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Review Article

Brain Tumors in Pediatric

Brain Tumors in Pediatric Patients

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Abstract: Pediatric brain tumors are the most common solid tumors in children, comprising a diverse group of neoplasms that vary in histology, location, and behavior. Common types include astrocytomas, medulloblastomas, ependymomas, and brainstem gliomas. Symptoms often depend on the tumor's location and may include headaches, nausea, vomiting, balance issues, and cognitive or behavioral changes. Advances in imaging, surgical techniques, and therapies, including radiation and chemotherapy, have improved outcomes. However, treatment can have long-term effects on cognitive and physical development, making comprehensive care and follow-up essential for pediatric patients. Early published reviews on pediatric brain tumors may have several lacunae, such as limited data on long-term outcomes, emerging treatment modalities, and the genetic and molecular underpinnings of various tumor types. They might also inadequately address the psychosocial impacts on patients and families. Therefore, a comprehensive review is needed to synthesize the latest research on pediatric brain tumors, encompassing advancements in diagnosis, treatment, and survivorship care. This updated review will provide valuable insights for clinicians, researchers, and policymakers to improve managing and supporting children with brain tumors. The review covers various aspects of pediatric brain tumors, focusing on choroid plexus tumors and spinal cord tumors. It discusses treatment strategies, highlighting surgical, radiotherapy, and chemotherapy options.

Keywords: Pediatric brain tumors, Astrocytomas, Medulloblastomas, Choroid plexus tumors, Treatment strategies, Long-term outcomes

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1. INTRODUCTION

Pediatric central nervous system (CNS) malignancies rank as the second most prevalent kind of cancer and the most frequent type of solid tumor in this particular age range. The incidence rate of primary malignant and nonmalignant brain and other CNS cancers in children and adolescents is around 5.67 cases per 100,000 person-years [1]. According to the Surveillance, Epidemiology, and End Results Program, brain tumors are the leading cause of death in children with cancer [2]. The symptoms and signs of brain tumors vary based on factors such as the specific location of the tumor, the age of the child, and the rate at which the tumor grows. Supratentorial tumors are mostly seen in neonates, children aged 0 to 3, and those beyond the age of 10. Conversely, tumors located posterior to the tentorium are often seen in children between the ages of 4 and 10. Embryonal malignancies, such as medulloblastoma or AT/RTs, are more prevalent in younger children, whereas tumors arising from glial cells are more often seen in older children. The etiology of the bulk of brain tumors in children remains poorly understood. Various genetic abnormalities, including neurofibromatosis type 1 (NF-1), tuberous sclerosis, Li-Fraumeni syndrome, Gorlin syndrome, and Turcot syndrome, may elevate the probability of developing brain tumors. Recent study findings suggest that around 8% of cancer cases in children and adolescents may be attributed to genetic predisposition syndromes. This ratio is expected to rise when further investigations are carried out [3]. Aside from inherited illnesses, radiation exposure is the only consistently acknowledged environmental risk factor for brain tumors. Childhood main CNS malignancies include many types of tumors, about 50% of which originate below the tentorium. Supratentorial tumors often arise from the suprasellar and pineal regions. CNS malignancies are categorized based on their histologic characteristics and presumed source inside the brain [4]. Brain tumors are the second most prevalent kind of cancer in children, behind leukemia. These tumors are the most common kind of solid tumors in this age group, exceeding sarcomas, carcinomas, and lymphomas in terms of frequency. Moreover, brain tumors are the predominant cause of mortality in pediatric patients [5,6]. Proton nuclear Magnetic resonance spectroscopy (MRS), often known as 1H-MRS, is a technique used to analyze the substance's chemical composition by measuring its protons' magnetic properties. It is a noninvasive technology used in vivo to diagnose brain tumors. This technique provides metabolic diagnostic signals that go beyond anatomical data and are often used for this specific purpose. MRS aids radiologists in identifying tumor tissue, classifying tumors, discerning between various types of tumors, distinguishing active tumors from radiation necrosis or scar tissue, guiding the choice of stereotactic biopsy locations, and assessing early treatment responses. [7,8] Studies indicate that the majority of malignant tumors have reduced levels of N-acetyl-aspartate (NAA), except in energy deprivation (tumor necrosis) when creatine (Cr) levels remain constant. Furthermore, tumors have elevated choline levels (Cho), suggesting an accelerated process of cell membrane renewal and cellular density [9]. Short echo-time (TE) spectroscopy allows for the detection of metabolites with shorter T2 relaxation times, such as taurine (Tau), glutamine plus glutamate (Glx), myo-inositol plus glycine (ml + Gly), and alanine (Ala)[10], with a higher signal-to-noise ratio, compared to long TE spectroscopy. These metabolites have shown effectiveness in differentiating certain tumor histologies [11]. Pediatric brain tumors (PBT) display considerable diversity in their histology, molecular features, and prognosis. The categorization of these cancerous growths mostly comprises glial and neuronal tumors [12]. Frequently seen gliomas in children consist of astrocytomas, oligodendrogliomas, ependymomas, brain stem gliomas, and optic nerve gliomas. Diffuse intrinsic pontine glioma (DIPG) is a rare kind of brain tumor composed of glial cells. Frequently, it results in the death of neonates. Neuronal malignancies mostly consist of embryonal cancers, with the most common types being medulloblastoma, AT/RTs, and CNS PNETs (CNS PNET)[13,14]. Gliomas account for 53% of all primary brain and CNS tumors in children aged 0-14, as reported by the Central Brain Tumor Registry of the United States (CBTRUS)[15]. Pilocytic astrocytoma accounts for 33% of these cases, whereas other low-grade gliomas comprise 27%. Embryonal tumors constitute 15% of the total number of primary CNS malignancies. The two most common subtypes are medulloblastoma, accounting for 62% of cases, and AT/RTs, accounting for 15% of cases [16]. The occurrence and outlook of PBTs vary substantially based on factors such as tumor kind, tumor site, age at diagnosis, and the individual's race, ethnicity, and gender. Although adolescent brain tumors are common and have significant impacts on patients, our knowledge of their causes and molecular features is still restricted. The etiology of the majority of brain tumors remains elusive. However, some factors have been associated with certain categories of neoplasms. Turcot syndrome, Li-Fraumeni syndrome, and Gorlin syndrome may lead to the formation of high-grade glioma (HGG) and medulloblastoma[17,18,19]. A successful strategy for controlling brain tumors in children requires a comprehensive plan that incorporates several disciplines. Ideally, therapy should occur in specialized pediatric institutions equipped with the necessary resources and staffed by specialists. The team should include crucial individuals such as pediatric neurosurgeons, oncologists, neuropathologists, neuro radiologists, radiation oncologists, endocrinologists, and physical rehabilitation specialists. Common symptoms seen in children affected by this condition include increased intracranial pressure, cranial nerve paralysis, impaired coordination, epileptic seizures, visual impairment, and impaired growth.

1.1 Classification of brain tumors in childhood

Brain tumors are primarily classified based on their anatomical location and histological features. Tumor classification sometimes involves microscopic analysis to identify the probable cells of origin and assign a histologic grade indicating the abnormalities' extent. Progress in understanding the growth and the study of the characteristics and symptoms of malignancies in the CNS has resulted in modifications to their classification. The World Health Organization (WHO) recently updated the classification of malignant neoplasms in the CNS, specifically classifying tumors that affect children according to their histological characteristics [20]. AT/RTs is a very aggressive and malignant tumor that mostly impacts children aged three to five. Recent genomic research has shown that medulloblastomas, formerly classified as a subtype of primitive neuroectodermal tumor (PNET) found in the cerebellum, are separate and

different entities [21]. The category includes desmoplastic infantile astrocytomas and excludes non-neoplastic lesions. Significant disparities exist in the site and attributes of malignancies in pediatric and adult populations. Malignant gliomas, meningiomas, and metastases are often seen in adults, although children seldom have these disorders. However, cases involving children are often linked to low-grade gliomas and other embryonal cancers. A recent comprehensive study using the WHO criteria reclassified primary CNS malignancies in children. The study revealed that the majority of cases (60.9%) were seen in boys, with a greater prevalence of tumors in the supratentorial area (53.3%). The research showed that there were low-grade WHO I/II tumors, making up 51.5% of cases, while high-grade WHO III/IV tumors account for the remaining instances. Constitute 48.5% of the whole amount [22]. Reclassifying these categories has profound ramifications for examining disease patterns, determining treatment options, and evaluating patient results and prospects.

1.2 Medulloblastoma

Medulloblastoma is a cancerous tumor that often develops in the back part of the skull in children. It accounts for around 20% of all brain tumors in pediatric patients [23.] It often manifests before age 15 and is more common in boys. The WHO classification system was revised in 2016 to include molecular subtypes for medulloblastoma. The classification was determined by using both histology and genetic data. These subgroups exhibit unique characteristics regarding tumor biology and a wide range of variables, such as demography, dissemination, and patient outcomes. By categorizing these molecular classifications into a maximum of eleven subtypes, it is anticipated that the precision of outcome prediction would be enhanced, and more targeted treatment plans will become feasible. Medulloblastoma is the most common kind of tumor seen in children, comprising 40% of all cancers located in the posterior area of the brain. It is the predominant malignant neoplasm of the brain in pediatric patients. These tumors originate in the occipital region of the skull and are distinguished by a high cell count and histological diversity[24]. Medulloblastomas may arise at any time throughout childhood, although they are more likely to happen between the ages of 3 and 4 and again between the ages of 7 and 10. Approximately 15% to 20% of documented cases consist of infants, whose underdeveloped CNS is especially susceptible to the adverse effects of neurotoxic therapies. Medulloblastomas often arise in the fourth ventricle and have fast proliferation. Consequently, there are deficits in the midline cerebellar function and an elevation in intracranial pressure due to the obstruction of cerebrospinal fluid circulation. At the time of diagnosis, almost 80% of people display hydrocephalus. In the other 20% of instances, mostly seen in infants and adults, the tumor arises in the lateral hemisphere of the cerebellum, leading to distinct deficits in the cerebellum on one side and abnormalities in the cranial nerves [25]. Medulloblastomas may be distinguished from the four primary pediatric malignancies in this brain region by their clinical and radiological features. Children aged 3 and above who have medulloblastoma often get conventional treatments, including a combination, regardless of the specific molecular subtype and the potential therapy methods. The available treatment modalities are surgical excision, radiation therapy, and chemotherapy. The first phase of therapy is the surgical excision of the tumor. Multiple studies consistently showed that the total or almost complete removal of the primary tumor is associated with better outcomes, particularly in persons without spreading disease [26]. Posterior fossa syndrome, commonly referred to as cerebellar mutism, is seen in around 25% of individuals after the surgical removal of midline cerebellar tumors [27]. The precise etiology of this syndrome remains elusive; nonetheless, it is hypothesized to be associated with injury to the dentate nucleus, leading to disruption of the dentato-thalamo-rubral pathway. Delayed-onset mutism is frequently seen in patients after surgery, sometimes accompanied by other neurological symptoms. This syndrome may last for many weeks to several months and may have lasting effects, perhaps lasting up to a year after the surgical treatment. Medulloblastomas exhibit unique histological and radiological features and are classed with embryonal tumors such as PNETs and atypical teratoid/rhabdoid malignancies[28]. These tumors have a primitive or undifferentiated cellular structure, possess a rapid growth rate, and can spread via the cerebrospinal fluid. Histological alterations rather than molecular indicators determine the current categorization of these cancerous growths. Patients with medulloblastoma are categorized as high-risk. The risk is determined by the degree of tumor removal, the metastasis amount, and the patient's age of [29]. Treatment often entails a synergistic approach including surgical interventions, radiation treatment, and chemotherapy, leading to a significant decrease in mortality rates. Nevertheless, it often leads to significant neurological side effects. Recent clinical trials suggest that most neonates diagnosed with medulloblastoma may achieve remission by having surgery and chemotherapy, eliminating the requirement for radiation and thereby avoiding possible long-term adverse effects [30-32]. This therapeutic procedure efficiently mitigates the adverse health consequences induced by treatment, and ongoing research is focused on identifying the specific patient cohorts that will benefit most from this approach.

1.3 Supratentorial Embryonal Tumors

Embryonal tumors that include a significant quantity of neuropil and authentic rosettes, together with ependymoblastomas and certain medulloepitheliomas, are classified as embryonal tumors displaying multilayered rosettes. The histological characteristics of these tumors determine their classification as either embryonal tumors with multilayered rosettes, NOS (not otherwise specified), or medulloepithelioma. In CNS embryonal tumors, NOS denotes CNS PNETs that lack identifiable genetic abnormalities[33]. The histologic subtypes of PBTs vary according to age. Non-posterior fossa embryonal tumors, also known as CNS-PNETs are rare malignant brain tumors that account for less than 3% of occurrences in young persons. These tumors often have an unfavorable prognosis[34,35]. The 2016 WHO classification system incorporates the amplification status of the C19MC region on chromosome 19 as a factor for classifying different groups [36]. Every embryonal tumor in the CNS is very malignant and classified as grade IV according to the WHO. Genetic analysis reveals that some malignancies, including supratentorial embryonal tumors, have commonalities with other tumor types like high-grade gliomas and ependymomas based on their histological features. The findings of this study have important consequences for treatment decisions, namely with the size of the area to be treated with radiation and the

selection between adjuvant chemotherapy or biologic therapy. These tumors are rapidly proliferating neuroepithelial tumors with little cellular specialization. While they exhibit histological similarities to medulloblastomas, they also have different biochemical differences [37]. Elderly children often display indications of increased intracranial pressure, whereas younger children and newborns may manifest nonspecific symptoms such as irritability, weariness, or gradual enlargement of the head. Depending on the location of the tumor, patients may also have localized neurological deficits or seizures. The current treatment approach involves completing a thorough surgical excision of the afflicted region, followed by whole-brain and spinal radiation therapy, as well as targeted radiation to the precise site. In addition, an intensive chemotherapy regimen is given, which is comparable to the treatment protocols used for individuals diagnosed with high-risk medulloblastoma. While adjuvant chemotherapy is believed to improve survival, a definitive treatment regimen has not yet been developed. Younger persons need to have an extensive and protracted regimen of multiagent chemotherapy as a means to delay or prevent the need for radiation treatment. This method has less effectiveness in enhancing survival rates [38-40]. This indicates that the existing treatment options must be improved to address biological complexities.

1.4 Atypical Teratoid/Rhabdoid Tumors

The recognition of atypical teratoid/rhabdoid tumors (AT/RTs) was established in the early 1990s [41]. These cancers possess distinct histological and molecular genetic characteristics. AT/RTs have histological characteristics characterized by rhabdoid cells and areas resembling PNETs. They have a deficiency in their genetic makeup at the molecular level. The SMARCB1 gene produces a crucial part of the SWI/SNF chromatin remodeling complex. More than 50% of children identified with atypical AT/RT have been found to possess germline mutations. AT/RTs are rare malignant tumors that mostly occur in neonates and young children. These tumors constitute a mere 1% to 2% of all brain tumors in children, although they contribute to around 10% to 20% of CNS malignancies in children under the age of three [42,43]. AT/RTs were first misclassified until they were later identified as a separate clinical entity in the 1980s. AT/RTs are mostly characterized by genetic mutations in the SMARCB1 gene. [44] Approximately 33% of patients have a germline mutation in SMARCB1 and, less often, in SMARCA4 [45]. AT/RTs have histological features such as abnormal cells with nuclei located distant from the center, tiny nucleoli, and a substantial amount of eosinophilic cytoplasm. These cells often exhibit a variety of mitotic patterns. Immunohistochemistry is essential for diagnosis, namely to identify the absence of INI1 nuclear staining, which confirms the presence of biallelic SMARCB1 mutations on chromosome 22 in the tumors [46]. Similar to other types of brain tumors, AT/RTs subgroups have a propensity to originate in certain regions of the brain[47]. The therapy remains a topic of dispute due to the absence of consensus over the most efficient method, mostly because there is a need for randomized controlled studies. The dominant methods include multiagent treatment methods, such as chemotherapy and radiation. Nevertheless, radiation is often circumvented in early children. Comprehensive multimodal treatment has significantly improved survival rates, especially in elderly patients and those with localized disease, resulting in a potential 50% probability of survival. Continuing research is now underway to investigate targeted therapies and identify promising molecules. For instance, the aurora kinase, which blocks the activity of certain molecules, has shown beneficial effects in some cases of recurrent or progressing AT/RTs, a kind of tumor [48]. The existing therapy for AT/RTs is inadequate. For older children, using a therapeutic strategy that combines prompt craniospinal radiation therapy following surgery with multiagent chemotherapy has led to 5-year survival rates of up to 50%. Nevertheless, most newborns get a mix of chemotherapy drugs that are also used for treating sarcomas and medulloblastomas in pediatric patients. Despite these efforts, the survival rates for infants remain very low. The neuroimaging features of AT/RTs may exhibit resemblances to those of medulloblastoma in the posterior fossa, germ-cell tumors, and supratentorial PNETs. Nevertheless, the outlook for AT/RTs is often bleaker compared to medulloblastoma.

1.5 Ependymomas

Ependymomas rank as the fourth most common tumors. Medulloblastoma, cerebellar astrocytoma, and brainstem glioma are the common kinds of brain cancers that often occur in the posterior fossa of young individuals. The main imaging characteristic used to detect an ependymoma is its enlargement via the openings of the fourth ventricular outflow. Acknowledging that this characteristic is not entirely restricted since certain medulloblastomas may potentially spread via these foramina is crucial. Ependymomas often have a bigger, rounded protrusion and restricted spread, unlike the smaller tissue expansion frequently seen in MBs. CT scans indicate the presence of small, pinpoint-like calcifications in over 50% of individuals diagnosed with ependymoma. The magnetic resonance imaging of these tumors shows heterogeneity, indicating the existence of many components, such as the possible findings, including solid tumor, cyst, calcification, necrosis, edema, or bleeding. Ependymomas and gliomas rank as the third most prevalent forms of brain tumors in children, comprising around 8% to 10% of all malignant tumors [49] in the CNS of young individuals. Neuroepithelial cancers may arise in the cerebral cortex, cerebellum, and spinal cord, impacting individuals of all age groups, including both children and adults. The majority of brain tumors in children are situated inside the cranial cavity, with around two-thirds of them being placed in the posterior fossa[50,51]. Individuals with neurofibromatosis type 2 (NF-2) have an increased susceptibility to the development of ependymomas inside their spinal cord. The clinical manifestation differs depending on the precise location of the tumor. Most children with tumors in the posterior fossa have symptoms that suggest increased pressure within the skull, including headaches, vomiting, enlargement of the optic disc, problems with coordination, and paralysis of several cranial nerves. On the other hand, individuals with supratentorial lesions may exhibit certain neurological abnormalities or suffer from seizures. Dissemination is seen in less than 10% of individuals upon initial diagnosis. Ependymomas arise from radial glial cells inside the ventricles' ependymal lining or the spinal cord's central canal. They are more prevalent in males under the age of 5. Children diagnosed with neurofibromatosis type 2 have a greater likelihood of developing spinal ependymomas. However, this connection is not seen in

intracranial ependymomas. The prognosis of ependymoma exhibits significant variability, particularly in infants who have very unfavorable outcomes, leading to a death rate above 50%. The WHO now categorizes ependymomas into four main categories based on histology. Ependymomas may be classified into many kinds, including subependymoma, myxopapillary ependymoma, classic ependymoma, and anaplastic ependymoma. In 2016, ependymomas with RELA fusion were categorized as a separate subgroup. DNA methylation profiling has recently been used to detect distinct molecular subgroups within each subtype, aiding in prognosis prediction. Of these options, persons diagnosed with infratentorial posterior fossa ependymoma group A (PF-EPN-A) or supratentorial RELA-positive ependymoma have less prognosis. PF-EPN-A, which mostly impacts newborns and young children, presents a notable surgical difficulty because of its position on the side, resulting in a considerable likelihood of recurrence. On the other hand, PF-EPN-B is often seen among teenagers and young people and typically has a more positive outlook. Ependymomas may cause symptoms in both the brain and spine in children since these tumors have the potential to form anywhere along the neuraxis. They constitute around 10% of all brain tumors in pediatric patients. Among juvenile patients, intracranial ependymomas, especially those situated in the posterior fossa, have a higher incidence than spinal tumors. Categorizing the risks of ependymomas according to age, location, and distinct physiological subtypes may be more appropriate than depending on the old WHO grading system, which treated them as a single kind of tumor with varying grades.

1.6 Craniopharyngioma

Craniopharyngiomas are benign tumors composed of epithelial cells. They arise from residual embryonic tissue known as the "Rathke pouch", located in the suprasellar area, close to the optic chiasm. Brain tumors in children account for around 5% to 10% of all brain tumors[52,53]. The symptoms manifest when nearby brain structures are squeezed, leading to visual problems, hormonal imbalances, panhypopituitarism produced by pressure on the pituitary gland or stalk, and indications of increased intracranial pressure owing to blockage of the cerebrospinal fluid channel.[54,55] Typical visual symptoms may include reduced clarity or irregularities in the visual field in either one or both eyes. These symptoms determine whether the tumor's solid or fluid-filled parts directly or indirectly interfere with the optic chiasm. The diagnosis is often established many months after the first manifestation of hormonal symptoms. Damage to the pituitary stalk may result in many abnormalities, including inhibited growth, compromised sexual function, lack of menstruation, and, less often, diabetes insipidus [56]. Tumors are often identified after reaching a significant size and commonly exhibit calcifications in the suprasellar region and one or more cysts. This disorder may be classified into two categories: adamantinomatous and papillary. The adamantinomatous form has a higher frequency of recurrence [57]. Despite being histologically non-malignant, juvenile craniopharyngiomas pose challenges in treatment due to their proximity to vital structures and the necessity for long-term management of treatment-induced late effects. The main treatment for this illness is surgery, which has a progression-free survival rate of over 85% after total excision. It is crucial to acknowledge that surgery might lead to cognitive difficulties and enduring hormone abnormalities. Malignant transition is rare, especially in young individuals. When total excision is not possible, radiation treatment offers a method for establishing long-term control. Less invasive alternative treatments include undergoing endoscopic cyst fenestration or the use of an Ommaya reservoir for the administration of antineoplastic or radiolabeled medications.

1.7 Choroid Plexus Tumors

Choroid plexus tumors are uncommon, accounting for fewer than 1% of all brain tumors and 3% to 4% of malignancies seen in young persons [58]. Patients often display signs of hydrocephalus resulting from the tumor's excessive secretion of cerebrospinal fluid (CSF), which may sometimes result in blockage.[59,60] The tumors in question are papillary neoplasms inside the ventricles and derived from the epithelial cells of the choroid plexus. Choroid plexus tumors may exhibit variations in their histological features. These growths are harmless and well-developed, specifically called choroid plexus papillomas (CPPs), and categorized as WHO grade I. They can also be categorized as atypical CPPs, officially defined as WHO grade II. Aggressive choroid plexus carcinomas (CPCa) are classified as WHO grade III. Roughly 50% of these tumors have their origins. Around 40% of the tumors develop in the fourth ventricle, whereas 5% are found in the third ventricle, and an extra 5% occur in several ventricles. An additional 50% of malignancies arise in the lateral ventricles. Extraventricular choroid plexus tumors are rare. However, they have been seen in various brain areas, such as the brainstem and posterior fossa. Li-Fraumeni syndrome individuals have a higher incidence of CPCa (Colorectal Prostate Cancer). However, most CPCa patients do not possess a TP53 gene mutation [61]. Cyclic polypeptides (CPPs) have been associated with aicardi syndrome, and a total excision of the tumor is often efficacious in treating choroid plexus papilloma (CPP), but, the highly aggressive nature of choroid plexus carcinoma (CPCa) poses challenges in achieving total eradication, requiring the use of further therapies. Although radiation therapy is effective, it is often avoided in young children. Combining chemotherapeutic drugs may delay or eliminate the need for radiation in this category. Although receiving treatment, the prognosis for individuals with CPCa remains grim, with a survival rate of less than 50% beyond 5 years

1.8 Spinal Cord Tumors

Spinal cord tumors occurring in children are uncommon, occurring in fewer than 1 out of every 100,000 children per year [62]. They make up less than 6% of all CNS malignancies in young people [63]. Diagnosing these cancers is challenging due to the vague and often elusive nature of the symptoms. Spinal cord tumors may result in local and distant symptoms by obstructing the pathways of the spinal cord that extend vertically. The symptoms often emerge gradually and may be particularly challenging to identify in neonates. While the duration of symptoms does not affect survival, it is typical for patients to have symptoms for more than 6 months before being diagnosed [64]. The severity of neurological deficits at the first evaluation is strongly linked to more unfavorable results after surgical procedures, emphasizing the need for prompt intervention [65]. Spinal cord tumors may be classified into three categories based on their location: The categorization

of spinal cord tumors has three primary classifications: Intramedullary, intradural-extramedullary, and extradural. Gliomas are the predominant kind of spinal cord tumors seen in children, whereas ependymomas are the second most frequent [66,67]. Surgical excision is the primary method to treat low-grade gliomas (LGGs) in the spinal cord. When total removal of a tumor is not possible, radiation and chemotherapy have shown a certain level of effectiveness. These therapies are often reserved for malignancies that grow after significant surgical intervention. After surgical removal, high-grade gliomas are often administered a regimen of radiation treatment and chemotherapy.

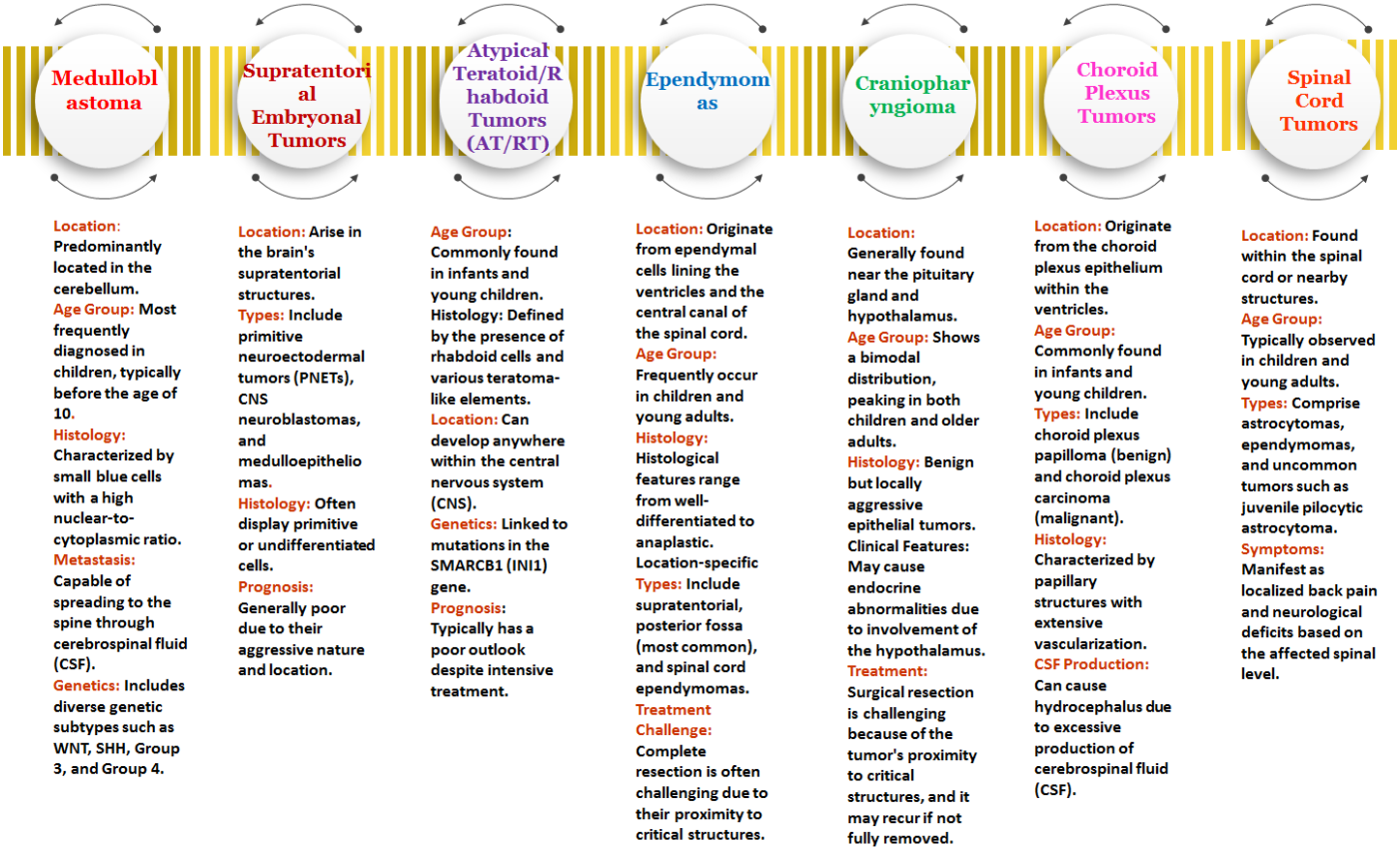

Fig 1: Unique features of Pediatrics brain tumors

2. SIGNS AND SYMPTOMS OF BRAIN TUMORS IN CHILDREN

Brain tumors in children may manifest a diverse range of indications and symptoms, which often vary based on the specific location of the tumor within the brain. Obstruction of CSF fluid flow by a developing tumor often results in increased intracranial pressure, which may manifest as chronic headaches, nausea, vomiting, and visual disturbances such as blurred or double vision. Tumors situated in the suprasellar area may result in visual field deficits and hormonal imbalances, which may manifest as development retardation, puberty disturbances, or other endocrine-related complications. Posterior fossa tumors, located near the brainstem and cerebellum, have the potential to disturb motor coordination, leading to ataxia, clumsiness, and challenges with balance and precise motor abilities. Tumors located in the cortical regions, namely in the frontal lobes, might present as seizures or observable alterations in personality and behavior [68]. These modifications might include increased irritation, sadness, or cognitive deficiencies, which can be misconstrued as developmental or psychiatric problems. In addition, children may exhibit symptoms such as muscle weakness or alterations in sensory perception in a specific body area, which is determined by the precise location of the tumor and the brain areas it impacts [69]. Scientists progressively acknowledge that comprehending a tumor's genetic and epigenetic traits might provide vital knowledge about its behavior, development patterns, and reaction to therapies. The current stage of evaluating brain tumors' genetic and molecular properties is nascent. However, it has significant promise. The emerging discipline has the potential to transform the treatment and results for children with primary brain tumors by enabling more accurate and focused treatments that are tailored to the unique genetic characteristics of each tumor. Customized therapeutic strategies have the potential to enhance effectiveness and minimize negative outcomes, providing a promising outlook for improved long-term predictions.

3. TREATMENT STRATEGIES

Although surgical procedures, radiation therapy, and advancements in medical treatments like chemotherapy have greatly improved, the chances of survival for individuals with medulloblastoma, a considerable number of patients still experience long-lasting neurological complications due to their tumors and the treatments they receive. Posterior fossa syndrome occurs in around 40% of cases after surgical excision and is characterized by cerebellar mutism, substantial dysfunction, and various palsies [70]. The exact cause is uncertain; however, it is believed to stem from disruptions during the removal of the tumor. Subjecting young children to radiation therapy increases the probability

of acquiring secondary brain tumors and has enduring effects on cognitive performance and cerebrovascular health. The progress in molecular categorization might aid in the risk classification process, thereby allowing for the implementation of tailored medicines. Scientists are now studying specific treatments for various subtypes of diseases, such as using SMO inhibitors to target malignancies within the SHH-subgroup [71-73]. Intensive screening efforts are concentrated on identifying drugs such as pemetrexed and gemcitabine for clinical trials to address group 3-subtype medulloblastoma, which is associated with the worst prognosis [74]. Currently, there are no groundbreaking therapies available for tumors of the Group 4-subtype. Performing molecular profiling is a crucial first step in creating effective medications. Surgery is the primary treatment for brain tumors in children. However, solid malignancies located outside the CNS often need significant resection. However, eliminating CNS malignancies might be challenging because of the risk of damaging healthy tissue and their proximity to vital structures. However, debulking surgery is often recommended for most brain cancers because adjuvant radiation treatment and chemotherapy provide optimal outcomes when the residual tumor mass is less. Radiation therapy for the brain might be focused on a particular region, applied to the whole brain, or given to the entire CNS based on the likelihood of the tumor spreading to the subarachnoid space. This tendency determines the size of the radiation area. Craniospinal radiation therapy is often used for cancers that have a substantial propensity to metastasize to other regions of the body. Examples of such tumors include high-grade fourth ventricle ependymomas and medulloblastomas. Certain malignancies, such as brain stem gliomas and low-grade supratentorial astrocytomas, are unlikely to spread to other body parts. On the other hand, some types of tumors, such medulloblastomas and high-grade fourth ventricle ependymomas, have a pronounced inclination to metastasize to other regions of the body. Conversely, tumors that have a minimal probability of metastasizing to other body areas, such as brain stem gliomas and low-grade supratentorial astrocytomas, are subjected to targeted radiation therapy. Treating brain cancers sometimes requires delivering large doses of radiation, often ranging from 4,500 to 5,500 rad, over six to eight weeks. The time, dosage, and extent of radiation therapy are regularly reevaluated. While chemotherapy is increasingly used in treatment, its immediate repercussions might be similar to or even more difficult than radiation therapy. However, the enduring effects are often less severe. Systemic administration of chemotherapeutic medicines may have limited effectiveness in treating brain cancers due to difficulty in penetrating the blood-brain barrier. Factors that enhance the transportation of drugs into the CNS include a small molecular size and a high lipid solubility, less binding to proteins in the blood plasma, and the lack of ionization at physiological pH values.

4. CONCLUSION

Pediatric central nervous system (CNS) malignancies, particularly brain tumors, pose a significant health challenge and are a leading cause of cancer-related deaths in children. These tumors exhibit diverse characteristics, making their classification and treatment complex. Recent molecular and genetic research advancements have improved our understanding of these tumors, leading to more precise classification systems. Techniques like proton nuclear magnetic resonance spectroscopy (MRS) offer non-invasive diagnostic tools for brain tumors, aiding treatment decisions. While progress has been made, challenges remain, especially in the treatment of aggressive tumors like medulloblastoma and atypical teratoid/rhabdoid tumors (AT/RTs). Continued research is crucial for developing targeted therapies and improving outcomes for children with CNS tumors.

5. AUTHORS CONTRIBUTION STATEMENT

Dr. Anand Mohan Jha contributed to the data extraction, analysis, and article preparation. Dr. Kumud Kumari contributed by being a part of writing the article.

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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