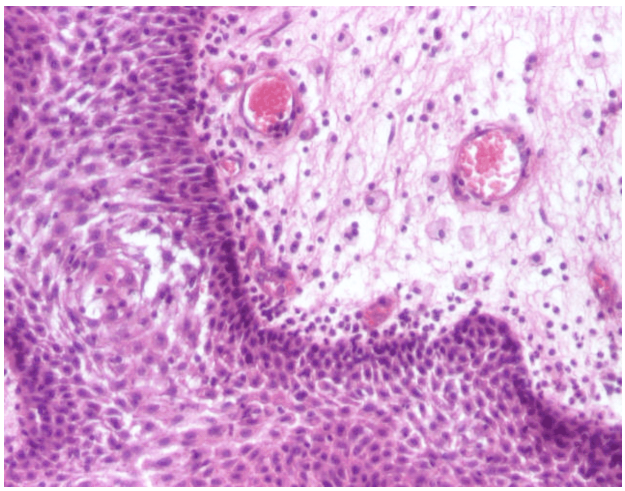

Figure 5 – ***Craniopharyngioma: tumor trabeculae with palisading epithelium (HE staining, ×100).***

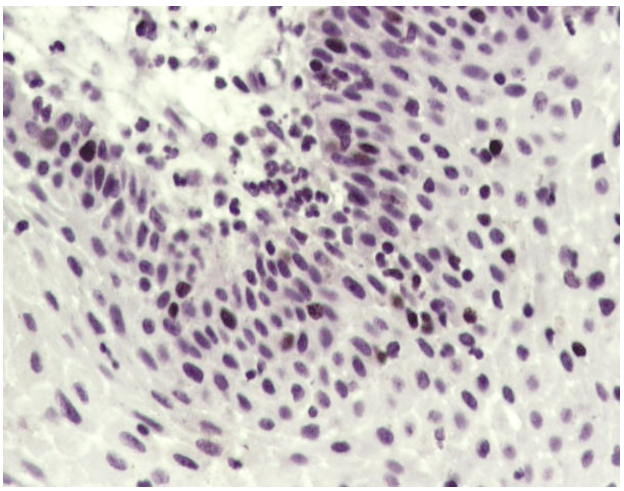

Figure 6 – ***Craniopharyngioma: low Ki67 immunostaining (Anti-Ki67 antibody immunomarking, ×200).***

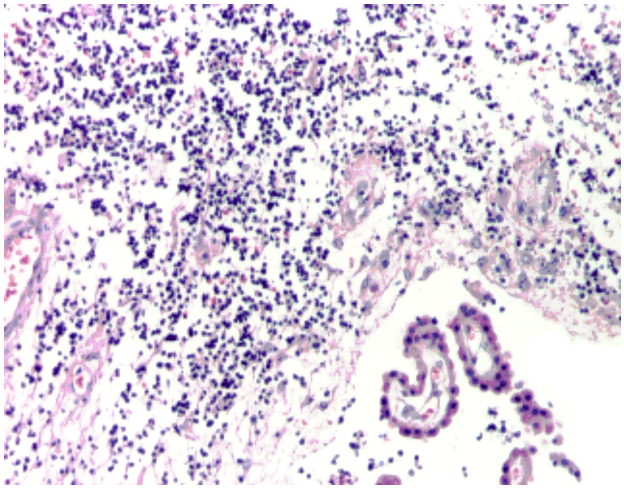

Figure 7 – ***Medulloblastoma: small round undifferentiated cells in cerebellum (HE staining, ×40).***

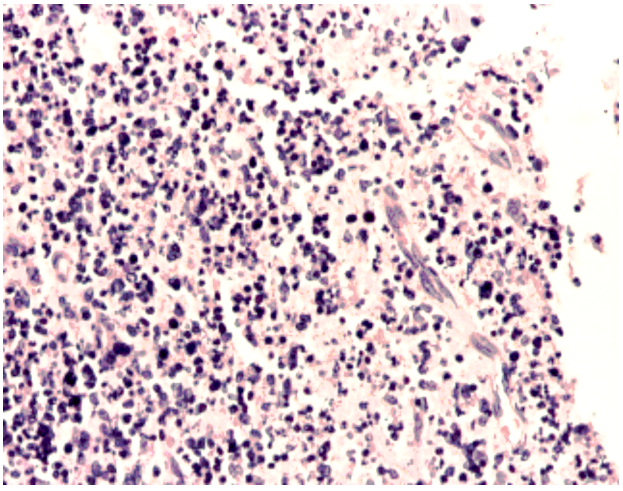

Figure 8 – ***Medulloblastoma: undifferentiated tumor cells in cerebellum (HE staining, ×100).***

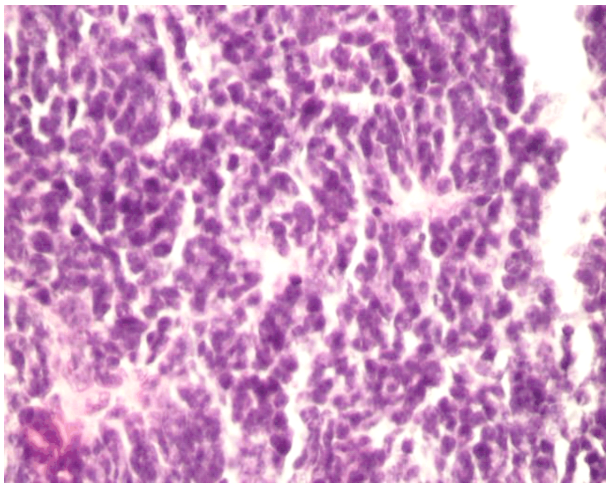

Figure 9 – ***Medulloblastoma: tumor cells with moderate pleomorphism (HE staining, ×200).***

Genetic characteristics of brain tumors

As in other neoplastic processes, knowing the signaling pathways involved in the carcinogenesis is very important. Generally, in oncogenesis, a growth factor binds to its specific receptor, activating various cellular events and promoting cell proliferation and survival [15].

Mutations in any oncogenic signaling pathway may induce the appearance of one distinguishing feature of a tumor: activating mutations of proto-oncogenes encoding growth factors, growth factor receptors, signal transduction proteins, transcription factors or cell cycle components. A growth factor receptor mutation may result in the formation of a complete new receptor that activates signaling pathways even in the absence of an activator, whereas a tumor suppressor gene mutation promotes a persistent proliferation [16].

The genetics and epigenetics discoveries of the last decades oriented the classical diagnosis of the CNS tumors based mainly on microscopic characteristics towards a molecular approach [17]. Activations of different signaling pathways, such as the sonic hedgehog (SHH) cascade or wingless/integrated (WNT) signaling pathway and markers, such as isocitrate dehydrogenase (IDH) mutation status, 1p/19q co-deletion, play an essential role in identifying the nosological entity and also help in increasing the accuracy of the diagnosis [18].

Recent studies discuss the role of five genes encoding three human IDH catalytic isoenzymes: IDH10, IDH2, and IDH3. It has been noticed that IDH1 and IDH2 form homodimers, while IDH3 forms a heterotetramer containing two α subunits, one β and one γ [19]. IDH is the enzyme involved in the oxidative decarboxylation of isocitrate, using nicotinamide adenine dinucleotide phosphate ($NADP^+$), as a cofactor to generate reduced form of $NADP^+$ (NADPH), the final product of this reaction being α-ketoglutarate (αKG). Although with different cellular locations (IDH1 in the cytosol and peroxisomes, IDH2 in the mitochondria), the IDH1 and IDH2 enzymes have similar structures and catalyze the same reversible reactions. These two enzymes are encoded by two different genes: 2q33 for IDH1; 15q26 for IDH2. The IDH3 isoenzyme is involved in catalyzing the decarboxylation reaction of isocitrate to generate αKG within the Krebs cycle (uses NAD^+ as a co-factor) [20]. The most common mutations cause the substitution of arginine 132 in IDH1 or at R172 and R140 analogous of IDH2, the consequence being the excessive accumulation of the 2-hydroxyglutarate metabolite [21].

1p/19q co-deletion is characterized by the complete deletion of the short arm of chromosome 1 (1p) and of the long arm of chromosome 19 (19q). The possibilities of highlighting the 1p/19q co-deletion are: fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), chromogenic hybridization *in situ* or molecular genetic testing [22].

The hedgehog (*HH*) gene was discovered in 1980 by Nüsslein–Volhard & Wieschaus through the genetic analysis of *Drosophila melanogaster*, the vinegar fly. Ten years later, three other homologues of the *HH* gene were discovered in vertebrates: SHH, Indian hedgehog (IHH), and desert Hedgehog (DHH) [23]. The SHH pathway plays a pivotal role in the embryogenesis and morphogenesis of neuronal structures, as well as in the

proliferation of cerebellum granule neuron precursors. The SHH ligand, secreted by Purkinje cells, takes part in the formation of the external germinal layer with granule cell precursors (GCPs) [24]. The SHH-protein binds to patched (PTCH) receptors and enhances the activity of smoothened receptors (SMOs), which results in the transcription of glioma-associated oncogene homologs (Gli1/2/3). Abnormal functioning of the SHH pathway promotes gastric cancer, medulloblastoma, skin cancer and also glioblastoma formation [25].

A variety of processes, such as embryonic development, cells physiology, and homeostasis, are influenced by the WNT signaling pathway. The *WNT* gene, also called integration 1 (Int1), was first described in 1982, by Nusse & Varmus, at mice with mammary tumors. After several years, it was recognized as the mammalian equivalent of the wingless (Wg) phenotype of *Drosophila*. Subsequently, the research continued and thus, this signaling pathway and its associated protein were defined [26]. Wnt proteins are glycoproteins with a crucial role in embryogenesis, differentiation, motility, proliferation and homeostasis of adult tissues. The Wnt signaling pathway proteins emit signals to cells *via* surface receptors. The WNT pathway can be differentiated into three parts: the canonical Wnt pathway (β-catenin dependent), the non-canonical planar cell polarity (PCP) Wnt pathway, and the Wnt/Ca^{2+} pathway [27]. The role of the Wnt signaling pathway in the neuronal development, through the renewal and differentiation of neural stem cells is well known.

In a study performed by Morris & Huang, adult progenitor cells from hippocampus were used. The up-regulation of β-catenin induced an increase in the hippocampus dimensions, while the down-regulation phenomenon led to the appearance of a small hippocampus. Similar results were obtained for gain-of-function mutations and, respectively, for the loss of β-catenin function mutations [25]. Thus, gain-of-function mutations increased the proliferation of neural stem cells in the periventricular area, leading to abnormal enlargement of the brain, whereas loss-of-function mutations resulted in a clearly noticeable reduction in brain volume [25]. The development of sequencing technology with comprehensive structural characterization of the genome of cancer cells has identified that mutations in the Wnt pathway are common in human cancers. Although the main components of this pathway have been described, the function of Wnt signaling in the biology of cancer is intriguingly complex and only partially understood [28].

The new findings in the field of genetics have allowed the modification of standard terminology by combining HP and molecular characteristics. Therefore, the HP name is followed by the genetic characterization [*e.g.*, diffuse astrocytoma, *IDH*-mutant, medulloblastoma, *WNT*-activated]. For tumors with more than one genetic determinant, the HP name is followed by multiple molecular characteristics (*e.g.*, oligodendroglioma, *IDH*-mutant and 1p/19q-encoded). In case of tumors that do not present any gene mutation, the wild type concept can be used: *IDH* wild-type glioblastoma. In the absence of access to molecular diagnostic tests, the unspecified term (not otherwise specified – NOS) can be used. NOS can also be used when the genetic test results are inconclusive.

Basically, using the NOS term means that there is not enough information as to assign a specific name to the respective tumor. When a specific genetic alteration is present, the term "positive" (for example, the ependymoma, *RELA* fusion positive) can be used [22].

Medulloblastoma, which is the most common CNS embryonal tumor of childhood and second in incidence only to pilocytic astrocytoma, is categorized according to molecular characteristics taking into account its clinical utility, but when molecular analysis is restricted the HP features outlines the diagnosis (Table 2) [1, 22].

Table 2 – ***Genetic classification of medulloblastoma according to the WHO 2016***

Medulloblastomas, genetically defined	Genes with germline mutations	Genetic mutations
Medulloblastoma, *WNT*-activated	*APC*	*CTNNB1* mutation *DDX3X* mutation *TP53* mutation
Medulloblastoma, *SHH*-activated and *TP53*-mutant	*TP53*	*TP53* mutation
Medulloblastoma, *SHH*-activated and *TP53*-wild type	*PTCH1* *SUFU*	*PTCH1* mutation *SMO* mutation (adults) *SUFU* mutation (infants) *TERT* promoter mutation
Medulloblastoma, non-*WNT*/non-*SHH*	–	*PVT1–MYC* *GFI1*/*GFI1B* structural variants

WHO: World Health Organization; *WNT*: Wingless/integrated; *SHH*: Sonic hedgehog; *TP53*: Tumor protein p53; *APC*: Adenomatous polyposis coli; *PTCH1*: Patched 1; *SUFU*: Suppressor of fused homolog (*Drosophila*); *CTNNB1*: Catenin beta 1; *DDX3X*: DEAD-box helicase 3 X-linked; *SMO*: Smoothened, frizzled class receptor; *TERT*: Telomerase reverse transcriptase; *PVT1–MYC*: Plasmacytoma variant translocation 1–Avian myelocytomatosis viral oncogene homolog; *GFI1/GFI1B*: Growth factor independent 1/1B transcriptional repressor.

Therapeutic approaches

The encouraging results of the prospective multicenter trials conducted over the past 30 years have led to an improvement in the management of pediatric tumors. Current therapeutic protocols recommend triple therapy, consisting in the surgical resection of the tumor, radiotherapy and chemotherapy. Despite of a superior result in increasing survival rates, the toxicity associated with this multimodal therapy affects the long-term quality of life. Current imaging investigations allow, on the one hand, the evaluation of tumor localization, with the appreciation of its intracranial extension and, on the other hand, the making of a differential diagnosis. The new magnetic resonance imaging methods discern between brain tumors and other neurological entities, as well as identify complications that may occur in the natural evolution of tumors, such as intracranial hypertension, edema or intracranial hemorrhage [29].

Current studies show that the long-term survival rates in patients with childhood brain tumors are over 70%. However, at least half of this population will develop chronic pathologies, as a consequence of the tumoral process or as a post-therapeutic effect. Long-term repercussions

include chronic neurological deficits (focal sensory deficit, motor deficit, seizures, neurocognitive deficits with developmental delays, learning delays) and neuroendocrine deficiencies (hypothyroidism, growth retardation, delay or absence of puberty).

A multidisciplinary approach of children with brain tumors, during both treatment and post-therapy period can greatly improve the prognosis of the disease. The multidisciplinary team must be formed of a neurologist for a proper anticonvulsant therapy, an endocrinologist able to establish an optimal level for growth hormone and/or for thyroid hormones, a kinetotherapist. Also, in order to increase the life quality of the survivors, it is necessary to include them and their families in personalized educational programs [13].

The treatment aims to eradicate the intracranial tumor without injuring the healthy tissues and the neighborhood structures. The success of the therapy depends on the precociousness of establishing the diagnosis and of initiating the treatment, age of the child, type of surgery (total/partial), result of the histological examination, chemotherapy protocols and type of radiotherapy. Poor prognostic factors include late diagnosis, altered general status and incomplete treatment response [30]. Early diagnosis together with rapid initiation of treatment are indispensable conditions for a good prognosis, with an increased survival rate and a better quality of life [31].

Conclusions

In childhood and in adolescence, primary tumors of the CNS are the second most common malignancy after leukemia. The etiology is multifactorial, but still incomplete elucidated, the analysis of risk factors being of great importance. For a proper classification of the tumors and a right therapeutic conduct, molecular and epigenetic biomarkers play an extremely important role. The HP examination of the samples obtained by biopsy establishes a clear diagnosis. New therapeutic approaches, such as immunotherapy and gene therapy, continue to be a challenge, further investigation and further consideration being necessary in order to confirm their promising role in the management of pediatric brain tumors.

Conflict of interests

The authors report no conflict of interests.

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