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Primary Brain Tumors in Childhood

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Abstract

This chapter offers literary review of most frequently observed brain tumors in childhood. It offers basics of epidemiology, clinical presentation and diagnostics of most often occurring types of tumors according to new WHO classification of brain tumors from 2016 and emphasizes molecular biological characteristics and role of altered genes and genetic pathways in brain tumor etiology, classification and treatment. This review not only concentrates on gliomas, medulloblastomas and ependymomas, but also offers characterization of other less frequently observed lesions. Each tumor characteristics also contains basics of therapeutical possibilities of these lesions with focus on targeted and individually designed therapy according to molecular and genetic alterations found in tumor tissue sample.

Keywords: brain tumors, childhood, glioma

1. Introduction

Brain tumors are the second most common group of tumors (following hematological malignancies) as well as the most frequent solid tumors in childhood [1] in age category up to 1 year and between 5 and 19 years of age, even the most common childhood malignancy [2], as well as the most frequent death cause from all oncological diagnoses [3]. Despite the significant progress in imaging and neurosurgical techniques, molecular genetic diagnostics and therapeutic protocols as well as the introduction of concomitant chemoradiotherapy, cure and survival rates of these children did not significantly change – except for medulloblastoma [4].

2. Epidemiology of brain tumors in children

The incidence of pediatric CNS tumors varies worldwide with an average of 4 cases per 100,000 children with the highest occurrence is in the United States [3]. By age groups, the highest incidence is in adolescents (15–19 years, 6.38/100,000), followed by a group of children under 1 year (6.2/100,000). Subsequently, it is slightly declining, with 5.5/100,000 children aged between 1 and 4 years; in 5–14 years, the incidence is 5.1/100,000 [2, 5]. About 25–30% are in supratentorial localization, followed by the cerebellum (15–20%), the brain stem (10–12%), the pituitary and suprasellar region (10–15%), cranial nerves (6–7%), brain ventricles (5–6.4%), spinal cord (4.3–4.6%) and 2.6–2.9% are tumors of meninges [2, 6], as shown in **Figure 1**. Also a typical localization and histological type occur in certain age group. By 1 year of age, tumors most often occur at multiple locations in the brain and in ventricles. At the age of 1–4 years, the most common site is the cerebellum, cerebral hemispheres and brain stem. In the age range from 5 to 9 years, tumors occur frequently in the cerebellum, brain stem and cerebral hemispheres. At the age from birth to 9 years, the most common tumors are gliomas and embryonal tumors (up to 1 year is the most common embryonic atypical teratoma/rhabdoid tumor (AT/RT), in the older children it is medulloblastoma (MB)). In 10–14 year age group, the most typical site is cerebral hemisphere and most frequently occurring are gliomas, tumors of the pituitary region and embryonal tumors. Adolescents (aged 15–19 years) most often have pituitary tumors, then astrocytomas and neoplastic tumors, but the incidence of meningiomas also increases. Typical localizations in this age group are the pituitary and suprasellar regions, followed by cerebral hemispheres and cerebellum. In general, brain tumors are more common in boys [2, 5].

There are many risk factors for brain tumor development, but to date only some hereditary syndromes (type 1 and 2 neurofibromatosis, tuberous sclerosis, Li-Fraumeni syndrome, Gorlin syndrome, Turcot syndrome, Cowden syndrome, Rubinstein-Taybi syndrome and hereditary retinoblastoma) and ionizing radiation have been verified. Other possible risk factors include: a personal history of previous cancer treatment, a family history of the CNS tumor, the parent age at the time of conception, the later contact of the child with common childhood infectious

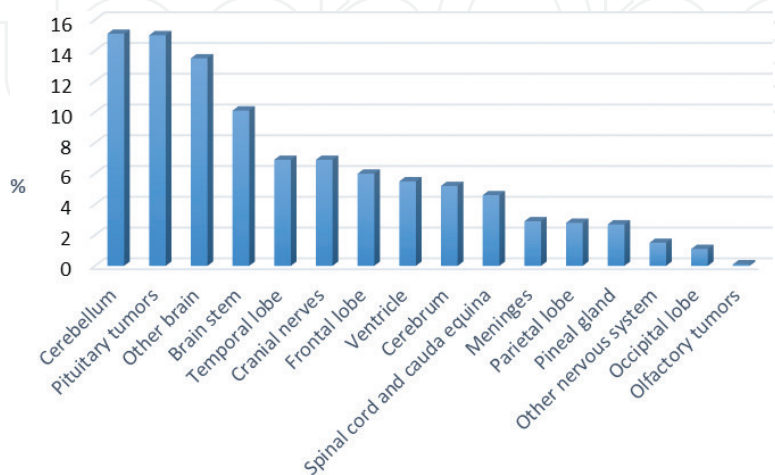


Figure 1. Localization of CNS tumors in pediatric population [5].

diseases [7], congenital anomalies [8], higher birth weight and larger head circumference [9]. Interestingly, the results of studies suggest lower incidence of CNS tumors in children with allergies and asthma [10, 11].

3. Classification of brain tumors in children

The new WHO classification of CNS tumors from 2016 for the first time uses molecular genetic characteristics for tumor classification in some cases. In this new edition, some new tumor entities appeared, some have been merged while others were excluded. Changes involving childhood tumors include: inclusion of epithelial glioblastoma, removal of the term brain gliomatosis, reclassification of the diffuse intrinsic pontine glioma to diffuse midline glioma, *H3 K27*–mutant, inclusion of the ependymoma, *RELA* fusion–positive as a separate unit and inclusion of the diffuse leptomeningeal glioneuronal tumor. The change also affected the classification of medulloblastomas, where genetically defined classification was added. The term primitive neuroectodermal tumors (CNS PNET) was eliminated while an embryonal tumor with multilayered rosettes, *C19MC*–altered was included [12].

Childhood brain tumors are also classified according to their localization into: infratentorial, supratentorial tumors and tumors of parasellar region. Most frequently observed histological types of pediatric CNS tumors are shown in **Figure 2**.

Infratentorial localization is typical for cerebellar astrocytoma (pilocytic astrocytoma – PA, but also diffuse less frequently anaplastic astrocytoma and glioblastoma), medulloblastomas, ependymomas, brain stem gliomas (most commonly diffuse midline glioma, *H3 K27*–mutant, PA), AT/RT and choroid plexus tumors.

Supratentorial localization are common: low-grade glioma—LGG (PA, diffuse astrocytoma, oligodendroglioma, mixed oligoastrocytoma, subependymal giant cell astrocytoma—SEGA, pleomorphic xanthoastrocytoma—PXA), high-grade glioma—HGG (anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma), neuronal and mixed neuronal-glial

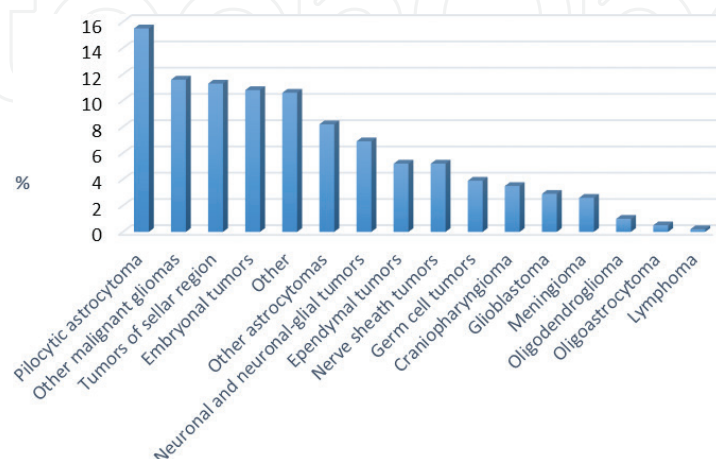


Figure 2. Most frequent histological types of CNS tumors in children [5].

tumors (ganglioglioma—GG, desmoplastic infantile astrocytoma—DIA, ganglioglioma—DIGG, dysembryoplastic neuroepithelial tumor—DNET and papillary glioneuronal tumor), embryonal tumors (embryonal tumor with multilayered rosettes, *C19MC*-altered—ETMR, medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma, CNS embryonal tumor and CNS embryonal tumor with rhabdoid features), AT/RT, ependymomas, meningiomas, choroid plexus tumors, pineal tumors (pineocytomas, pineal parenchymal tumor of intermediate differentiation and papillary tumors of the pineal region) and rarely metastases of extra-neural malignant tumors.

Tumors occurring in **parasellar** region usually are: craniopharyngiomas, adenomas, LGG astrocytomas (tumors of central regions, chiasma, hypothalamus, thalamus, PA or diffuse astrocytomas) as well as germ cell tumors.

4. Brain tumors symptoms in children

Symptoms of brain tumors can develop gradually and worsen over time, or they may manifest suddenly and dramatically. Symptoms may be general or specific, resulting from tumor localization. **General symptoms** are manifestation of intracranial hypertension that is caused either by tumor growth, brain swelling or onset of hydrocephalus or a combination of these factors. Symptoms of intracranial hypertension include: headache (especially in the morning after awakening), nausea or vomiting, diplopia and strabismus, disturbances of balance, personality changes, epileptic seizures or loss of consciousness. Infants may experience irritability, loss of appetite, delay or regression of psychomotor development. There is also bulging of the fontanelle and the disproportionate enlargement of the head circumference. Children of school age may suffer from increased fatigue, psychological changes, impairment of school performance, disturbances of memory and impaired concentration. Regarding the localization of the tumor, other locally **specific neurological symptoms** may also occur: visual disturbances, narrowing and outages of visual field, abnormal bulb movements, nystagmus, hearing or speech disorders, paresis or hemiparesis, muscle weakness, loss of sensitivity or coordination, ataxia, posture disorder, walking instability, tingling of body parts, cranial nerves palsy as well as hormonal disorders.

5. Brain tumors diagnostics

Diagnosis of brain tumor is based on a patient history and complete neurological examination. Imaging examination is performed when a brain tumor is suspected. Basic imaging examination is **magnetic resonance imaging (MRI)**. It is the most spectacular imaging for intracranial structures that is currently available in medicine. In brain tumor diagnostics the use of contrast media—gadolinium—is essential. **MR-angiography** displays brain vessels alongside with pathological tumor vasculature, what is important for planning of the surgical treatment. **MR-spectroscopy** is a metabolic examination of the brain. The **perfusion MRI** monitors blood flow in the investigated area. Tumors are metabolically active and require greater blood supply. **Functional MRI** and **MR-tractography** are used for planning of surgical approach.

Preoperatively, the navigational MRI is performed for the needs of intraoperative navigation. Among the disadvantages of MRI is relatively longer duration, which in smaller children requires general anesthesia. However, a huge advantage is the absence of radiation [13].

Computer tomography (CT) is mostly used for the display of bones and their lesions, which do not appear in detail in MRI. Another indication may be **CT-angiography**. Due to the high dose of radiation; however, CT is reserved for cases of sudden changes in the neurological condition when rapid imaging is necessary.

Positron emission tomography (PET) uses radioactive fluorodeoxyglucose for visualization of tumor tissue that is metabolically more active. The radioactive load is very low and is excluded in 1 day. It can be used preoperatively for diagnostics as well as for postoperative distinguishing between residues, recurrences and postoperative changes in unclear cases [14].

Angiography (mostly DSA) uses vessel imaging after contrast agent administration to assess tumor vascular supply. It is also associated with radiation and though is currently replaced by MR- or CT-angiography. However, it remains reserved for preoperative embolization of the tumor, which is carried out by DSA [13].

Specimen of CSF obtained from **lumbar puncture** is used for cytological examination to detect the presence of tumor cells that occur in CSF in tumor dissemination or in leukemia tumors. It is also used to detect the presence of tumor markers, in particular bHCG and AFP in germ cell tumors. It also serves to verify the presence of infection, especially in the postoperative period [13].

Biopsy of brain tumor is essential for definitive diagnosis. In most cases, tissue sample is obtained during surgery. However, there are also cases of inoperable tumors according to their localization or extent. If a tumor resection cannot be performed, a stereotactic biopsy can be useful. In some cases, however, the biopsy is too risky, and therefore the diagnosis is determined only by MRI (e.g., diffuse pontine gliomas).

Also **other examinations** could be useful, such as: EEG, evoked potentials, evaluation of neurocognitive functions, ophthalmological examination (papilledema of optic nerve and perimeter), evaluation of hearing disorder and hormone levels and function [13].

6. Treatment of brain tumors

Treatment consists of surgical intervention, followed by oncological and symptomatic treatment and requires multidisciplinary approach.

Surgical treatment is the basis of treatment and, in some tumors, it is the only sufficient form of therapy. Also histologically, benign tumors can be a surgical challenge by their localization. An essential part of brain tumor surgery is the use of microscope and micro instruments. Nowadays, it belongs to the usual equipment of surgical department, as well as ultrasonic aspirator, **navigation systems**, intraoperative sonography and possibility of realization of electrophysiological monitoring. **Electrophysiological monitoring** requires appropriate instrumentation and personnel equipment that enhances the safety of the operation to the

full possible extent in the eloquent areas of the CNS. Use of 5-aminolevulinic acid is very helpful in operations of HGG. Patient ingests this acid prior to surgery, and then during surgery, with use of fluorescence on the microscope, high-grade glial cells begin to gleam, which also contributes to performance of accurate resection and representative tumor sampling for histological examination. **Awake operations** with the possibility of intraoperative stimulation, in which the patient is conscious either during the entire procedure or in a certain part of it, are used in adult patients, especially in tumors in motor, sensory and speech areas. In children, it is significantly limited by age and ability to cooperate. They are mainly performed in older age groups of children [15].

According to extent of resection, we divide surgical treatment into: **total resection**, **near-total resection**, **partial resection** and **biopsy**. In most tumors (except well-defined benign tumors or well-defined metastases), total resection is only a radiological rather than a biological term. The surgical approach can serve (though not as a standard treatment method) for the targeted administration of radiotherapy in the form of **intraoperative radiotherapy** with a single irradiation of the tumor bed directly after resection of the tumor [16] or **chemotherapy**—for example, intraoperative administration of biodegradable carmustine [17]. In addition to **craniotomy**, other techniques—for example, **endonasal trans-sphenoidal approach**—can also be used, including endoscopy for pituitary tumor tumors. Another option for biopsy or tumor removal (often when located in brain ventricles) is **endoscopic surgery**. From other surgical methods, shunts in hydrocephalus can be used, most commonly **ventriculoperitoneal shunt**. Another option is implantation of Ommaya reservoir, which is useful for repeated sampling of CSF for laboratory examinations, for therapeutic evacuation puncture of CSF, as well as for the local administration of chemotherapy.

Chemotherapy is part of adjuvant oncological treatment after surgical resection alone or along with radiotherapy. It can be administered **systemically** (intravenously or orally), **locally** during surgery, or postoperatively into an implanted reservoir. Most serious side effects of chemotherapy are: bone marrow depression, nausea, vomiting, diarrhea and temporary hair loss. Generally, children better tolerate high doses of chemotherapy compared to adults, which may increase the aggressiveness of treatment if necessary.

Targeted biological therapy is directed against the specific protein and gene targets of the tumor, or against the environment that affects its growth and survival. But even all tumors of the same histological type do not have the same alterations and the treatment goals. Therefore, it is essential to examine each tumor sample for the presence of altered genes and proteins in order to determine targeted individualized treatment. One of the best known drugs is bevacizumab with an antiangiogenic effect, which stops the nutrient intake into the tumor by blocking of angiogenesis. This treatment is used for HGG. However, the effect of this treatment is lower than expected. Therefore, it is reserved as supportive treatment in relapsing non-responding tumors. Also used is everolimus, the *mTOR* pathway blocker in the treatment of subependymal giant astrocytoma, or tyrosine kinase inhibitors, in particular *EGFR* (erlotinib and gefitinib) in the treatment of ependymomas [18]. Patients with HGG with a proven *BRAF V600E* mutation also receive *BRAF* inhibitors (vemurafenib and dabrafenib) with partial effects [19].

Radiotherapy is also often used in treatment of pediatric brain tumors, either alone or as part of concomitant therapy. It uses high energy RTG beams to damage tumor cell DNA. It can

take various forms, using external radiotherapy as well as local forms. **External radiotherapy** is mostly accomplished with a linear accelerator by various techniques, such as conventional radiotherapy, 3D conformal radiotherapy, modulated beam intensities, stereotactic radiotherapy using stereotactic frames or radio-surgical methods (single irradiation) that use a linear accelerator, gamma knife or cyber knife as the source of radiation. **Local forms** of radiotherapy require an invasive approach. This group includes intraoperative radiotherapy, which is applied during surgery and interstitial brachytherapy requiring surgical delivery of emitters close to the tumor. Subsequently, radiotherapy is applied in the postoperative period. Local forms have, of course, a minor incidence of undesirable radiotherapy effects, of which the most common are: fatigue, hair loss, radiation dermatitis, brain edema and presence of post radiation necrosis and encephalopathy. Proton therapy is becoming increasingly popular.

The novelty in the treatment of HGG is the use of an **alternating electric field**. It appears to be the most effective in connection to concomitant chemoradiotherapy. It is recommended for treatment of recurrent tumors [20].

Very necessary is also **supportive medical treatment**, in particular corticosteroids which suppress perifocal and postoperative edema, anticonvulsants (in the presence of epileptic seizures), analgesics, antiemetic drugs, nutritional support and oncological rehabilitation [21].

7. Most common brain tumor types occurring in childhood

The most common CNS tumors in children are: gliomas, ependymomas, neuroglial tumors, embryonal tumors, choroid plexus tumors, craniopharyngiomas and germ cell tumors.

7.1. Gliomas

Glial tumors account for 55% of pediatric CNS tumors [3]. It is a heterogeneous group of tumors that varies from a well-defined, potentially curable low-grade pilocytic astrocytoma and diffusely growing astrocytomas (grade II) to high-grade, aggressive and incurable tumors, such as diffuse glioma of midline structures. They arise from CNS glial precursor cells: astrocytomas originate in astrocytes, oligodendrogliomas in oligodendrocytes, mixed gliomas are derived from astrocytes, oligodendrocytes and ependymal cells. The histologically most common glioma in children is astrocytoma.

7.1.1. Low-grade gliomas in children

The most common LGG in children are: pilocytic astrocytoma—PA (grade I), diffuse astrocytoma (grade II), oligodendroglioma (grade II), subependymal giant astrocytoma (SEGA) and pleomorphic xanthastrocytoma (PXA). The prognosis of LGG in children is relatively good, especially in well-defined grade I lesions with the possibility of total resection. Dissemination within the CNS is rare, but may be multifocal, especially in patients with neurofibromatosis type 1 syndrome [22]. Unfavorable prognostic factors include: low age, impossibility of total resection, diffuse growth (especially *IDH* mutated), diencephalic syndrome, presence of symptoms of intracranial hypertension and metastasis [23].

7.1.1.1. *Pilocytic astrocytoma WHO grade I*

This tumor is the most frequent LGG in children (up to 85%). Typical localizations are: cerebellum, diencephalon, optic tract, basal ganglia or brain stem [3]. Various localizations of this tumor also have their typical genetic characteristics. Its autosomal dominant forms are part of NF type 1 syndrome and tuberous sclerosis with typical localization over the course of the optical pathway, less often in hypothalamus. However, sporadic forms are more frequent. It may contain a *BRAF-KIAA* fusion that is connected to better prognosis. Conversely, the higher MIB-1 proliferation index is associated with shortened survival [24]. Therapy consists of surgical treatment. Despite the limited growth and the benign nature, the possibility of its removal is sometimes limited by its localization.

Its subtype is a **pilomyxoid astrocytoma** with a typical angiocentric array of myxoid matrix. It is most common in infants and children of pre-school age with a typical hypothalamus and chiasm localization. Due to its localization, total resection is less probable and thus has a slightly worse prognosis compared to pilocytic astrocytoma [25].

7.1.1.2. *Diffuse gliomas WHO grade II*

Diffuse low-grade gliomas account for 10% of all LGG in children [3]. Histologically, most common types are: **astrocytoma**, **oligodendroglioma** and **mixed oligoastrocytoma**. The most frequent group is the diffuse astrocytoma (DA), which is mainly located in hemispheres (especially in the frontal and temporal lobe), brain stem, optic pathway, hypothalamus and thalamus. Although they may appear to be similar to diffuse gliomas of adulthood, they have different genetic characteristics and typical biological behavior. Unlike DA of adulthood, for which the presence of *IDH1* and *IDH2* mutations is typical, these are very rare in children. *MAPK* pathway and *BRAF* gene alterations are more common [26]. Unlike diffuse adult LGG, DA of pediatric type usually do not undergo malignant transformation into higher grade glioma, so their prognosis is more favorable. Especially in older children it is important to provide genetic diagnostics of the tumor type and differentiation between the more favorable type of LGG (DA without *IDH* mutation or diffuse oligodendroglioma without *IDH* mutation and 1p/19q co-deletion) and adult LGG type that may occur in older children and adolescents [27]. Up to 75% of adult LGG types in childhood are subject of malignant transformation. Treatment consists of surgical removal of the tumor and subsequent observation, but their infiltrative growth pattern generally does not allow their total resection. In case of relapse and progress in tumor growth, chemotherapy with carboplatin (with or without vincristine) may be used. Alternatively, the TPCV regimen (thioguanine, procarbazine, lomustine and vincristine) may be used, rarely in the second line with vinblastine and temozolomide. In relapsing non-responding tumors, bevacizumab is given in combination with irinotecan [28] and in some cases accompanied with radiotherapy. For early and late side effects of radiation, chemotherapy is preferred in children (in opposite to adult treatment). In pediatric patients, tumor localization and age at diagnosis are stronger factors for choosing therapy modality than the histological characteristics of the tumor itself [29, 30].

7.1.1.3. *Subependymal giant cell astrocytoma WHO grade I*

This tumor type is most frequently diagnosed in patients with tuberous sclerosis and mutations in *TSC1* and *TSC2* genes. Its typical location is a lateral ventricle, mostly growing subependymal

near the foramen Monroi [6]. Growth pattern is slow without infiltration of surrounding tissues. Surgical resection, if possible, is a modality of choice in treatment of this tumor. SEGA is one of few tumors with proven efficacy of targeted treatment with mTOR inhibitors, everolimus or sirolimus, which may also eliminate the necessity of surgical treatment [31].

7.1.1.4. *Pleomorphic xanthoastrocytoma WHO grade II*

PXA is relatively rare tumor, which accounts for 0.5–1% of all CNS tumors in childhood [3], typically occurring supratentorially, especially in the temporal lobe. It grows in the cortex, sometimes infiltrating meninges [6]. The most common symptoms are epileptic seizures. Frequently, *V600E* mutation of the *BRAF* gene occurs, especially in temporal lobe localization [32]. This tumor may undergo malignant transformation into an anaplastic form, which is classified as a separate type of tumor in the new WHO classification, has grade III and belongs to the HGG. Like grade II pleomorphic xanthoastrocytoma, it often shows a *V600E* mutation of the *BRAF* gene [33].

7.1.2. *High-grade gliomas in children*

High-grade gliomas account for 15–20% of all pediatric CNS tumors [3]. HGG in children include **anaplastic astrocytoma (grade III)**, **glioblastoma** and its variants (**grade IV**) and **diffuse gliomas of midline structures** (including diffuse pontine glioma). They are characterized by very high mitotic activity and in grade IV also with presence of microvascular proliferation and necrosis as it is in adult HGG. Despite these common histological features, children's HGG differ from adult tumors by their typical localization, genetic alterations and clinical behaviors. Pediatric HGG almost always grow as primary malignancies and their malignant transformation from LGG is extremely rare [34]. Besides localization in cerebral hemispheres, which is also typical for adult forms of HGG, pediatric HGG occur more often in midline structures, such as thalamus, cerebellum or pons. Pontine HGG are typical for pediatric age group (account for 50% of all HGG in children) and have even worse prognosis than hemispheric tumors [35]. Children's HGGs (especially tumors in children under 3 years of age) have significantly less genetic alterations than adult forms [36]. On the basis of a recurring combination of genetic and epigenetic features and characteristic biological and clinical behavior, 6 subtypes of HGG were determined (**Table 1**).

The K27 subtype is characteristically found in pons, thalamus and cerebellum in younger children. Its typical alterations are: mutation of *K27*, *TP53* and *ATRX* genes, *PDGFRA* amplification, *ACVR1* mutation (typical for localization in pons) and mutation of *FGFR1* which is typical for thalamic site of tumor. Among all subtypes it has the shortest survival—from 6 to 9 months [37, 38].

The G34 subtype is more frequent in adolescents and young adults and typically grows in cerebral hemispheres. It most commonly contains mutations of the *G34*, *TP53* and *ATRX* genes. The survival time is about 1 year after the diagnosis is determined [37].

The IDH subtype with typical *IDH1*, *IDH2*, *TP53* and *ATRX* mutations, grows usually in the hemisphere. Tumors with *IDH* mutations account for less than 10% of children's HGG, they occur more commonly in adults. This type can also arise from malignant transformation of

| Type | K27 | G34 | IDH | RTK-I | Mesenchymal | Epitheloid |
|--|---|---|--|--|---|---|
| Age | Young child | Adolescent | Adolescent | All | Adolescent | Young child |
| Typical location | Cerebellum, pons, spinal cord, thalamus | Brain hemispheres | Brain hemispheres | Brain hemispheres | Brain hemispheres | Brain hemispheres |
| Typical alteration | <i>H3.3</i> or <i>H3.1</i> mut. <i>K27</i> , <i>TP53</i> , <i>ATRX</i> , <i>ACVR1</i> (pons), <i>FGFR1</i> (thalamus), ampl. <i>PDGFRA</i> | <i>H3.3</i> , mut. <i>G34</i> , <i>TP53</i> , <i>ATRX</i> | mut. <i>IDH1</i> , <i>IDH2</i> , <i>ATRX</i> , <i>TP53</i> | ampl. <i>PDGFRA</i> , <i>EGFR</i> , mut. <i>TP53</i> , del. <i>CDKN2A/CDKN2B</i> | mut. <i>NF1</i> , <i>TP53</i> , ampl. <i>PDGFRA</i> , <i>EGFR</i> , del. <i>CDKN2A/CDKN2B</i> | mut. <i>BRAF V600E</i> , del. <i>CDKN2A</i> |
| Gene expression | Proneural | Mixed | Proneural | Proneural | Mesenchymal | Unknown |
| Median survival | 6 months | 1 year | >2 years | 1 year | 1 year | >4 years |
| Mut., mutation; ampl., amplification, del., deletion [38]. | | | | | | |

Table 1. Characterization of pediatric HGG subtypes.

LGG, what is generally rare in children. According to prognosis, this type belongs to more favorable subtypes with a survival period of more than 2 years [34, 38].

The RTK-I (receptor tyrosine kinase inhibitor) subtype grows in cerebral hemispheres and occurs throughout the pediatric age spectrum. Typically, it includes: amplification of *PDGFRA* and *EGFR*, *TP53* mutation and *CDKN2A/CDKN2B* deletion. Patients with this tumor subtype have a worse prognosis of survival, generally within 1 year [36, 38].

Mesenchymal subtype is most common among adolescents and young adults. It also occurs in cerebral hemispheres and contains mutations of *NF1* and *TP53*, amplification of *PDGFRA* and *EGFR* and deletion of *CDKN2A/CDKN2B*. It also belongs to worse types according to prognosis, with a survival of up to 1 year [36, 38, 39].

The last subtype is **epithelioid glioblastoma** which is similar to pleomorphic xanthoastrocytoma. It grows in cerebral hemispheres, in younger children and typically displays *BRAF V600E* mutation and *CDKN2A* deletion. It belongs to most favorable subtypes with a survival of more than 4 years [6, 12].

The presence of oncogene amplification, such as *MYCN*, *PDGFR* and *EGFR*, is associated with a worse prognosis in all types [40]. The most important prognostic factor is histological tumor grading and the extent of surgical resection. Radiotherapy is used in subsequent oncological treatment. Its combination with chemotherapy with temozolomide is therapeutically less successful than in adults [35]. Lomustine, vincristine and prednisone may also be used in chemotherapy. In case of recurrent HGG, repeated resection is considered individually, depending on the histological nature of the original tumor, the recurrence localization or the length of the progression free period. Reoperation could be also necessary for obtaining of fresh tissue samples for targeted treatment or for local administration of chemotherapy. In patients whose initial treatment failed, high-dose chemotherapy with total bone marrow suppression and subsequent hematopoietic stem cell transplantation [41] or clinical trial of new treatment modalities may be attempted. Molecular targets are very limited. Patients with *BRAF V600E* mutation are tested for *BRAF* inhibitors (vemurafenib and dabrafenib) with partial effect [19].

7.1.2.1. Diffuse midline glioma, H3 K27 M-mutant

The previous WHO classification is also called diffuse intrinsic pontine glioma (DIPG). The new edition classifies this tumor as diffuse midline glioma because it also appears in thalamus, cerebellum and spinal cord. It is predominantly considered childhood tumor, although it may also occur in adults. It contains a typical *K27 M* mutation of the histone H3 gene *H3F3A* (less frequently the *HIST1H3B* gene) and grows typically diffusely and infiltrates surrounding tissues [37]. It is classified as WHO grade IV, regardless of the presence or absence of anaplastic features [12]. A tumor growing in the ventral pontine region is a highly aggressive, destructive neoplasm that accounts for up to 80% of all glioma in the brain stem of children. The mean age at diagnosis is 6–7 years and median survival is 9 months [42]. Cranial nerve lesions, long-tract lesion symptoms, ataxia and behavioral disorders appear as leading clinical symptoms. The first symptom is often the abducens nerve palsy, which is also a negative prognostic factor. Also facial nerve palsy may occur. Obstruction of CSF pathways could lead to hydrocephalus [43]. Typically, on MR image

tumor occupies more than half of the axial diameter of the pons. It has no exact borders and does not enhance after gadolinium administration. Due to the typical MRI image and its localization, biopsy is rarely indicated, but in some cases stereotactic biopsy could be beneficial [44]. This tumor is known to spread to the distal parts of the brain stem and along the white matter tract to both the cerebellum and the thalamus in over half of the patients. Supratentorial spreading and leptomeningeal dissemination are uncommon [39]. Total resection due to its localization and growth pattern is not possible, so the most common treatment is radiotherapy, which helps to control symptoms and generally prolongs patient's survival. Because of the known CNS spread, irradiation of the entire head or the entire neural axis is sometimes chosen [39]. Systemic administration of chemotherapeutic agents has been shown to be ineffective for insufficient passage through the hematoencephalic barrier to pons [45]. The administration of chemotherapy (especially topotecan) is also attempted locally, directly to the tumor, using a stereotactic catheter. However, the results are not yet clear [46]. Children under age of 3 have a slightly better prognosis, probably due to different molecular genetic characteristics [47].

7.1.3. Ependymomas

Ependymomas are tumors originating from ependymal cells, which form a lining of CSF pathways and produce cerebrospinal fluid. They form the second most common group of children's CNS malignancies. They occur supratentorially, in the posterior fossa and in the spinal cord, mostly in children under 10 years of age [48]. Clinical signs depend on localization. In the most frequent, infratentorial localization, they present with the development of obstructive hydrocephalus, ataxia, cervical spinal pain and symptoms of cranial nerve lesion can also be present. Supratentorial localization often causes headaches, epileptic seizures and depending on localization, the development of focal neurological deficit. In case of suspicion on ependymoma, it is necessary to realize the MRI of whole craniospinal axis even before surgery. If possible, lumbar puncture with CSF sampling is recommended.

Ependymomas could be histologically: **subependymoma (grade I)**, **myxopapillary ependymoma (grade I)**, **ependymoma (grade II)**, **ependymoma, *RELA* fusion-positive (grade II–III)** and **anaplastic ependymoma (grade III)**. Subependymoma and myxopapillary ependymoma appear almost exclusively in adults. The existence of several molecular subtypes of ependymomas, which differ in their localization, molecular genetic characteristics, typical age group of patients and prognosis, are known.

Two genetically distinct subgroups are distinguished in **ependymomas of posterior fossa** localization [49]. **Group A** occurs more frequently (up to half the ependymomas of all localizations) affecting predominantly younger children (3 years of age) and has a worse prognosis. In these tumors, fewer gene alterations occur and the *VEGF*, *PDGFR*, integrin and *MAPK* signaling pathways are most commonly affected [50]. Epigenetic suppression of differentiation genes is often present in this group of tumors [51]. Duplication of 1q occurs in 25% of group A ependymomas and it is a common negative prognostic feature [52]. Less frequently occurring **group B** affects predominantly adolescents and young adults. It contains frequent chromosome changes and its prognosis is more favorable than in group A. In both groups, the mutation rate is relatively low and gene mutations occur sporadically [50].

Up to 70% of **supratentorially localized ependymomas** harbor fusion of *C11orf95-RELA* on chromosome 11q [50]. This change never occurs when locating in the posterior fossa. The discovery of the presence of this fusion was so significant that in the new WHO classification of brain tumors from 2016 the **ependymoma with the *RELA* fusion** was classified as a separate entity [12]. Homozygous deletion of *CDKN2A* with or without the presence of duplication of 1q is a negative prognostic factor [53]. The most frequent occurrence is in children with an average age of 8 years. **The fusion of *YAP1*** (with *MAMLD1* or *FAM118B*) occurs in supratentorially localized ependymomas without *RELA* fusion. These tumors are more common in younger children with an average age of 1.4 years. From all ependymomas, the worst prognosis has supratentorial *RELA* positive tumors and group A ependymomas in the posterior fossa. At the same time, they are the most common forms (together make up two-thirds of all ependymomas) that occur predominantly in children [53].

Therapeutic modality is extensive surgical removal followed by radiotherapy, which can only be used in the treatment of children aged more than 1 year. Currently, the use of chemotherapy (especially vincristine, cyclophosphamide, cisplatin and etoposide) is in clinical trials [38]. The choice of the treatment scheme determines the age of the child, the histological type of tumor, the extent of the resection performed and the presence of dissemination in the CSF pathways.

7.2. Neuronal and mixed neuronal-glial tumors

It is a heterogeneous group of tumors with neuronal or mixed neuroglial morphology. They are mostly grade I, but their anaplastic forms can also occur. Following tumors are most frequently present in children.

7.2.1. *Desmoplastic infantile astrocytoma (DIA) and ganglioglioma (DIGG)*

These grade I tumors account for 0.5% of CNS childhood tumors [3]. They occur almost exclusively in children under 2 years of age. MRI verifies a large cystic tumor, especially in the frontal or parietal lobe. They are histologically and genetically almost identical, the only difference between them is the neoplastic neuronal component. Approximately 40% of these tumors display *MET* amplification and about 10% also *BRAF V600E* mutation [54].

7.2.2. *Ganglioglioma (GG)*

These tumors are characterized by a combination of neoplastic ganglion cells with a glial component similar to PA or diffuse glioma (especially astrocytoma). They occur mainly supratentorially. Seizures are usually leading symptom [33]. GG often harbor *BRAF V600E* mutation. The glial component of GG can undergo malignant transformation to anaplastic form that has higher mitotic activity, endothelial proliferation and necrosis in 3–5%. Up to half of the anaplastic GG is characterized by the presence of the *BRAF V600E* mutation, a minor part of the *TP53* mutation [6].

7.2.3. *Dysembryoplastic neuroepithelial tumor (DNET)*

It is a low-grade tumor (grade I), which occurs mainly supratentorially in the temporal lobe. It often manifests as drug-resistant epilepsy. There are several histological subtypes, which do

not differ in typical age of origin, the nature of epileptic seizures or prognosis. Most of these tumors show alterations of *FGFR1* and *BRAF V600E* mutation [27].

7.3. Embryonal tumors

This group of tumors originates from embryonal cells that remain present in the CNS after birth. They are the most common childhood malignant CNS tumors (15–20%) in children under the age of 14 [12]. In adults, they are extremely rare. Most frequently occurring embryonal tumors are: medulloblastoma, atypical teratoid/rhabdoid tumor and CNS embryonal tumors (better known under the older name CNS primitive neuroectodermal tumors—PNETs). All tumors of this group tend to spread along the CSF pathways. Therefore, it is recommended to perform MR of whole craniospinal axis prior to surgery. CSF sampling is also indicated, as the finding of circulating tumor cells can appear earlier than dissemination in MRI. The prognosis of embryonic tumors depends on the age of the patient, dissemination of the tumor within CNS at the time of diagnosis, the size of the postoperative residue and on the histopathological and molecular biological properties of the tumor.

7.3.1. Medulloblastoma (MB)

It is the most common malignant brain tumor type in children. MB is a group of lesions that differ significantly by their genetic alterations, histological features and prognosis. In all cases, however, they are grade IV and fast-growing. Characteristic localization is infratentorial and leptomeningeal spread is typical. MB often manifests by symptoms of intracranial hypertension and blockage of CSF pathways as well as other symptoms, such as ataxia and nystagmus. Medulloblastoma may also occur as part of hereditary syndromes: Turcot, Rubinstein-Taybi, Gorlin, Li-Fraumeni syndrome and Fanconi anemia. There are four **histological variants** (classic type, desmoplastic nodular type, medulloblastoma with extensive nodularity and large cell and anaplastic type) and four subtypes depending on the signal pathway involved or genes altered: *WNT* (10%), *SHH* (30%), group 3 (15%) and group 4 (45%). WHO classification of brain tumors from 2016 classifies genetically defined MB into: *WNT*-activated, *SHH*-activated and *TP53*-mutant, *SHH*-activated and *TP53*-wildtype and non-*WNT*/non-*SHH* medulloblastoma, which is divided into MB group3 and MB group 4 [12].

The *WNT* medulloblastoma is the less frequent group (10%), which is typically found in the brain stem area in children aged 10. Often displays classic histology. The incidence of CNS metastases is very low. Activation of the *WNT* signaling pathway is characteristic [55]. About 90% of these tumors present with *CTNNB1* mutation. Mutations of *DDX3X*, chromatin remodeling genes and *TP53* are also common. *TP53* mutation in this type of tumor is not associated with a worse prognosis as it is in *TP53* mutated *SHH* MB. In general, *WNT*-activated MB has a very good prognosis.

The *SHH* group of medulloblastomas accounts for 30% of all MB and is the most heterogeneous. All histological types could occur. Dominant localization is in cerebral hemispheres. The most commonly affected age group is up to 4 years of age and then adolescents over 17 years of age. In children up to 4 years of age, it is most commonly present MB with extensive nodularity and in group 4–17 years of age, it is classic and large cell anaplastic type.

Desmoplastic nodular type is typical for patients over 17 years of age [56]. Genetic alterations also vary by age category. Mutation of *SUFU* gene is commonly present in age group up to 4 years, whereas *SMO* mutation occurs mainly in patients over 17 years of age. Between 4 and 17 years of age, amplification of *MYCN* and *GLI2* occurs. *PTCH1* alterations and *TERT* promoter mutation occur in all age categories [57]. While MBs of children under 4 years with extensive nodularity generally have a better prognosis, MBs with large cell anaplastic characteristics, presence of *MYCN* amplification or *TP53* mutation are very aggressive. They tend to metastasize within the CNS, and therefore are associated with a very poor prognosis [55, 56]. *SHH*-activated MBs with *TP53* mutation are classified separately. In children with *TP53* mutation, it is often a germline mutation that is part of the Li-Fraumeni syndrome [58].

Non-WNT/non-*SHH* MB is divided into **group 3** and **group 4**. While group 3 forms 15%, group 4 45% of all MBs. Although genetically different, some characteristics and genetic alterations are common. There is a higher occurrence in boys in both groups, structural anomalies are common—especially the formation of isochromosome 17q. A structural alteration that aberrantly induces the activity of *GFI1* or *GFI1B* proto-oncogenes is common in both groups, particularly in group 3 [59]. The worst prognosis of all types has group 3 (particularly in boys), with large cell anaplastic morphology and with proven *MYC* over-expression and amplification. Group 4 is the most common molecular type with a pronounced predominance in boys. Nearly all tumors in this group have classic morphology. The prognosis of patient survival is moderate—except those with proven *MYC* amplification, which have worse prognosis [55]. Patients with metastasis present at diagnosis have a high risk of relapse, with the exception of patients with isochromosome 17, who make up a subgroup with more favorable prognosis [60].

The diagnosis is based on preoperative MRI examination of the craniospinal axis. Over the past 30 years, the most fundamental shift has been made in treatment of MB among all CNS childhood tumors and has changed from a fatal disease to a tumor with a 70% curability. The basis is surgical treatment with the maximal possible extent of resection. In the postoperative period, MRI is again indicated to evaluate the postoperative residue and the examination of cerebrospinal fluid is also beneficial. Medulloblastoma has as one of the few CNS tumors **staging system** that has 5 degrees (M0 = not disseminated, M1 = positive cytology of CSF without MR image of dissemination, M2 = nodular proliferation in cerebellar and cerebral subarachnoid spaces and in ventricles, M3 = nodular proliferation in spinal subarachnoid spaces, M4 = extra-neural propagation). Surgery is followed by chemotherapy and radiotherapy with whole CNS irradiation for frequent dissemination of medulloblastoma within the CNS. The chemotherapy regimens use either a combination of cisplatin, lomustine and vincristine or a combination of cisplatin, cyclophosphamide and vincristine [61]. Radiotherapy is administered at a dose of 54 Gy targeted to the tumor bed, followed by irradiation of the craniospinal axis at a dose of 24–36 Gy. The introduction of chemotherapy into the treatment scheme reduced the dose necessary to irradiate the craniospinal axis, thereby reducing the incidence of side effects of radiation [62]. However, radiotherapy in children under 3 years of age is not used for serious adverse effects on brain development. To potentiate the effects of standard chemotherapy, methotrexate is concomitantly administered to children under 3 years, either systemically or locally [63].

7.3.2. Atypical teratoid/rhabdoid tumor (AT/RT)

This high-grade neoplasm (grade IV) accounts for 1–2% of pediatric CNS tumors. Typically, it occurs in the age category up to 5 years, and in children under 1 year of age, it is the most common malignant CNS tumor. As it grows very quickly, clinical manifestations occur early. AT/RT is often localized supratentorially and also in the posterior fossa [3, 64]. About 20% of patients have already dissemination of the tumor at the time of diagnosis, usually along leptomeninges. Rare coincidence with renal tumors may occur [65]. Genetically, it is characterized by deletion on the 22nd chromosome and loss of *INI1/SMARCB1/BAF47* expression due to germline or somatic mutations. Evaluation of *SMARCB1* expression is necessary to distinguish AT/RT from other embryonic tumors [66]. This tumor was the first primary CNS tumor in which the major tumor suppressor gene was identified, namely *SMARCB1*. The presence of *SMARCB1* germline mutation is the basis for identifying the **syndrome predisposing to the rhabdoid tumor**, which is common in patients with coincidence of AT/RT with rhabdoid tumor of the kidney. The greatest risk of developing tumors in this syndrome is during the first year of age, which requires monitoring and active screening in children from these families. Immunohistochemical evidence of cytokeratin, epithelial membrane antigen, glial fibrillary acidic protein, synaptophysin, desmin and vimentin is also necessary. The MIB-1 proliferation index is high, 50–100% [67]. MRI of the entire craniospinal axis as well as examination of CSF for the presence of tumor cells is useful in diagnosis. There is no standard treatment regime for AT/RT. Treatment is based on surgical resection. The localization of the tumor and the extent of its spread is crucial for the choice of treatment modalities. Prolongation of survival requires a combination of postoperative systemic and intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) with radiotherapy. Negative prognostic factors include: the presence of *SMARCB1* germline mutations, postoperative residues, dissemination at the time of diagnosis and the age under 2 years [64].

7.3.3. Embryonal tumor with multilayered rosettes, C19MC-altered (ETMR)

This tumor typically occurs in children under 3 years of age. It has a poor prognosis, most patients die within 1–2 years after diagnosis [68]. Characteristic is the 19q13.42 locus amplification, which contains a cluster of microRNA (C19MC) and a fusion between *TTYH1* and *C19MC* [69]. Treatment begins with a surgical resection, followed by adjuvant oncology treatment with chemotherapy and radiotherapy. In children under 3 years, radiotherapy is not indicated.

7.3.4. Neuroblastoma and ganglioneuroblastoma CNS

These two neoplasms belong to embryonal tumors but show neuronal differentiation, in the case of ganglioneuroblastoma also the presence of ganglionic cells. They most often occur in early childhood. In general, neuroblastomas are a frequent diagnosis, but especially in the chest and abdominal cavity (in the brain they are rare). Some of these include gene alterations leading to increased expression of the transcription factor *FOXR2* [70]. The treatment scheme is the same as for other embryonal tumors – surgery followed by chemotherapy in children less than 3 years of age and addition of radiotherapy in older children.

7.4. Pineoblastoma

In the past, this tumor was classified as embryonal, but in the new WHO classification it was reclassified to a group of pineal tumors. Its histological and molecular biological properties are similar to embryonal tumors. Because of its location, obstructive hydrocephalus is predominantly caused by blockage of CSF passages at the level of the third ventricle, and symptoms of the pressure on tectum—especially oculomotor disorder, poor reaction of pupils to light with present reaction to accommodation, later hemiparesis and ataxia. Often occur germline mutations of the *RB1* and *DICER1* genes [71]. Pineoblastoma is often found in children with congenital retinoblastoma. It can rarely disseminate along CSF pathways. A **staging system** similar to embryonal tumors is used. The primary therapeutic step is surgical resection. However, due to localization, total resection is unlikely, with only partial resection or biopsy performed in the majority of patients. This is followed by oncological treatment that combines chemotherapy and radiotherapy with a dose of 54 Gy on tumor bed and 24–36 Gy for craniospinal axis. A different therapy management is used in children under 3 years of age who undergo biopsy, followed by chemotherapy or high-dose chemotherapy with bone marrow ablation followed by hematopoietic stem cell transplantation.

7.5. Germ cell tumors

Intracranial germ cell tumors are a heterogeneous group that accounts for 3–4% of brain tumors with the exception of Japan where the incidence is higher, up to 15% [72]. Based on histopathological characteristics, they are divided into **germinomas** and **nongerminomas** (embryonal carcinoma, choriocarcinoma, mature or immature teratoma, teratoma with malignant transformation, yolk sac tumor and mixed germ cell tumor). In some countries, dividing into **secretory** and **non-secretory** tumors is also used—depending on the presence and absence, respectively, of elevation of serum and CSF tumor markers [12].

The most common localization is the pineal and suprasellar area, where they form either solitary or multiple lesions. The pineal region is much more frequent, but up to 10% of patients have both sites at the time of diagnosis, which is typical for pure germinomas [73]. Rare localities include basal ganglia, brain ventricles, cerebral hemispheres and thalamus. Tumor in the suprasellar region is often presented by hormonal expression. Often occur diabetes insipidus, enuresis, anorexia and also psychological changes [74]. Pineal localization has usually earlier manifestation, with hydrocephalus and diplopia developing from pressure to the tectal and aqueductal region. The most common germ cell tumor is germinoma. Mutations of the *KIT*, *KRAS* and *NRAS* genes are common [75]. Half of germinoma cases harbor deregulation of the *KIT/RAS* and *AKT/mTOR* pathways. The germline variations of *JMJD1C* occur more frequently in Japanese, which is probably related to the higher incidence of germinomas in this country. This gene is important for maintaining male germ cells [76].

In the diagnosis, apart from MRI, cytological examination of CSF and evaluation of **alpha-fetoprotein (AFP)** and **beta human chorionic gonadotropin (bHCG)** concentrations in both serum and in CSF is used [77]. In addition, hormonal examination of hypothalamic and pituitary function and examination of the visual field in suprasellar and hypothalamic tumors are

necessary. The essentials of the treatment are chemotherapy and radiotherapy, but biopsy is required for reliable diagnosis. Only in tumors with unambiguous MRI image and positive tumor markers in CSF can be treated without biopsy.

7.6. Choroid plexus tumors

These rare intraventricular tumors account for 1% of all brain tumors and 2–4% of pediatric tumors. They arise from neuroectoderm and consist of differentiated epithelial plexus cells that produce CSF. They most often occur in the age group under 2 years of age. The most common site are lateral ventricles (less often the 3rd and 4th ventricle), but could also occur in the cerebellopontine angle and in the cerebral parenchyma. They mostly manifest by symptoms of intracranial hypertension from hydrocephalus, both from overproduction of the CSF as well as from obstruction of the CSF pathways. Sometimes, however, they can also manifest suddenly, in case of bleeding into the tumor [78]. This group of tumors consists of: **choroid plexus papilloma (grade I)**, **atypical choroid plexus papilloma (grade II)** and **choroid plexus carcinoma (grade III)**. There are no genetic differences between papilloma and atypical papilloma. In both, immunoreactivity to cytokeratin, vimentin, S100 protein and synaptophysin is present. On the other hand, carcinoma is genetically different. The germline mutations of *TP53* as part of the Li-Fraumeni syndrome predispose to the formation of plexus carcinoma. Somatic *TP53* mutations are present in up to 60% of the plexus carcinomas and the more copy of the mutated *TP53* is present, the worse is the prognosis [79]. Chromosome alterations are rarely detected.

MRI showing relatively well-defined extra-axial mass that does not invade the brain tissue with gadolinium enhancement and containing calcification and microhemorrhages is essential. Surgical treatment is the method of choice. Due to the rich vascular supply, preoperative tumor embolization is preferred in some cases. Hydrocephalus treatment is also necessary—sometimes requires external ventricular drainage. In some patients hydrocephalus is permanent, and therefore ventriculoperitoneal shunt or the endoscopic ventriculostomy of the 3rd ventricle are required [80]. There is no need for further treatment in the papilloma, radiotherapy, radiosurgery or chemotherapy with bevacizumab may be used in atypical or recurrent forms. Chemotherapy has been proven in choroid plexus carcinoma, which can spread along CSF pathways [81].

7.7. Craniopharyngioma

Craniopharyngiomas are rare tumors, accounting for 3–5% of pediatric brain tumors. They occur in two subtypes: adamantinomatous and papillary [12]. The **adamantinomatous variant** for which the *CTNNB1* mutation is typical, is often found in children [6]. Their congenital origin is assumed to be from the ectodermal residues of the Rathke capsule or from another embryonal epithelium. They most commonly occur in the suprasellar area with intrasellar propagation. Symptoms include: endocrine disorders, visual disturbances, hydrocephalus symptoms and very rarely when growing in the posterior fossa—headache, diplopia, ataxia and hearing loss [82]. The diagnosis is made by MRI that displays a tumor with a solid and cystic component and with intratumoral calcifications. Evaluation of hormonal function and visual field is also necessary. The therapy of newly diagnosed craniopharyngiomas is a combination of surgical treatment, radiotherapy and a drainage of the cyst. The prognosis is good, 90% of patients survive more than 10 years [83]. Total resection may have serious complications, including: need

for hormone replacement therapy, severe obesity, behavioral disorders, blindness, epileptic seizures, postoperative CSF leak, pseudoaneurysms, oculomotor disorders, severe postoperative bleeding and hypothalamic injury [84]. While recurrent craniopharyngiomas are treated by resection, radiotherapy or radiosurgery, tumors with unresponsive cystic component can be treated by administration of P32, bleomycin or interferon alpha directly into the tumor bed. It can be supplemented by systemic administration of interferon [85].

7.8. Other pediatric CNS tumors

Schwannomas are in children rare, mostly benign neoplasms originating from Schwann cells of cranial or other nerves. Some of these tumors are present as a part of the NF2 type genetic syndrome, especially at bilateral occurrence. From cranial nerves, this tumor mostly affects VIII cranial nerve and is called vestibular schwannoma or acoustic neurinoma [86]. Vestibular schwannomas can cause loss of hearing and tinnitus. Diagnosis is mainly based on MRI. The method of choice is resection of the tumor, further treatment is usually not necessary. In rare cases, radiotherapy can be used in the presence of postoperative residues [87].

Meningiomas that grow from meninges are much rarer in children than in adults—they account for about 2.6–2.9% of CNS childhood tumors [2]. It occurs most often between 6 and 12 years of age. Children have a higher incidence of tumors growing from the skull base and a higher incidence of atypical (grade II) and anaplastic (grade III) meningiomas compared to adults. Chromosome 22 abnormalities are often present, also as a part of the NF2 type syndrome. Tumors connected with NF2 occur at younger age (about 2 years) and may also be the first symptom of this disease. In benign tumors, surgical treatment is largely sufficient, but in the case of incomplete resection and in tumors of higher grade, is usually combined with radiotherapy. Favorable prognostic factors include: age up to 10 years, superficial localization, total extirpation and absence of NF2 syndrome, where localization and resection extent are stronger predictive factors than histological grade [88].

Primary CNS lymphomas (PCNSL) are rare in children. Patients with immunodeficiency have an increased risk of developing CNS lymphomas [89]. They occur mainly in children around 14 years of age with moderate predominance in boys [90]. They are mostly localized in brain hemispheres. Clinical symptoms include symptoms of increased intracranial pressure, ataxia, hemiparesis, epileptic seizures and cranial nerve palsy. MRI and CSF sampling is used in diagnostics. MRI verifies solid lesion (even with a possible cystic component). Histologically, **mature aggressive B cell lymphoma (B-NHL)**, as well as **anaplastic large cell lymphoma (ALCL)** or **peripheral T cell lymphoma (PTCL)** are most often present. Pediatric B-NHL has a low to moderate proliferation index, a lower Bc12 protein expression and a higher frequency of the Bc16 + GC fetal center phenotype, indicating a better prognosis [91]. While the prognosis of PCNSL in adults is very poor, in children is better. Interestingly, localization of PCNSL in deep brain structures does not affect the prognosis [90]. In chemotherapy, methotrexate or cytarabine at high doses are mostly used, usually providing satisfactory remission without need for use of radiotherapy (often used in ALCL form). It has been found that the exclusive use of chemotherapy is more effective than combined chemoradiotherapy. Explanation could be the use of lower doses of chemotherapy in combined therapy. High-dose therapy of methotrexate, which appears to be the most effective, is better tolerated by children compared to adults. Radiotherapy is therefore reserved for recurrent forms [89].

8. Conclusion

Pediatric CNS tumors are diagnostic and therapeutic challenge. A lot of specialists are involved in their management: pediatricians, neurologists, neurosurgeons, radiologists, radiation and clinical oncologists, endocrinologists and others. Due to the development of MRI and its techniques, use of invasive examinations is minimalized. Over the past decades, there has been a significant refinement of operational technologies, enabling the most extensive and yet safe resection of the tumor. Children CNS tumors are frequent, often with unfavorable prognosis. While in most malignant tumors the prognosis has not improved as hoped, in case of medulloblastoma there has been a significant survival prolongation during last decades. Undoubtedly, this is due to extensive research of the molecular genetic characteristics of tumors, which identified genetically defined subgroups of medulloblastoma with different treatment strategies. This change was also reflected in the new WHO classification, which also classifies medulloblastomas based on genetic alterations. Intense research also takes place in other tumor entities, where the discovery is yet about to come. Identifying molecular and genetic targets is the only possible way to target individualized therapy that appears both in treatment and in further prognosis improving in this age group as a key point.

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