Chapter

Pediatric Brain Tumors: From Modern Classification System to Current Principles of Management

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Abstract

Central nervous system (CNS) malignancies contribute significantly to the global burden of cancer. Brain tumors constitute the most common solid organ tumors in children and the second most common malignancies of childhood overall. Accounting for nearly 20% of all pediatric malignancies, these are the foremost cause of cancer-related deaths in children 0–14 years of age. This book chapter provides a state-of-the-art overview of pediatric brain tumors. It discusses their morbidity and mortality and introduces the WHO 2021 classification of CNS tumors, which is critical to therapeutic decision-making. It then describes the modern understanding of tumor grading and its clinical implications, followed by the general principles of diagnosis and management. The chapter then discusses, in detail, those brain tumors which have the highest disease burden in children, including medulloblastoma, astrocytoma, ependymoma, schwannoma, meningioma, amongst others. The landscape of treatment of pediatric brain tumors has been rapidly evolving, with several effective therapies on the horizon.

Keywords: CNS tumor, oncology, neuro-oncology, pediatric oncology, malignancy, neurology, neurosurgery, neuroradiology, brain tumor

1. Introduction

Central nervous system (CNS) malignancies contribute significantly to the global burden of cancer. The average annual age-adjusted incidence rate (AAAIR) of all CNS tumors, as estimated in the US population was 23.79 according to the most recent report of the Central Brain Tumor Registry of the United States (CBTRUS) [1]. Amongst individuals aged 15–39 years, CNS tumors constitute the third most common tumor overall, while amongst individuals aged 40 and above, they are the third most common cause of cancer death.

Brain tumors find an overwhelmingly high representation in the pediatric age group. They constitute the most common solid organ tumors in children and the second most common malignancies of childhood overall, accounting for nearly 20% of all pediatric malignancies [1]. The CBTRUS 2020 report estimated that the AAAIR of CNS tumors amongst children aged 0 to 14 was 5.83 per 100,000 individuals. The annual age-adjusted mortality rate (AAAMR) of CNS tumors in this age group was determined to be 0.71 per 100,000, leading to brain tumors being the biggest cause of cancer death

amongst 0 to 14 years of age. Despite the advances of the last few decades in imaging, molecular diagnostics, surgical techniques, and adjuvant therapy, unfortunately, less than required improvement has occurred in rates of survival in the pediatric age group.

Girardi et al., in a systematic review published in 2019, determined that little data from low and low-middle-income countries (LMICs) is available regarding long-term survival from pediatric brain tumors [2]. This sobering data stands amidst the backdrop of studies demonstrating that the nations with lower economic development deliver a significantly poorer quality of care [3].

Adult survivors of pediatric brain tumors face significant challenges. Several factors come together to drastically impact their neurocognitive and psychosocial outcomes. These include but are not limited to, the clinical features of the tumor itself, its treatment especially radiotherapy to a developing brain, access to support systems and quality of rehabilitative services, individual factors, amongst others [4].

The pediatric landscape is significantly different from the adult landscape with regard to brain tumors. Pediatric brain tumors have differing common sites of origin, histology, genetics, which lend themselves to dissimilar diagnostic and therapeutic considerations. As a rule of thumb, two-thirds of tumors in adults arise from sites above the tentorium cerebelli, while two-thirds of tumors in children arise from structures below the tentorium cerebelli. Several genetic syndromes also include pediatric brain tumors as one of their clinical manifestations. These include but are not limited to tuberous sclerosis, Li-Fraumeni syndrome, Turcot syndrome, Type 1 and 2 Neurofibromatosis, Gorlin syndrome, Cowden syndrome, amongst others.

Brain tumors that have the highest disease burden in children include medulloblastomas, astrocytomas, ependymomas, schwannomas, meningiomas, amongst others. Their details, along with their specific epidemiology, will be discussed in greater depth in further sections.

2. Classifying brain tumors: an evolving paradigm

The classification of tumors in the central nervous system (CNS) is the critical factor driving treatment decisions, given the wide variation amongst different tumors in response to each anti-cancer modality. For instance, some like midline pontine gliomas do not respond well to chemotherapy and are only partially amenable to radiotherapy.

Several classification schemas for CNS tumors exist. These range from those solely based on histology alone to those relying primarily on genetic and epigenetic features. While microscopic diagnosis finds utility in its low cost and accessibility, its insufficiently high inter-rater reliability along with the advancements in molecular biology have led to it not being the sole basis for classification [5].

Other simpler classification systems divide tumors based on the major site of origin. Supratentorial tumors are those which are located above the tentorium cerebelli and therefore may involve cerebral hemispheres. In children, these commonly include high-grade gliomas, low-grade gliomas, embryonal tumors, atypical teratoid/rhabdoid tumors, meningiomas, choroid plexus tumors, and pineal tumors. In contrast, infratentorial tumors are located below the tentorium and, therefore, originate from the brainstem, the cerebellum, and the 4th ventricle. In children, these commonly include medulloblastomas, cerebellar astrocytomas, ependymomas, brainstem gliomas, atypical teratoid/rhabdoid tumors, and rarely choroid plexus tumors. The sellar region is a region at the base of the skull around the sella turcica where the major tumors of note in children include pituitary adenomas, craniopharyngiomas, gliomas, and germ cell tumors.

3. The WHO 2021 classification of CNS tumors

The World Health Organization (WHO) has developed and published updated versions of the most widely used classification system for CNS tumors for decades. The WHO 2007 classification schema was the last iteration to primarily be based on histology [6]. Very recently, the WHO 2021 classification (WHO CNS5) has been published, which functions as an integrated histo-molecular classification system [7].

3.1 Key updates in the WHO 2021 classification

The WHO CNS5 classification, a broad overview of which is given in **Figure 1**, adheres to the landmark recommendations made by the cIMPACT-NOW group, especially the ones made at the Utrecht Meeting in 2019. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO (cIMPACT-NOW) is an influential group of neuro-oncologists and neuropathologists which was established in 2016 to provide recommendations regarding the upcoming WHO classification [8]. Based on the cIMPACT-NOW recommendations, WHO CNS5 makes new categories, merges a few ones, and introduces new entities. These updates include the following:

I. Greater integration of histology has been done with immunohistochemical, ultrastructural, and molecular features of tumors.

II. Arabic numerals (1, 2, 3, and 4) for tumor grade have replaced Roman numerals (I, II, III, and IV) to have CNS tumor grading consistent with other systems and prevent typographical errors.

III. Grading of tumors is to be done *within* tumor types (rather than across different tumor types).

IV. Gliomas have been separated into pediatric-type and adult-type, with several subcategories. This change carries several key clinical implications.

V. The term 'glioblastoma' is reserved for IDH wild-type tumors and only refers to grade 4 tumors

VI. IDH-mutant astrocytoma will be graded based on histo-molecular features

VII. Layered reporting of medulloblastoma is recommended:

a. Integrated Diagnosis (combining histology and biology)

b. Histological Diagnosis

c. CNS WHO Grade

d. Molecular Information

VIII. Ependymomas have new sub-categories including Posterior Fossa A Ependymoma, Posterior Fossa B type Ependymoma, etc.

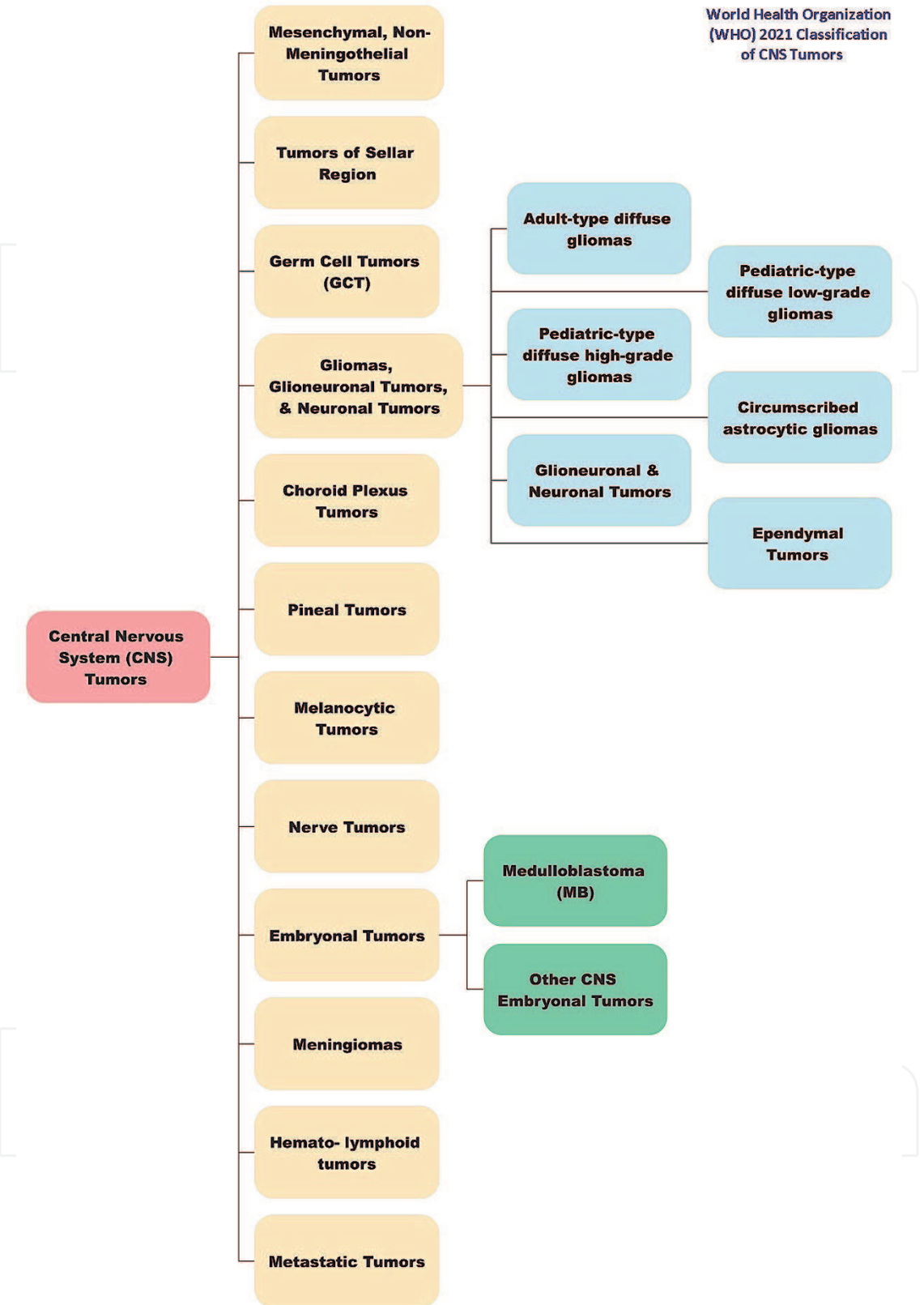

Figure 1.
A broad overview of the World Health Organization (WHO) 2021 classification of central nervous system (CNS) tumors. This original figure has been drawn from [34], published online ahead of print, 2021 Jun 29, noab106, where the full classification is available.

3.2 Modern understanding of tumor grading and its clinical implications

CNS tumor grading has been long-known to be linked closely with clinical-biological features, and this has been augmented with recent works in genomics and

methylomics. Tumor grading guides treatment decisions and the four WHO tumor grades have been historically essential in determining prognosis.

Previously, WHO used to assign a grade to one tumor type (e.g. anaplastic astrocytoma to grade 3), and grading was done across tumor types. With WHO CNS5, this has been radically shifted to grading within tumor types, similar to non-CNS tumors where the latter had been the norm for decades. This approach, while enhancing flexibility while grading, also highlights the pathobiological similarities within tumor types, rather than simply trying to crudely approximate clinical behavior across entities [7].

The current grading paradigm is a combination of histological and molecular featusres, rather than solely being based on microscopic features alone. Key examples of this are reflected in the Update 3 and 5 of cIMPACT-NOW [8]. The newly introduced integrated grading system continues to retain some features from prior WHO classification editions. For instance, meningiomas can only go from grade 1–3, and therefore it is not possible to have a '*CNS WHO Grade 4 Meningioma*'. Additionally, because these malignancies were traditionally graded based on their natural history as well, therefore, current therapeutic options lead to a conflict between the grade and the expected outcome. For instance, a medulloblastoma can be assigned a CNS WHO grade 4, yet a WNT-activated medulloblastoma has good survival outcomes when given effective therapies [7].

4. Clinical features of pediatric brain tumors

Pediatric brain tumors are usually suspected based on their specific clinical features. Details regarding the clinical presentation of some common tumors are given in their respective sections. However, in general, these tumors find their manifestation in two major ways, one due to raised intracranial pressure, and the other due to the specific location of the tumor involving adjacent neural structures [9].

In children, raised intracranial pressure may be due to the tumor mass itself, or secondary to hydrocephalus, or maybe a consequence of cerebral edema. Acutely, this may manifest as headache, nausea and vomiting, altered sensorium, irritability, papilledema, hypertension, abnormal breathing, seizures, etc. In the long-term, this may manifest as macrocephaly, loss of appetite, delayed psychomotor development, personality changes, etc. [10].

Brain tumors also may manifest through the involvement of adjacent structures. Focal neurological deficits such as arm or leg weakness in case of cerebral tumors, ataxia and torticollis in posterior fossa tumors, endocrinopathies such as precocious puberty, obesity in case of sellar/parasellar tumors, vision impairment due to cranial nerve involvement, etc. [10].

5. Principles of diagnosis and treatment of pediatric brain tumors

An experienced, multidisciplinary team is essential for the management of pediatric CNS tumors, consisting of pediatrician, neuro-radiologist, neuro-oncologist, neurosurgeon, radiation oncologist, physiatrist, and other ancillary services.

5.1 Diagnosis

Brain imaging is the mainstay of diagnosis. Computed tomography (CT) and magnetic resonance (MR) imaging are both often required. While the former allows a better assessment of bony involvement and tumoral calcifications, the latter helps

to closely delineate the tumor and the involved anatomy of the region, along with helping predict the type of tumor. MR imaging with gadolinium contrast is often the single most valuable diagnostic test for CNS tumors.

MR Angiography (MRA) is useful for visualizing blood vessels, which helps determine the surgical approach. MR Spectroscopy allows for non-invasive determination of tissue properties of intracranial structures, helping differentiate between neoplastic and non-neoplastic lesions. MR Perfusion helps visualize blood flow to the involved areas [11].

Advances in imaging in the last few decades have led to increasing utilization of additional imaging methods. Diffusion tensor imaging (DTI) for evaluating the involvement of white matter tracts, can be combined with functional MRI to help in preoperative surgical planning. Positron emission tomography (PET) helps to visualize small metastases which may be missed, along with helping differentiate between normal postoperative changes and residual tumor.

Preoperative biopsy serves as the confirmatory tool in determining the presence and the type of tumor. Additionally, in some cases, the preoperative biopsy is not performed and diagnosis is made only based on MR imaging, for instance in diffuse pontine glioma. In other cases, the imaging allows narrowing down to few differentials, the surgery is begun and intraoperative frozen section is viewed to arrive at a tentative diagnosis, after which the definitive surgery is completed.

In addition, coupled with the advent of histo-molecular classification, immunohistochemistry, molecular genetics, and molecular profiling arrays, have all become a key tools of management, especially in well-resourced regions globally. Methylome profiling, which refers to the utilization of broad arrays to find out genome-wide methylation patterns in the DNA, has taken on a greater role as well in helping determine an integrated diagnosis and, thereby, provide effective targeted treatment. The WHO CNS5 provides for the specific methylation signatures for the vast majority of CNS tumors.

Finally, electroencephalography (EEG), audiological and ophthalmological testing, pituitary hormone profile, etc. also are useful tools in the clinician's armamentarium. Lumbar puncture and CSF analysis also serve as an adjunct in some cases, for instance, in the detection of tumor markers in germ cell tumors of the CNS.

5.2 Treatment approaches

3 major anti-cancer approaches, in various combination treatment protocols, are the pillars of treatment in pediatric brain tumors: surgery, radiotherapy, and chemotherapy. As discussed prior, these three approaches have extremely varying efficacy in different tumor types and grades.

5.2.1 Surgery

When undertaken with curative intent, surgery often serves as a major player in reducing the bulk of the tumor. It is extremely valuable in tumors with low grade e.g. a CNS Tumor Grade 1 Meningioma. However, its utility is reduced in tumors that lie close to critical structures such as diffuse pontine glioma.

Surgery may be done through the conventional open approache or a microsurgical approach or an endoscopic endonasal approach. The latter may prove invaluable for selected tumors, as in tumors of the sellar/parasellar region [11]. When resecting a tumor, the surgery may be classified based on the residual tumor into subtotal resection, gross total resection, supra-maximal resection, etc. While the subtotal approach leaves behind residual neoplastic tissue to avoid damage to critical structures, a supramaximal resection aims at reducing the tumor burden as much as

possible grossly. Global consensus continues to evolve into the exact definition of these terms and the varying utility of these different resections in different tumors.

Newer methods are pushing the boundaries of safe and effective surgery. Combined with MR Angiography, DTI, and fMRI, along with intraoperative neuromonitoring, surgery can be performed in challenging locations, such as those close to eloquent areas. Furthermore, awake surgery with intra-operative stimulation may be utilized for tumors in eloquent areas in older children [11]. Additionally, 5-Amino Levulinic Acid (5-ALA) based techniques are allowing better intraoperative visualization of residual tumor, thereby assisting in enhanced resection, especially in high-grade gliomas.

A small surgical procedure to insert a ventriculoperitoneal shunt remains a key measure for alleviating hydrocephalus, which is a common complication of brain tumors in the pediatric age group, especially those of the posterior fossa.

5.2.2 Chemotherapy

It finds less value in the brain than in other organs due to the blood–brain barrier which prevents adequate permeation of drugs administered. However, it is still a useful adjuvant approach for several common pediatric tumors, such as medulloblastoma. Notably, intrathecal chemotherapy based on methotrexate and cytarabine is significantly useful in intracranial lymphomas/leukemias [12]. The Ommaya Reservoir is a useful tool for repeated chemotherapy administration as well as repeated CSF withdrawal for either diagnostic and/or therapeutic purposes [13].

5.2.3 Radiotherapy

It has been a cornerstone of preventing recurrence after surgery and in treating tumors that are not amenable to resection. It may be given as teletherapy, in the form of conventional beam radiotherapy, or can be given as brachytherapy, via surgical delivery of emitters into the brain. Radiotherapy is especially valuable in tumors with rapidly dividing cells and/or those having high tumor grade. However, radiotherapy carries significant risks in the growing brain, where it can adversely impact neuronal development and hamper long-term cognitive outcomes. Proton therapy, albeit significantly more expensive, is slowly replacing conventional photon beam therapy [11].

5.2.4 Newer approaches

In addition, other therapeutic approaches have been coming up but are yet to become the standard of care for most tumors. Immunotherapy has been less than successful in pediatric brain tumors [14]. Meanwhile, targeted biological therapies have found greater utility in specific tumors, such as the role of BRAF-inhibitors in tumors with BRAF V600E mutation [15].

5.2.5 Supportive care

Amidst all of this, the role of supportive care, including physiotherapy and rehabilitation cannot be understated. Brain tumors rob children of the joy of their life and their devastating symptoms cause immense stress to both children and their guardians. Corticosteroids for managing cerebral edema, opioids for pain management, antiemetics, anticonvulsants for prophylaxis and treatment of seizures, baclofen for management of spasticity, adequate nutritional support, psychosocial care, etc. all help enhance the quality of life of brain tumor patients [11].

5.3 Summary

Having covered the general principles of management, this chapter now proceeds to examine specific brain tumors that have a high burden amongst children.

6. Medulloblastoma

Medulloblastoma (MB) is an embryonal tumor of the cerebellum having discrete origins from the neuronal stem or progenitor cell populations during early life. The peak age of diagnosis is 6–8 years. MBs are rarely seen in infancy or during adulthood [16].

6.1 Epidemiology and genetics

Medulloblastoma is the most common childhood malignancy of the brain accounting for 20–30% of all pediatric tumors and 64% of all intracranial embryonic tumors [17, 18]. The overall annual incidence rate is approximately 5 cases per million, which does not vary substantially across ethnicities or geographical regions [19, 20]. The male to female ratio is 1.8:1 [21, 22]. A wide range of syndromes like Gorlin syndrome, FAP syndrome, ataxia-telangiectasia, Bloom syndrome, Fanconi's anemia, Li-Fraumeni syndrome and Xeroderma pigmentosum have been implicated in MB pathogenesis [23].

Four subgroups of MB have been defined based on the age of onset, genetic alterations, and prognosis. These are the WNT subgroup MB (10% of MB), the SHH subgroup MB (10–15% of MB), the Group 3 MB (25% OF MB), and the Group 4 MB (50% of MB) [23]. Activating mutations of CTNNB1 stabilize Beta-catenin leading to the constitutional activation of WNT signaling in 85–90% of the WNT subgroup MB, which has a good prognosis in children [24, 25]. Germline/somatic mutations in genes of the SHH signaling pathway (PTCH1, SUFU, SMO, GLI1/2, and MYC) lead to its constitutional activation in SHH subgroup. MYC activation is characteristic for Group 3 MB. Several mutations are implicated in Group 4 MB with no clear majority, including transcriptional repressors like PRDM6 and histone modifiers like KDM6A and KMT2C [26].

6.2 Clinical features

The various manifestations of MB are largely attributed to an increase in ICT and cerebellar dysfunction. These include nocturnal or morning headache, nausea, vomiting, and altered mental status. These symptoms evolve over a period of a few weeks to months. Specific cerebellar symptoms include ataxia, visual disturbances (eg. strabismus), impacted fine motor skills (eg. clumsy handwriting) that reflect in the patient's school performance [26]. These commmon clinical features may be accompanied by syndrome-specific presentations. If spinal drop metastasis has occurred, presenting features may include back pain, gait disturbances, bladder and bowel abnormalities. The tumor grows rapidly, worsening the symptoms. If accelerated growth occurs before 18 months, macrocephalus can delay diagnosis in a subset of children owing to the non-fusion of skull sutures [9].

6.3 Diagnosis

The diagnosis of MB is based on clinical features, radiology, and histopathology. CSF cytology for microscopic metastasis and molecular analysis for prognostication

are done. MRI shows a midline mass involving the vermis or the fourth ventricle, rarely seen laterally encroaching the cerebellar hemispheres [27, 28]. T1-weighted imaging finds a hypodense to isodense lesion and T2/FLAIR yields a hyperdense tumor. On diffusion-weighted imaging, the lesion shows reduced diffusion due to high cellularity and nucleus-to-cytoplasm ratio [29]. Imaging the spine is more fruitful in detecting drop metastasis than CSF analysis. MB subgroups show characteristic localizations. For instance, the WNT subgroup is usually located in cerebral peduncle/cerebellopontine angle, the SHH subgroup in cerebellar hemispheres, the Group 3 and Group 4 MBs usually located along the midline with extension into the 4th ventricle [30–32].

Medulloblastoma is a round blue cell tumor, having characteristic microscopic appearance. Histopathology and molecular diagnosis distinguish it from other posterior fossa tumors like ependymoma, pilocytic astrocytoma, and other embryonal tumors. These reveal a combination of patterns including classic, desmoplastic/nodular, MB with excessive nodularity, large cell, and anaplastic [33]. A combination of histologic and genetic variants is integrated for diagnosis.

6.4 Treatment and prognosis

The treatment approach includes a combination of maximal safe surgical resection, radiotherapy, and systemic chemotherapy [34]. Though gross total resection remains the mainstay of surgery, patients with minimal residual tumor can be expected to have similar outcomes. The morbidity of a complete resection should be adequately assessed by the surgeon against leaving a part of the tumor [35, 36]. Since MB usually pushes the vermis in a posterior direction, there are high chances of damaging it with tumor removal. Telovelar and transvermian approaches are used to preserve vermis and deep cerebellar nuclei as much as possible. Neuronavigation and neuroimaging are useful in identifying the anatomy correctly to avoid entry into the brainstem and preserve the large draining veins to prevent significant bleeding [37]. Complications following resection include cerebellar mutism syndrome or posterior fossa syndrome possibly due to splitting of the inferior vermis [38].

Adjuvant radiation therapy is initiated 3–4 weeks after surgery. It should involve the entire craniospinal axis and is termed craniospinal irradiation [39]. Focal radiation to surgical bed is not inferior to entire posterior fossa radiation, hence it should be preferred due to less exposure. Outcomes that are based on genomic drivers and prognostic indicators warrant an individualized approach [36]. Proton beam and volumetric arc/ intensity-modulated radiation therapy are being evaluated [39].

Histological subtypes have varying sensitivity for chemotherapy in patients <3 years old and ≥ 3 years old groups. Conventional chemotherapy was found sufficient for patients after gross total resection but not with metastasis or incomplete resection [40]. However, adjuvant chemotherapy and radiotherapy have better outcomes in patients who have undergone partial resection [41].

The overall survival rate is approximately 75% [40]. Age, disseminated or metastatic disease, residual disease after resection, MYC amplification, and large cell anaplastic pathology are all associated with poor prognosis. Infants and children less than 3 years of age have a poor prognosis with a 40–50% survival rate [42].

7. Craniopharyngiomas and pituitary tumors

Craniopharyngiomas (CPs) are benign tumors that develop along the hypothalamo-hypophyseal tract, constituting 6–9% of pediatric brain tumors [43]. They arise from remnants of the Rathke's pouch - the craniopharyngeal duct epithelium and may be sellar or suprasellar [44].

7.1 Epidemiology and genetics

The incidence of CPs worldwide has been estimated to be 1.33–1.56 per million children per year worldwide [45]. In the United States, the incidence is approximately 2.0–2.3 per million children per year [1], while Japan has a much higher incidence of 3.8 per million children per year [20].

There are two histologic subtypes of CPs - papillary CP (PCP) and adamantinomatous (ACP). Both subtypes have highly specific mutations - ACPs are characterized by somatic mutations in CTNNB1 (encoding β-catenin) that increase β-catenin stability, leading to the activation of the WNT pathway, while PCPs are characterized by BRAF V600E mutations. PCPs are mostly restricted to adults, so our discussion here will be restricted to ACPs [44].

7.2 Clinical features

Childhood CPs most commonly occur in the age groups of 6–10 years, followed by 11–15 years [46]. The diagnosis of CP is usually delayed, even by a few years, after symptom onset [47]. Symptoms reflect the location of the tumor, and usually progress with time, due to slow growth.

Features by which these tumors of the sellar region clinically present include:

- Headache is seen in approximately half of all CP patients [47, 48].

- Endocrine deficiencies due to disturbances of the hypothalamo-hypophyseal tract - diminished growth hormone (GH), gonadotropin, thyroid-stimulating hormone (TSH), or adrenocorticotropic hormone secretion (ACTH), in that order of frequency [44]. In children, this most commonly manifests as growth failure. Central diabetes insipidus is also common. At least one endocrine deficit as the first symptom is reported in nearly 87% of all cases [44]

- Visual deficits - symptoms are present, or deficits are unearthed on formal ophthalmologic examination, in 70–80%. The classical bitemporal hemianopia is seen in about half the cases [43].

- Others - depression, regardless of any hormonal deficiency, may occur [48]. Diencephalic syndrome leading to cachexia is a rare manifestation [44].

7.3 Diagnosis

A simple rule of thumb is that nearly 90% of pediatric CPs demonstrate calcification, approximately 90% of tumors are predominantly cystic, and about 90% take up the contrast in the cyst walls [47] CT remains the gold standard for the identification of calcifications [44]. The mixed solid and cystic components appear hypodense compared to surrounding cerebral parenchyma. Fluid within the cysts will be of slightly greater density than cerebrospinal fluid due to the higher protein content. CT can also illustrate secondary skull base changes useful for surgical planning [43].

MR Imaging and MR Angiography provide greater clarity regarding the relationship of the tumor with vascular structures. MR spectroscopy (MRS) can identify characteristic elevated peaks of lactate or lipids, to differentiate them from gliomas and pituitary adenomas [43]. Finally, an endocrinological evaluation also reveals deficient hypothalamic function, which is particularly relevant preoperatively [43].

7.4 Treatment and prognosis

Each case must be decided on its own merit [43] as there is no consensus. Surgery is indicated in almost all cases. Two broad approaches are used - aggressive surgery at diagnosis, or more conservative surgery with radiotherapy [48].

The choice of surgical approach i.e. endoscopic or open or combined depends on the surgeon's level of comfort, and the location of the tumor. Teams that prefer limited surgical resection only use surgery to alleviate visual or other neurologic deficits, and prevent further progression, with RT used for long-term control. Proton beam therapy for CP has shown great promise [47]. For cysts specifically, repeated aspiration and/ or injection of a sclerosant, or local radiation may be attempted [44, 47, 48]. These may help in postponing RT, particularly in younger children [44].

Postoperative sequelae include panhypopituitarism and hypothalamic obesity, which can be challenging to treat [48]. Others include neurocognitive deficits, sleep disorders, and exacerbated visual deficits [48]. Patients remain at greater risk of ischemic stroke, and secondary malignancy owing to radiation exposure.

Overall, the survival rates are high, around 90%, but due to postoperative sequelae, quality of life is impaired [49]. With recent advances clarifying the pathogenesis of adamantinomatous CPs, there is hope for the development of targeted therapies [50].

8. Astrocytoma

Astrocytoma is a tumor arising from the astrocytes, which are a type of glial cells found in the central nervous system (CNS).

8.1 Epidemiology and genetics

According to the WHO CNS5 classification, astrocytomas (IDH mutant) are categorized under the broad heading of adult-type diffuse gliomas. Meanwhile diffuse astrocytomas (MYB or MYLB-1 altered) are classified into pediatric type diffuse low-grade gliomas; circumscribed astrocytic glioma encompasses pilocytic astrocytoma, high-grade astrocytoma with piloid features, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, choroid glioma and astroblastoma (MN1-altered) [34]. Astrocytomas do not have any racial or ethnic inclination and are usually sporadic.

8.2 Clinical features

Clinical features include headache, seizures, and focal neurological deficit, as discussed in previous tumors [51]. In few cases, these tumors may be associated with Li-Fraumeni syndrome and Lynch syndrome.

8.3 Diagnosis

Contrast-enhanced MRI is the mainstay of diagnosis. High-grade gliomas are usually associated with hypointensity on T1-weighted imaging and heterogenous contrast-enhancement. They have increased choline and reduced N-acetyl aspartate on magnetic resonance spectroscopy due to their higher vascularity as well as increased metabolism [52]. Histologically, astrocytomas include cells with irregular, hyperchromatic nuclei and glial fibrillary acidic protein (GFAP) in the cytoplasm, and increased mitotic

activity. Molecular testing plays a key role in the diagnosis, treatment, and prognosis of the patient [52, 53]. IDH mutation testing and, 1p/19q codeletion testing is done.

8.4 Treatment

Treatment in most cases is a combination of surgery followed by radiotherapy. Surgery for astrocytoma has benefitted greatly from recent advances, including 5-ALA based resection, awake surgery, intraoperative stimulation, and neuronavigation, allowing for tumor resection close to eloquent structures and critical vessels.

9. Ependymomas

Ependymomas are a subset of glial tumors arising from radial glial cells in the subventricular zone, located in or adjacent to the ependymal lining. Most commonly, they are associated with the fourth ventricle [54].

9.1 Epidemiology and genetics

Ependymomas account for 10% of all brain tumors making them the third most common intracranial pediatric malignancy, with a sex ratio of 1.77:1 [54]. The annual incidence rate amongst children is 0.46 per million in the United States [1].

WHO classifies ependymomas according to a combination of histopathological and molecular features into supratentorial ependymomas with ZFTA, RELA, YAP1 or MAML2 mutation, posterior fossa ependymomas with H3K27-mutation, EZHIP mutations, and spinal ependymomas with NF2, MYCN mutations. Molecular classification of myxopapillary ependymoma and subependymoma do not add to clinical utility, hence they are studied as separate entities [7].

9.2 Clinical features

The age and the site of origin determine presentation. Failure to thrive, lethargy, and irritability like non-specific clinical features are observed in very young children. Posterior fossa tumors present with increased intracranial pressure, nerve palsies, neck pain, and/or ataxia. Supratentorial tumors present with limb weakness, bowel bladder dysfunction, paraesthesia, and pain [55].

Seizures with or without focal neurological deficits are also commonly seen in supratentorial tumors. This may be due to the surrounding edema and mass effect. Spinal cord tumors involve ascending or descending tracts and manifest as specific anatomical lesions. Very rarely, CSF seeding may accompany both infratentorial and supratentorial ependymomas [56].

9.3 Diagnosis

The imaging modality of choice is an MRI scan of the brain and spine to evaluate for leptomeningeal dissemination [57]. T1 hypointensity and T2 hyperintensity with heterogeneous enhancement on T1 sequences post-gadolinium enhancement is seen in both spinal and intracranial tumors. Cysts and calcification can be observed, usually with supratentorial tumors. Spinal ependymomas can be differentiated from astrocytomas by a sharp margin and central location. Leptomeningeal spread can be suspected by smooth enhancement along the surface of the spinal cord, nerve root thickening, or irregular thecal sac, and confirmed by cytological assessment post lumbar puncture. Testing for the mutations discussed prior can be done if resources are available.

9.4 Treatment and prognosis

Pediatric ependymomas are treated with surgery and radiotherapy [58]. The surgeon's decision about the extent of resection is the most important prognostic factor. Posterior fossa tumors may limit the extent of resection due to involvement of lower cranial nerves and brainstem, thus incomplete resection warrants a second look surgery since overall survival for incomplete resection is much lower than gross total resection [59].

Postoperative radiotherapy is recommended for children as young as 18 months but dose modifications to reduce toxicity should be done [60]. Hypofractionated stereotactic boost in addition to conventional radiotherapy, especially for incomplete surgery, is being studied and shows promise [59]. To avoid radiation exposure to children, chemotherapy use has been investigated but its role remains equivocal [61]. Though long-term follow-up studies of radiotherapy toxicity are pending, the higher progression-free survival with radiotherapy has led to the abandonment of radiotherapy deferral strategies for children below 12 months [62].

Patients with intracranial ependymomas usually have a significant risk of recurrence and decreased 5-year overall survival, nearing approximately 50–70% [62].

10. Germ cell tumors

According to the W.H.O. CNS tumor 2021 classification, germ cell tumors are classified into mature teratoma, immature teratoma, teratoma with somatic-type malignancy, germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and mixed germ cell tumor [34].

10.1 Epidemiology and genetics

The incidence of all types of CNS germ cell tumors (GCT) is greater in males of 10–14 years of age. These tumors also possess a racial inclination towards Asians and Pacific Islanders [63]. Although GCTs can arise anywhere in the CNS, the pineal gland is most commonly involved, followed by the suprasellar/ neurohypophyseal area and the basal ganglia. A bifocal tumor is one where both the pineal gland and the neurohypophyseal region are involved [64].

10.2 Clinical features

Obstructive hydrocephalus can result from the compression of the cerebral aqueduct by the tumor, often manifested as headache [65]. The damage to the optic nerve due to the mass effect of the tumor can cause visual field defects and decreased visual acuity [66]. Neurophypophyseal tumors can often lead to hypopituitarism, diabetes insipidus [66]. GCT of the basal ganglia can present with hemiparesis. Intracranial hemorrhage is also a complication of GCTs [66]. Due to the involvement of the optic nerve, often the ophthalmologists are the first ones to interact with the patients of CNS GCT, and play a crucial role in the diagnosis.

10.3 Diagnosis

The tumor markers associated with CNS GCTs are the following: beta subunit of human chorionic gonadotropin (β -HCG), alpha-fetoprotein (AFP), and placental alkaline phosphatase, which are raised in different types of GCTs differently. In choriocarcinoma, the β-HCG value is >500 mIU/mL, while in germinoma with

syncytiotrophoblastic giant cells, β-HCG is <100 mIU/mL. β-HCG is also increased in mixed germ cell tumors. AFP is raised in yolk sac tumors and mixed germ cell tumors.

The findings on imaging include a typical pineal mass on MRI or CT, usually with calcifications, and signs of obstructive hydrocephalus on CT. Germinomas are generally of uniform intensity with blurred margins. Pineal teratomas appear as heterogeneous well-demarcated masses with occasional calcifications, irregular cysts, or fatty tissue and thus show a peculiar pattern on both CT and MRI [64]. For GCTs occurring in the basal ganglia, enhancement is minimal, and the only detectable abnormality is an occasionally increased signal intensity on FLAIR [64].

10.4 Treatment and prognosis

According to the Japanese Pediatric Brain Tumor Study Group, patients with CNS non-seminamatous GCT may be divided into three categories (based on their prognosis): good (mature teratoma and pure germinoma), intermediate (e.g. immature teratoma), and poor (e.g. choriocarcinoma, yolk sac tumor). The 5-year overall survival rate varies as per the histologic type from 10 to over 98%. As for non-seminomatous germ cell tumors, the group reported a 5-year survival rate of 67% with platinum-based chemotherapy followed by surgical resection and craniospinal irradiation together with focal boost [67, 68].

11. Brain stem gliomas

Brainstem gliomas constitute 10–20% of all pediatric CNS malignancies and can be broadly divided into focal brainstem gliomas (FBGs) and diffuse intrinsic pontine gliomas (DIPGs) [1, 69].

11.1 Epidemiology and genetics

11.1.1 FBG

FBGs usually arise in the midbrain or the medulla and are well-circumscribed, low-grade tumors – usually being pilocytic or diffuse astrocytomas. These may be associated with Neurofibromatosis 1 (NF1). Characteristic mutations include chromosome 7q34 duplications, resulting in a KIAA1549-BRAF fusion, in pilocytic astrocytomas, and a BRAF V600E mutation in fibrillary astrocytomas, the majority of pleomorphic xanthoastrocytomas, and nearly half of the gangliocytomas [69–71].

11.1.2 DIPG

DIPGs constitute 80% of all pediatric brainstem tumors and are diffuse, high-grade, and infiltrative. 80% of these have H3K27 mutations on two histone H3 genes, identified primarily through autopsy studies [69]. EGFR mutations are also common [72]. Histologically, these are usually high grade, although a significant proportion may appear low grade, which is ultimately irrelevant for prognosis.

11.2 Clinical features

11.2.1 FBG

These usually present insidiously over many years [69–71]. Isolated cranial nerve deficits, neck stiffness, and pain, contralateral hemiparesis are common [69–71].

Medullary tumors may cause dysphagia or apnea, while cervicomedullary tumors may present with ataxia and/ or lower motor neuron signs. Hydrocephalus is uncommon, except in posteriorly extending tumors and tumors of tectal origin [69–71].

11.2.2 DIPG

Patients typically present around the age of 7 years, with a short history, sometimes for less than a month [69, 73, 74]. The classical triad of (1) cranial nerve palsies, most commonly VI and VII - facial asymmetry and diplopia (2) long tract signs - upgoing Babinski, and hyperreflexia, and (3) cerebellar signs - ataxia, dementia is seen in over 50% [73]. Symptoms and signs of raised ICT are seen in less than 10% at diagnosis and are more typical in the end stages of the disease [73].

11.3 Diagnosis

11.3.1 FBG

On MRI, these usually have well-defined borders, no edema, iso- or hypointensity on T1, and hyperintensity on T2 weighted images, with homogeneous contrast enhancement [69–71]. MR Spectrography can support the diagnosis, with the estimation of choline-to-N-acetylaspartate (Choline:NAA) ratios differentiating high grade from low-grade tumors. Diffusion Tensor Imaging (DTI) can also provide estimates of long tract disruption [69].

11.3.2 DIPG

DIPGs are typically hypointense on T1 and hyperintense on T2 weighted MRI [69, 73]. Contrast enhancement is variable. A diffuse expansion of the pons is typical. This may involve adjacent areas, such as the cerebellum and midbrain; the medulla is usually spared [69–71]. There is usually an exophytic component, and the tumor may surround the basilar artery. However, a serial assessment may be difficult due to their heterogeneous signal characteristics and interobserver variability. Here too, MR spectrography with Choline:NAA ratio estimation can support the tentative diagnosis and may provide prognostic information [71].

11.4 Treatment and prognosis

11.4.1 FBG

In surgically accessible regions, resection is performed. While complete resection is curative, it should not be performed at the cost of neurologic deficit, as even incomplete resection has excellent long-term outcomes [75].

Chemotherapy is preferred for inoperable tumors, symptom progression, or persistence after surgery. Tumor growth can at least be stabilized, delaying or even eliminating the need for RT in young children [69–71]. Two popular, effective combinations are that of vincristine and carboplatin, and another of 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV) [69]. TPCV has improved progression-free survival, but carries long-term risks associated with alkylator use [69]. Radiotherapy is an option for surgically inaccessible tumors but should be reserved for older children given the potential for significant morbidity [69–71]. Long-term overall survival approaches 100% [70], but chronic disability is common, resulting from both tumor expansion and RT [70].

11.4.2 DIPG

Surgery is usually not recommended [71]. The mainstay of treatment is fractionated radiotherapy alone [73]. There is still uncertainty regarding the mode of RT to be delivered, with future trials comparing fractionated and conventional RT encouraged [76]. Monotherapy or combination chemotherapy have proven ineffective.

With greater clarity regarding the genetic make-up and microenvironment of these tumors, immunotherapy and molecular targets, such as anti-GD2 chimeric antigen receptor (CAR) T-cell therapy and histone deacetylase (HDAC) inhibitors are showing promise [71, 73].

The prognosis remains dismal, with less than 3% surviving at 5 years [71]. Long-term survivors usually have neurological deficits and cognitive impairment [76].

12. Meningiomas

Meningiomas arise from arachnoidal cap cells in CNS.

12.1 Epidemiology and genetics

They are rare in children, representing only 2–3% of pediatric CNS tumors [77]. Their incidence is markedly greater in syndromes like Neurofibromatosis 2, Schwannomatosis, Gorlin syndrome, and familial meningioma syndrome [77, 78]. Exposure to irradiation in childhood predisposes to the development of meningiomas [77, 78].

12.2 Clinical features

Mostly, they present in the second decade of life [78]. The most common presenting symptoms are headache, seen in almost half, followed by seizures, seen in almost 30%. Focal findings such as visual deficits, cranial nerve signs may also be present.

12.3 Diagnosis

CT and MRI demonstrate a well-defined, extra-axial, dural-based mass, that displaces the normal brain. It is isointense or hypointense to gray matter on T1 and isointense or hyperintense on T2-weighted images [77]. Contrast enhancement is strong and uniform on both CT and MRI [78]. On histology, most are WHO Grade I. The best-characterized mutation is that of the NF2 gene, with other molecular mechanisms in the pediatric age group poorly characterized. Tumors in this age group are genetically distinct from their adult counterparts [78].

12.4 Treatment and prognosis

Symptomatic meningiomas require resection. The extent of initial resection is a prognostic factor, so total resection must be done where possible. Adjuvant RT is recommended for WHO Grade III tumors, while inoperable WHO Grade I and Grade II tumors require a case-by-case consideration [78]. The 5-year survival is approximately 90%. Those who undergo gross-total resection, those without NF2, and those with lower-grade tumors have higher survival rates.

13. Schwannoma

Schwannomas or neurilemmomas are tumors originating from schwann cells around the axons of the cranial nerves. They are encapsulated and do not transform into malignancies [79].

13.1 Epidemiology and genetics

Though schwannomas are more commonly seen in adults between the ages of 50-60 years, 89% of nerve sheath tumors are schwannomas even in children [79], the incidence of which is 0.44 cases per 100,000/ year [80, 81]. Most (90%) of the schwannomas are sporadic and others occur as part of syndromes like NF2 and Carney complex. Inactivation of gene NF2 coding for the merlin protein (schwannomin) has been implicated in both sporadic and syndromic schwannomas. Spinal schwannomas may have SMARCB1 mutations [82].

13.2 Clinical features

These tumors grow slowly and may present much later with location-specific symptoms. Vestibular schwannomas may present with headache, imbalance, tinnitus, cranial nerve deficits and motor weakness. Spinal schwannomas may present with pain, paresthesia, and/or motor weakness [83].

13.3 Diagnosis

MRI is preferred over CT for diagnosis since plain radiographs are not specific. They usually show an oval or round mass with an isointense or hypointense signal on T1 and hyperintense, heterogeneous signal on T2 images [82]. Classically, microscopic findings include Antoni A and Antoni B areas, with Verrocay Bodies.

13.4 Treatment and prognosis

The benign course of these tumors may allow for observation and serial MRI scans for periodic assessment. Biopsy to confirm histology before resection is recommended. Surgical approaches include the retro-sigmoid, middle fossa, or translabyrinthine approach [84]. Stereotactic radiosurgery may be of benefit if complete resection cannot be done. Usually, these tumors have an excellent prognosis, however, postoperative complications which are more common in the pediatric population may worsen it [85].

14. Other tumors

14.1 Choroid plexus tumor

Choroid plexus tumors arise from neuroepithelial tissue that makes CSF in the ventricles, and therefore their distribution corresponds to the amount of the choroid plexus present in different ventricles [86]. Nearly 50% occur in the lateral ventricles, 40% in the 4th ventricle and merely 5% in the third ventricle. Meanwhile, multifocal occurrence is seen in around 5% of tumors. Overall, they are merely 1% of all pediatric brain tumors, but make up 15% of tumors in children aged <1 year. Headache and/or hydrocephalus are two common clinical presentations [87].

They are of two major varieties:

14.1.1 Choroid plexus papilloma (CPP)

These are likely hamartomas and therefore appear similar to normal choroid plexus tissue histologically. Classified as WHO grade I in general, they contain uniform cellularity with little/no atypia and KI-67 index <2%. Atypical CPPs have higher mitotic count (≥2 mitoses/high power field) and are classified as grade II [86]. They are calcified and enhance with contrast. On MR imaging they have flow voids due to their vascularity, with enlarged choroidal arteries on MR angiography. Asymptomatic tumors can be monitored conservatively and only resected if producing symptoms or enlarging. Surgery is the modality of choice for symptomatic and/or large CPPs. Adjuvant radiotherapy is usually not required and prognosis is excellent, with 10-year survival exceeding 80% [88, 89].

14.1.2 Choroid plexus carcinoma (CPC)

These are rarer than CPPs and can be a part of manifestation of Li-Fraumeni Syndrome. They are aggressive tumors, with their invasion making gross total resection insufficient. Radiotherapy is useful but prognosis is poor with median survival of <3 years [87].

14.2 Atypical teratoid/rhabdoid tumor

These are highly aggressive tumors which occur in children <3 years of age, with nearly two third occurring in the cerebellum, and nearly a fourth being supratentorial.

These have specific diagnostic criteria, of which the characteristic 'Rhabdoid Cells' are not a part. The criteria are (A) loss of INI1 nuclear staining (corresponding to biallelic inactivation of SMARCB1) and (B) loss of BRG1 staining (corresponding to inactivation of SMARCB4) [90, 91]. On MRI, they are hypo-intense on both T1 and T2, with several cysts and hemorrhages, leading to a heterogeneous appearance. Leptomeningeal enhancement may be visualized. Surgery has little role here. Combination chemotherapy followed by radiotherapy is utilized but is challenging to implement given the very young age of patients at the time of diagnosis. Therapy has to be closely matched to the child's age, AT/RT's location, and disease extent [92]. Prognosis is unsatisfactory, with nearly 30% 5-year survival [93].

14.3 Neuronal and mixed neuronal-glial tumors

Neuroepithelial tissues in the CNS give rise to mixtures of glial and/ or neuronal differentiated tumors. These are rare tumors in children.

14.3.1 Ganglioneuromas

These account for 0.3–1.4% of all CNS tumors, usually occurring in adolescents [94]. Focal motor seizures are the most common presentation involving the temporal lobe [95]. They are diagnosed by MRI and gross total resection is usually preferred for better survival rates [94].

14.3.2 Desmoplastic infantile ganglioglioma or desmoplastic infantile astrocytoma

They are supratentorial cystic tumors usually affecting children less than 2 years [96]. Frontal and parietal lobes are the most common locations which present as head enlargement, seizures, vomiting, and headache are observed. Diagnosed with

MRI, they are slow-growing tumors. They have a good prognosis after complete removal, rarely requiring radiotherapy and chemotherapy [97].

14.3.3 Dysembryoplastic neuroepithelial tumor

These tumors cause early-onset epilepsy in children with an incidence of 0.03 person-year per 100,000 and have slight male predominance [98]. The mesial temporal lobe is the most common location identified on imaging. Favorable outcomes are reached in 70–90% of cases after complete resection [99].

14.3.4 Papillary glioneuronal tumor

Characterized by papillary architecture and bipartite (astrocytic and neurocytic) cellularity, these tumors mostly occur near the lateral ventricles [100]. Imaging shows them as circumscribed lesions with frequent cystic alterations. Patients are either asymptomatic or complain of mild symptoms. Their benign course rarely warrants complete resection [101].

14.3.5 Rosette-forming glioneuronal tumor

Usually seen in children above 6 years of age, with a female predominance, their location in the 4th ventricle is one of the defining features [102]. Headache, nausea/vomiting, ataxia, and visual disturbances are common manifestations. MRI reveals solid or cystic or mixed solid and cystic masses rarely with calcifications. Full resection prevents recurrence [102].

14.3.6 Myxoid glioneuronal tumor

These are extremely rare tumors. They present as seizures and other focal deficits. A histopathological feature of myxoid stroma, somatic next-generation sequencing showing PDGFRA gene mutation, and MRI findings help in diagnosis. They have a benign course [103].

14.3.7 Diffuse leptomeningeal glioneuronal tumor

These tumors have variable neuronal components including neurocytes and ganglion cells [104]. The median age of presentation is five years with slight female predominance [105]. MRI shows meningeal enhancement in spinal cord and basilar [106]. Symptoms mimic meningitis and hydrocephalus. Chemotherapy and radiotherapy are first-line options [107].

14.3.8 Gangliocytoma

These account for 1–5% of all pediatric CNS tumors [108]. Majority of them occur in the temporal lobe, causing epilepsy, varied neurological signs/symptoms including cranial nerve deficits, focal weakness, and hydrocephalus [109]. Gross total resection yields a good prognosis.

14.3.9 Multinodular and vacuolating neuronal tumor

Very few cases have been reported diagnosing this new entity. Non-specific clinical features like chronic headache, paresthesias, and cognitive impairment are reported. MRI is used for diagnosis and studies of treatment modalities are yet unavailable [110].

14.3.10 Dysplastic cerebellar gangliocytoma or Lhermitte-Duclos disease

This is a rare entity in children that mimics low-grade glial tumors or infectious diseases. A slow-growing pattern and late clinical manifestations allow for conservative treatment and outpatient follow-up for asymptomatic children [111].

14.3.11 Neurocytomas

Depending on their location, these are divided into central, extraventricular, and cerebellar. They often mimic oligodendrogliomas and the confirmation of diagnosis rests on immunohistochemistry, histology and genetic studies. Safe maximal resection is considered the ideal option for a good prognosis. Adjuvant radiotherapy benefits incomplete resection [110].

14.4 Hemangiomas

Infantile CNS hemangiomas are rare benign tumors composed of endothelial cells. They are seen in about 1% of children with cutaneous hemangiomas and have a female predilection [112, 113]. They may be associated with PHACES (posterior fossa malformations, hemangioma, arterial anomalies, coarctation of the aorta/cardiac defects, and eye abnormalities) syndrome, and are more common in the posterior fossa [112]. GLUT1 represents a reliable marker. They have a rapid, early stage of proliferation followed by one of involution that usually extends from 1 year of age to 5 to 7 years of life [112]. Many are asymptomatic or undiscovered, but others can present with seizures, focal deficits, or symptoms of raised ICP [112].

During the proliferative phase, CT and MRI show a well-circumscribed lobular homogeneous soft-tissue mass with intense and persistent enhancement, with Doppler showing features of fast flow. In the involuting phase, they enhance to a lesser degree, have fewer radiographic signs of fast-flow vascularity, and appear heterogeneous. The final involuted phase is represented by fibrofatty tissue [112]. Imaging can establish continuity between the CNS tumor and the extra CNS component. Corticosteroids represent the mainstay of treatment. Interferon-alpha and propranolol may also be used [112]. For biopsy, or mass effect alleviation, excision may be tried.

15. Conclusions

Pediatric brain tumors have an immense disease burden, given their status as the most common solid organ tumors of children. The WHO 2021 Classification is a landmark change in the approach to diagnosing and treating these tumors. The landscape of their treatment has been rapidly evolving, with effective therapies on the horizon. In current clinical practice, surgery, radiotherapy and chemotherapy continue to be the mainstay of management.

Conflict of interest

The authors declare no conflict of interest.

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