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A Review of the Management of Paediatric Brain Tumours

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ABSTRACT

Background: Brain tumours are the second commonest tumours in children, and are associated with high mortality rate. A large number of these brain tumours are undiagnosed, until they increase to considerable size, due to the expansible nature of the skull in the infants, and the capacity of the developing brain to compensate for neurological deficits. Most have non-specific neurological features. Magnetic resonance imaging (MRI) scan is the radiological investigation of choice. The management of paediatric brain tumours entails multidisciplinary measures. **Objectives:** This is aimed at a general review of the management of paediatric brain tumours. **Materials and methods:** This study involved a review of existing literatures using several search engines such as Google scholar, Hinari, Scopus, Pubmed and other research tools. The search word was 'paediatric brain tumour, and also another search was addition of 'Nigeria' to the earlier search words. **Results:** A total of 59 articles were seen which discussed childhood brain tumours, but 39 articles addressed paediatric brain tumours. Each was thoroughly reviewed and used in the framework of this manuscript. **Conclusion:** Paediatric brain tumours are heterogenous group of tumours, and presents with varied clinical features and most requires a multimodal approach of treatment.

Keywords: Tumour, Brain, Paediatric, Multidisciplinary

INTRODUCTION

Brain tumours are the most predominant tumours next to hematological tumours (leukaemia and lymphoma} in the paediatric age-group [1,2,3].These tumours are the commonest solid tumour accounting for about 50% of all tumours. The yearly incidence ranges from 2 to 5 cases per 100,000 (World Health Organization, WHO) [9]. This is comparable to a report from Ibadan (Western Nigeria) cancer registrar, which confirmed that central nervous system (CNS) tumours accounted for 2.5% of all newly diagnosed registered tumours [5]. Another study was conducted in south-

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eastern Nigeria, and it showed the incidence of brain tumour was 11.5 cases and 27 percent of these constitute paediatrics brain tumour [6].

The frequency, site, and histopathological types of gliomas differ by age. Generally, roughly 50% of all brain and spine cord tumours in children < 5 years are gliomas. Astrocytomas are the most common supratentorial tumours in children [1]. The frequency and type of brain tumours are dependent on the age group. In the neonate, for example, tumours of the neuroectodermal origin such as the teratomas are predominantly seen either in-utero or shortly after birth [3,4].

This can be juxtaposed with a study in Nigeria, the commonest histological type of brain tumour is glioma which accounted for about 37.5%. This was followed by medulloblastoma (24.1%), craniopharyngioma (20.4%) and meningioma (3.7%). The remaining 14.8% were rare tumors like seminoma, pineoblastoma, neuroblastoma, neurofibroma, rhabdomyosarcoma and pituitary adenoma. Glioma and craniopharyngioma are the most common supratentorial tumour while medulloblastoma and glioma are the commonest infratentorial tumour [7]. A similar study revealed, 73% of intracranial tumour of children between 0 - 14 years are astrocytic tumours, Ependymomas, medulloblastomas and craniopharyngiomas [5].

The incidence, pathophysiology, treatment, and outcome of childhood brain tumours vary by age, tumour grade, histological subtype, site, and extent of surgical resection. The histopathological diagnosis is of paramount importance for clinicians to choose the most appropriate treatment option, and tailored the treatment approach to disease risk [8]. However, histopathological evaluation is often tasking, hence the need to seek a second expert opinion when in doubt. Information on molecular sequence in addition to neuropathological analysis aid in ensuring accurate diagnosis, improving risk stratification of patients, and help in identifying novel therapeutic targets for an individualized treatment approach [1-4].

The site of tumour is the limiting factor for surgical versus non-surgical management, because outcomes for all grades of gliomas have shown that increased extent of resection improves patient's overall survival (OS) and progression-free survival (PFS) [4,9-11]. Other tumours that cannot be safely resected can be biopsied; if there is a need for tissue diagnosis. Patients with tumours that are unresectable, but causing symptomatic hydrocephalus can undergo palliative surgery such as endoscopic third ventriculostomy or shunting procedure [4].Paediatric brain tumours that are resectable with attendant presence of symptomatic hydrocephalus, initial cerebrospinal fluid (CSF) diversion two weeks before definitive tumour resection surgery is recommended on account of intracranial pressure control and CSF hydrodynamics. This will help to lower operative mortality. Not all patients with hydrocephalus from a posterior fossa tumour will require shunting as significant numbers have been observed in literatures not to be shunt-dependent post-operatively [3,4]. There is the possibility of malignant tumour cells seeding to the peritoneum, as is the case with medulloblastoma when shunting is done. A few shunts may become infected before the surgery, leading to delay of definitive treatment, thereby increasing hospital stay. An upward transtentorial herniation may occur, if there is excessively rapid CSF drainage. Complications that may arise from operative intervention include hydrocephalus and cerebrospinal fluid leakage. A re-operation is an option for brain tumours that recur [3,4].

METHODOLOGY

This study involved a review of existing literatures using several search engines such as Google scholar, Scopus, Hinari, Pubmed and other research tools. The search word was 'paediatric brain tumour', and also another search was addition of 'Nigeria' to the earlier search words.

RESULTS

A total of 59 articles were seen which discussed paediatric brain tumours, but 39 of these articles

addressed brain tumours in the paediatric age-group. Each was thoroughly reviewed and used in the framework of this manuscript.

Classification of Paediatric Brain Tumours

Brain tissue consist of two cellular tissues called "neuron" and "glia" which are derivatives of the primitive neuroectodermal layer. Glial cells are subdivided into four main groups: astrocytes, oligodendrocytes, ependymal cells, and microglia [4,9]. Brain tumours are sub-grouped according to cellular morphology and malignant potentials. One classification categorizes brain tumours into glial tumours and non-glial (neuronal) tumours.

The vast majorities of primary brain tumours originate from glial tissue and are called "gliomas" in general terms. Gliomas are sub-grouped as astrocytomas, oligodendrogliomas, or ependymomas according to their specific cells of origin. Histologically, central nervous system tumours are uniformly diagnosed and graded by the World Health Organization classification (WHO)

World Health Organization Classification of Tumours of the Central Nervous System, fifth edition	
Glioma, Glioneuronal tumour and Neuronal Tumours	
Adult-type diffuse gliomas	Astrocytoma, IDH-mutant
	Oligodendroglioma, IDH-mutant, and 1p/19pcodelated
	Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma, MYB or MYBL-altered
	Angiocentric glioma
	Polymorphous low-grade neuroepithelial tumour of the young
	Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high grade gliomas	Diffuse midline glioma, H3 K27-altered
	Diffuse hemispheric glioma, H3 G34-mutant
	Diffuse pediatric-type high –grade glioma,H3 G34-mutant
	Infant –type hemispheric glioma
Circumscribed astrocytic gliomas	Pilocytic astrocytoma gliomas
	High-grade astrocytoma with piloid features
	Pleomorphic xanthoastrocytoma
	Subependymal giant cell astrocytoma
	Chordoid glioma
	Astroblastoma , MN1- altered
Glioneuronal and neuronal tumours	Ganglioglioma
	Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
	Dysembryoplastic neuroepithelial tumour
	Papillary glioneuronal tumour
	Rosette forming glioneuronal tumour
	Myxoid glioneuronal tumour
	Diffuse leptomeningeal glioneuronal tumour
	Gangliocytoma
	Multinodular and vacuolating neuronal tumour
	Dysplastic cerebellar gangliocytoma (Lhermite-Duclos Disease)
	Central neurocytoma
	Extraventricular neurocytoma
	Cerebellar liponeurocytoma
Ependymal tumours	Supratentorial ependymoma
	Supratentorial ependymoma, ZFTA fusion positive
	Supratentorial ependymoma, YAP1 fusion positive
	Posterior fossa ependymoma
	Posterior fossa ependymoma , group PFA
	Posterior fossa ependymoma, group PFB
	Spinal ependymoma, MYCN-amplified
	Myxopapillary ependymoma
	Subependymoma

Table 1(a) WHO classification of brain tumours[9]

World Health Organization Classification of Tumours of the Central Nervous System, fifth edition	
Choroid plexus tumour	Choroid plexus papilloma Atypical Choroid plexus papilloma Choroid plexus carcinoma
Embryonal tumour	
___ Medulloblastoma	Medulloblastoma , molecularly defined - Medulloblastoma, WNT-activated - Medulloblastoma ,SHH-activated and Tp53-wildtype - Medulloblastoma,SHH-activated and Tp53 mutant - Medulloblastoma, non-WNT/non- SHH Medulloblastoma, histologically defined
Other CNS embryonal tumours	Atypical teratoid/rhabdoid tumour Cribriform neuroepithelial tumour Embryonal tumour with multilayered rosettes CNS neuroblastoma, FOXR2-activated CNS tumour with BCORinternal tandem duplication CNS embryonal tumour
Pineal tumours	Pineocytoma Pineal parenchymal tumour of intermediate differentiation Pineoblastoma Papillary tumour of the pineal region Desmoplastic myxoid tumour of pineal origin SMARCB1-mutant
Cranial and paraspinal nerve tumour	schwannoma neurofibromal paraganglioma
Meningiomas	meningioma
Mesenchymal , non-meningoepithelial tumours	Soft tissue tumours- Fibroblastic and myofibroblastic tumours, Solitary fibrous tumour Vascular tumour- Hemangioma and vascular malformations, haemangioblastoma Skeletal muscle tumours- Rhabdomyosarcoma Uncertain differentiation- intracranial mesenchymal tumour, FET-CREB fusion-positive, CIC- rearranged sarcoma Primary intracranial sarcoma, DICER1-mutant, Ewing sarcoma

Table 1(b) WHO classification of brain tumours

Chondro-osseous tumours	Chondrogenic tumours Mesenchymal chondrosarcoma Chondrosarcoma Notochondral tumours Chondroma(including poorly differentiated chondroma
Melanocytic Tumours	Diffuse meningeal melanocytic neoplasm Meningeal melanocytosis and meningeal melanomatosis Circumscribed meningeal melanocytic neoplasms Meningeal melanocytoma and meningeal melanoma
Hematolymphoid tumours **CNS Lymphomas**	Lymphomas Primary diffuse large B –cell lymphoma of the CNS Immunodeficiency –associated CNS lymphoma Lymphomatoid granulomatosis Intravascular large B-cell lymphoma
Miscellanous rare Large-B cell lymphoma	MALT lymphoma of the dura Other low grade B cell lymphomas of the CNS Anaplastic large cell lymphoma(ALK+/ALK-) T cell and NK/T cell lymphomas
Histocytic tumours	Erdheim-Chester disease Rosai-Dorfman disease Juvenile xanthogranuloma Langerhans cell histocytosis Histiocytic sarcoma
Germ Cell tumours	Mature teratoma Immature teratoma Teratoma with somatic type malignant Germinoma Embryonal carcinoma Yolk sac tumour Choriocarcinoma Mixed germ cell tumour
Tumours of the sellarregion	Adamantinomatous carniopharyngioma Papillary craniopharyngioma Pituicytoma, granular cell tumour of the sellar region and spindle cell oncocytoma Pituitary adenoma/PitNET Pituitary blastoma
Metastases to the CNS	Metastasis to the brain and spinal cord parenchyma Metastases to the meninges

Table 1(c) WHO classification of brain tumours [9]

Keys: ***CNS, central nervous system, IDH- isocitrate dehydrogenase, NK, natural killer, PitNET, pituitary neuroendocrine tumour, SHH- Sonic Hedgehog***

[8]. The most recent (2021) WHO classification of central nervous system tumours is as shown in Table 1.9

Based on location; Paediatric brain tumours may be supratentorial or infratentorial, and there are common examples of tumours in these parts of the intracranial spaces. Majority of these brain tumours are infratentorial (The medulloblastoma's, ependymoma's, pilocytic astrocytoma's, and other glioma's seen in the brainstem) and lesser number do have supratentorial tumours such as craniopgyaryngioma's, pilocytic xanthoastrocytoma's, choroid plexus tumours amongst others[4].

Pathology

The term 'glioma' is made up of a wide range of histological types and subtypes. The WHO classified gliomas as tumours of neuroepithelial tissue and includes astrocytomas, oligodendrogliomas, oligoastrocytomas, and ependymomas. Gliomas are often categorized as low or high grade tumours. Low-grade gliomas (LGGs) include WHO grade 1 gliomas such as pilocytic astrocytoma (PA), pleomorphic xanthoastrocytoma (PXA), ganglioglioma (GG), dysembryoplastic neuroepithelial tumor (DNET), and WHO grade II astrocytoma and oligodendroglioma. High-grade gliomas (HGGs) include anaplastic astrocytoma (AA), anaplastic Oligodendrogliomas and glioblastoma multiforme (GBM) [10,11]. Pilocytic astrocytomas are relatively circumscribed, slowly growing tumours, and often cystic, occurring in children and young adults. Histologically, it is characterized by two-phasic pattern with varying ratios of compacted bipolar cells associated with rosenthal fibers and loose-textured multipolar cells associated with microcysts and eosinophilic granular bodies/hyaline droplets [10,11]. PXA is an astrocytic neoplasm with a relatively favorable prognosis, typically encountered in children and young adults with superficial location in the cerebral hemispheres and involvement of the meninges; The characteristic histological features include pleomorphic and lipidized cells expressing glial fibrillary acid protein (GFAP) and often surrounded by a reticulin network as well as eosinophilic granular bodies [16,17].

Gangliogliomas are well differentiated slowly growing neuroepithelial tumours seen predominantly in childhood, and composed of neoplastic, mature ganglion cells in combination with neoplastic glial cells [12-14]. Dysembryoplastic neuroepithelial tumours (DNET) is a benign glial-neuronal neoplasm, and it is usually supratentorial in location, occurring in children or young adults characterized by a predominantly cortical location and by drug-resistant partial seizures; typically exhibiting a complex columnal and multinodular architecture, and it is usually associated with cortical dysplasia [16,17].

The grade II astrocytomas are the diffusely infiltrating astrocytomas that typically affect young adults and are characterized by a high degree of cellular differentiation and slow growth; the tumour occurs throughout the CNS, but is preferentially located in the supratentorial region, and has the ability to transform to anaplastic astrocytoma and ultimately glioblastoma [9,11].

The Oligodendrogliomas can either be low grade (WHO grade II) or high grade (WHO grade III).They are diffusely infiltrating well-differentiated gliomas typically seen in adults. The high grade Oligodendrogliomas are the anaplastic oligodendrogliomas and the anaplastic Oligoastrocytomas [10,11].

The Glioblastomas are high grade astrocytic tumours (WHO grade IV) that may manifest at any age including the paediatric age groups, but usually affect adults. They are the most frequent and most malignant primary brain tumour, with predominantly astrocytic differentiation. They are highly infiltrative, invasive and complete resection is a difficult task to achieve, and despite progress in radiotherapy and chemotherapy, less than half of patients survive more than a year, with older age as the most significant adverse prognostic factor [10-11].

Two commonest among these tumours seen in the paediatric age group are the medulloblastoma and ependymoma. They are usually seen in the posterior cranial fossa, and are more often midline vermian tumours arising from the roof and floor of the 4th ventricle respectively. The medulloblastomas are WHO grade IV malignant invasive embryonal tumour of the cerebellum with in the younger age group. They have predominantly neuronal differentiation and an inherent tendency to metastasize through CSF pathways [10,11]. Medulloblastomas are sub-classified into medulloblastoma (molecularly defined), medulloblastoma (WNT activated), Medulloblastoma (SHH-activated and TP53-wildtype), Medulloblastoma (SHH-activated and TP53-mutant), Medulloblastoma (non-WNT/non-SHH), and Medulloblastomas, (histologically defined).[9] Microscopically, medulloblastomas are composed of densely packed cells with round-to-oval or carrot-shaped hyperchromatic nuclei surrounded by scant cytoplasm with Neuroblastic (Homer Wright) rosettes observed in less than 40% of cases [12-13]. The medulloblastomas involving the peripheral cerebellar hemispheres may occasionally appear as extra-axial tumours simulating meningiomas or vestibular nerve schwannomas [10-12].Other histological patterns of medulloblastomas that have been described include desmoplastic medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma and large cell medulloblastoma [12,13].

The ependymomas are slowly growing tumours of childhood originating from the wall of the ventricles or from the spinal canal and composed of neoplastic ependymal cells. They are generally WHO grade II tumours, except for subependymoma and myxopapillary ependymomas which are WHO grade I tumours as well as anaplastic ependymomas which is grade III [16]. The Ependymomas are further sub-divided into Supratentorial ependymomas (ZFTA fusion-positive), Supratentorial ependymomas (YAP1 fusion-positive), Posterior fossa ependymomas (group PFA), Posterior fossa ependymomas (group PFB), Spinal ependymoma, (MYCN-amplified), Myxopapillary ependymomas, Subependymoma and anaplastic ependymomas [14,15]. The most common or classic pattern of ependymoma is a well-delineated, moderately cellular gliomas with a monomorphic nuclear morphology characterized by round to oval nuclei with "salt and pepper" speckling of the chromatin. Key histological features are perivascular pseudorosettes and ependymal rosettes.

Aetiopathogenesis

The developing brain continues maturation within the first three years of life and are susceptible to different type of tumour with no clear defined cause. Embryological-sensitive mutations linked to age and precise neuro-anatomical locations can account for childhood brain tumours. Tight junction between endothelial cells and surrounding astrocyte foot process make up the normal blood-brain barrier (BBB). The loss of the physiological astrocyte –endothelial cell relationship occurs in adult brain tumors and primary brain tumours. This has not been studied in pediatric tumour [18,19]. The aetiology of paediatric brain tumour is not known [6]. However, genetic and environmental causes have been implicated. Identified predisposing factors include Ionizing radiation, N-nitroso compounds, pesticides, tobacco smoke, electromagnetic frequencies, infectious agents, parental occupational exposures, and medications [16,17]. It is speculated that vitamins with antioxidant properties and folic acid have preventive effects against childhood brain tumours. The protective mechanisms related to vitamins C and E may be related to the prevention of nitrosing processes in vivo [9].

Some of these brain tumours are associated with known syndromes that have cancer predispositions. Neurofibromatosis and tuberous sclerosis have identified to be associated with gliomas in the paediatric age-group. Genetic syndromes such as neurofibromatosis, Li-Fraumeni Syndrome, Basal

cell nevus (Gorlin Syndrome), Turcot Syndrome or ataxia-telangiectasia make up only about 5% of the causes. Trauma, ionizing radiation, and electromagnetic fields have been identified as the main physical causes of paediatric brain tumours [16,17].

In most patients with pilocytic astrocytomas, there is a duplication of 7q34 that results in a *BRAF* and *KIAA1549* gene fusion. This fusion is a rare event in both paediatric and adult diffuse low-grade astrocytoma and enables pilocytic astrocytomas (PAs) to be distinguished from the former. In incompletely resected pilocytic astrocytomas, the presence of *BRAF-KIAA1549* fusion also results in longer progression-free survival than in those without the mutation. More infratentorial tumours have also been noticed to harbour this mutation than supratentorial tumours [3,4, 10,11,16,17].

Pathophysiology

Brain tumour which involves the brain parenchyma and cranial nerves in a varieties of ways such as through invasion of the parenchymal leading to their destruction, compression by the tumour mass or peri-tumoural oedema or haemorrhage. These will lead to progressive focal neurological deficits such as weakness of one or more extremities, dysphasia or cranial palsies resulting in characteristic clinical features. Frontal lobe involvement will manifest with abulia, dementia, personality changes, apraxia, hemiparesis, and aphasia (with dominant hemisphere involvement). Patients with temporal lobe involvement will present with auditory or olfactory hallucinations, déja vu or memory impairment. Parietal lobe involvement may manifest with contralateral motor or sensory impairment, homonymous hemianopsia, and agnosias. Patients with occipital lobe tumour may have contralateral visual field deficits and alexia. Posterior fossa involvement may manifest with cranial nerve deficits, ataxia (truncal or appendicular) and raised intracranial pressure [20].

The involvement of the cerebellar vermis result in truncal ataxia, broad-based gait, and titubation. Lesions in the cerebellar hemisphere such as pilocytic astrocytoma may cause ataxia of the extremities, dysmetria, and intention tremor. Brainstem tumours such as diffuse infiltrative pontine glioma or tectorial glioma usually results in multiple cranial nerves and long tract signs, and this should be suspected when nystagmus is present (especially rotatory or vertical).

The neural tissue is pain insensitive and not link to headache associated with intracranial masses. However, patients may complain of headaches. This may be as a result of increased intracranial pressure (from mass effect due the tumour, oedema or haemorrhage, or hydrocephalus), invasion or compression of pain-sensitive structures (dura, blood vessels, and pericranium). Compression or invasion of the brainstem may affect the cranial nerves especially the occulomotor, trochlear and abducent nerves which may lead to dysfunction of extraocular muscles manifesting with ophthalmoplegia. Invasion or occlusion of the brain blood vessels may result in stroke-like syndromes or transient ischaemic attack. There may be endocrine dysfunction when there is pituitary involvement. Abducent nerve palsy from may occur due to raised intracranial pressure [20].

Clinical Presentation

In general brain tumour manifest with headache, focal neurological deficits, abnormal stretch reflexes, seizures, motor status change, poor school performance, papilledema, visual impairment, vomiting, head enlargement and endocrinopathy [21].

There are varieties of ways paediatric patients with brain tumours present clinically. This depends on the age of the patient, the type and location of the tumour. They may be asymptomatic when they are small especially those less than a year due to the non-closure of the sutures until they have occupied significant space in the brain[7]. In children < 3 years old, loss of developmental milestones, failure to thrive, irritability, and macrocephaly are common. Children older than 3 years, may present with features of increased intracranial pressure (ICP), especially if the tumour is infratentorial [17-19].

The clinical features of brain tumours are those of raised intracranial pressure, stroke, or dysfunctions of the part of the brain involved.

Most brain tumour patients present with progressive neurologic deficits, usually motor weakness. The most common presenting manifestations are vomiting, arrest or regression of psychomotor development, macrocrania, and poor feeding/failure to thrive. They may also present with focal seizures which may become generalized as a result of cortical irritation of the location of the tumour. This is commonly seen in supratentorial tumours and rare with posterior fossa tumours or pituitary tumours. Patients may have headache with or without raised intracranial pressure. This is worsen in the morning due to hypoventilation during sleep, aggravated by straining or leaning forward and relieved by vomiting. This classical presentation of headache is seen in 8% of patients.

Most posterior fossa tumours present with signs and symptoms of increased intracranial pressure. These include headache, nausea, vomiting (due to either raised intracranial pressure from hydrocephalus or direct pressure on the vagal nucleus), papilloedema due to impedance of cerebrospinal fluid flow, gait disturbances, vertigo, and cranial nerve six palsy [3, 24,25].

Investigation

The investigation aims to identify the exact site, extent of the tumour, and help to define the aims of surgery, which can be either total resection on one hand, and partial resection or biopsy on the other hand. Brain computed tomography (CT) scan, which is quick to perform compared to brain MRI [5], which is often the primary diagnostic tool. CT is superior to MRI in defining skull involvement, or for demonstrating tumour-related calcifications (such as in craniopharyngiomas), and is extremely important when evaluating skull base tumours that may invade the skull [5]. Although CT scan can be used to diagnose a brain tumour, MRI is the preferred imaging in the paediatric population with brain tumours due to better resolution and characterization, and has the advantage of absence exposure to radiation. It may also help to differentiate low grade tumours from high grade especially gliomas [8,26,27] .However, brainstem gliomas can be diagnosed based on MRI alone without the need for tissue biopsy [8,27].

The sagittal and coronal images are particularly helpful for midline tumours because it shows the tumour relationship to the brainstem, the ventricular system, and other surrounding structures, and thus aiding in the planning of tumour surgery. When dealing with potentially metastatic tumours (such as germ cell tumours, ependymomas, and medulloblastomas) and spinal screening. Spine MRI should be completed along with cranial MRI to detect spinal metastases and leptomeningeal spread before blood enters the canal during surgery, and makes it more difficult to distinguish between blood and tumour [26,27].

Diffusion-weighted and perfusion MRI may help characterize the tumour, and assess treatment response. The intensity of the tumour could help in the diagnosis of the tumour. For example, both astrocytoma and oligodendrogliomas are hypointense to gray matter on T1 and hyperintense on T2 and usually do not enhance. Pleomorphic xanthoastrocytoma, ganglioglioma, and pilocytic astrocytoma commonly have cystic and solid components with an enhancing mural nodule [8].

A variety of other imaging tools are available and useful in the proper context. Brain ultrasound (US), especially in infants with open fontanelles, may serve as a screening tool, but an MRS (Magnetic resonance spectroscopy) is indicated for further evaluation. MRS has been used in various applications, for diagnosis, differentiation between tumour recurrence and radiation necrosis, tumour follow- up, and prognosis. The sensitivity and specificity of MRS are not high, and thus MRS can only be used as a complementary tool to other studies or histological diagnosis. Nuclear medicine has a role in diagnosis and follow-up for children with brain tumours. Bone scans can be useful for showing 'hot areas' for skull- involving tumours such as Ewing sarcoma and osteosarcoma. Fluoro-Deoxy-Glucose Positron Emission Tomography

(FDG-PET) scans show hypermetabolism related to tumours, but this technique has a low spatial resolution and is also a complementary investigation. Similarly, Single-photon emission computed tomography (SPECT) scans may show increased uptake, especially in astrocytomas, but this too serve as a complementary investigation.

Serum tumour markers are also useful in diagnosing few childhood tumours. Examples include the germ cell tumours markers such as alpha-fetoprotein (αFP), beta-human- chorionic gonadotropin (βHCG), and placental alkaline phosphatase (PALP) in the serum and CSF. These markers serves aid in some treatment protocols for decision-making, and for follow- up. Cerebrospinal fluid and serum assays of α-FP, β-HCG, and PALP is helpful in the diagnosis of pineal region tumours. This when positive, it can be used to monitor response during treatment [27].

Tumours involving the visual pathway may benefit from a pre-operative and post-operative neuro-ophthalmologic evaluation. Other haematological investigations that are useful in the management include clotting profile, full blood count and serum electrolytes.

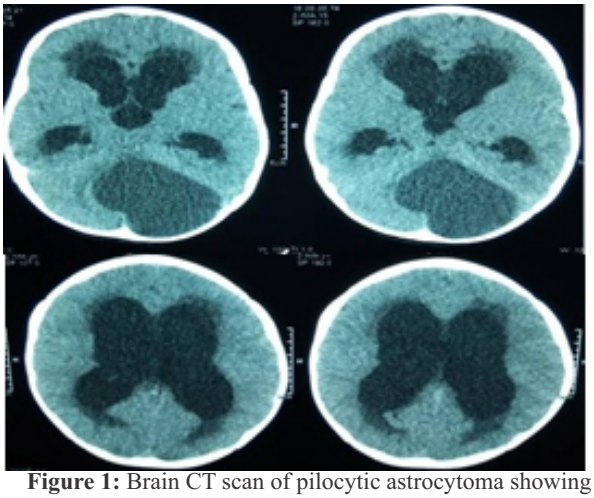

Figure 1: Brain CT scan of pilocytic astrocytoma showing a posterior fossa cystic mass more lateralized to the left cerebellum with features of acute obstructive hydrocephalus

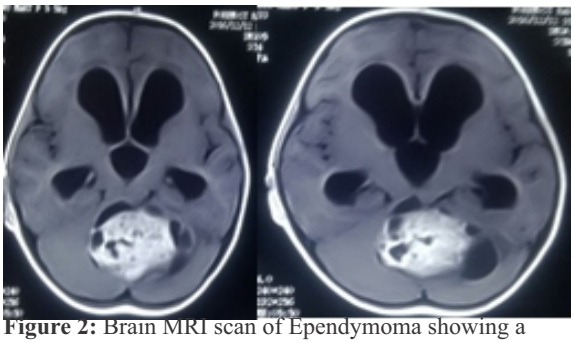

Figure 2: Brain MRI scan of Ependymoma showing a midline vermian heterogenous mass with areas of calcification in the floor of the 4th ventricle.

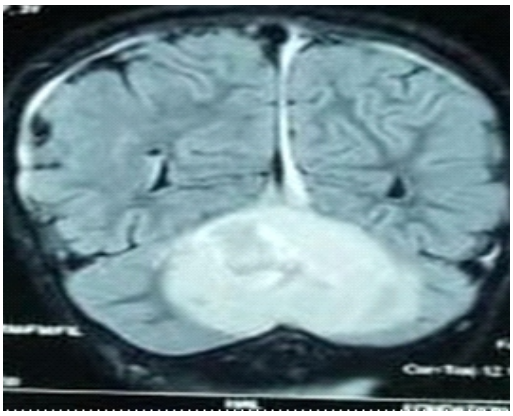

Figure 3: Brain MRI scan of Medulloblastoma showing a midline vermian mass draping the 4th ventricle with poorly heterogenous contrast enhancement.

Treatment

Treatment approaches for paediatric brain tumours differ depending on tumour types, patient demographics, and clinical context [3,25].These treatment options include surgery, chemotherapy, and radiotherapy. Surgery is considered the first treatment option for most types of childhood brain tumours, because both chemotherapy and radiotherapy pose risks for the developing brain compared to surgical resection [28, 29]. Patients with brain tumour may benefit from short course of steroids and anti-seizure drugs. Dexamethasone is a commonly used steroid in patient with vasogenic oedema and giving at a dosage ranging from 0.5–1 mg/kg/ intravenous as loading dose, and then

0.25–0.5 mg/kg/day per oral or intravenous 6 hourly. This drug dose can be doubled for patients already on steroid therapy [3, 25] ; this helps to reduce the vasogenic oedema and may improve outcome. Prolonged treatment with steroids should be avoided, because of the suppressive effect on children growth. About 20–40% of patients would have had a seizure by the time their tumour is diagnosed. Anti-seizure drugs may be of benefit for these patients. Prophylactic anti-seizure drugs do not provide substantial benefit and there are significant risks involved [30]. Each treatment approach is modified for the specific tumour types such as germ cell tumours, which are chemo-sensitive. The collection of CSF for cytology and tumour markers as seen in cases of pineal region tumours has important prognostic implications for those tumours. Note that lumbar CSF has much better predictive value and higher positively rate than ventricular CSF as regards tumour seeding [28,29,31]. 'The child is not a small adult,' and the neurosurgeon must be aware of the differences in surgical and anaesthetic techniques required for children compared to adults.

This particularly relates to the physiology and biochemical make-up of the paediatric age group airway. They are easily prone to hypothermia, hypovolemia, and anemia, all of which should be prevented. The young child needs a particularly gentle approach both in general body handling and during surgery, and blood loss is minimised with meticulous hemostatic techniques [3,25,28,29].Also, the sulci and Sylvian fissure are not well developed in young children and are not as readily used as planes of dissections or surgical corridors as compared to the mature brain. Surgical strategy varies and tumours that are treated solely by an aggressive surgical approach include some ependymomas, low- grade gliomas (including grade 1 and 2 astrocytomas), choroid plexus papillomas (including atypical), pituitary adenomas, and most meningiomas. However, certain tumours may not be amenable to total resection without significant associated morbidity, due to their invasive nature of critical structures, such as the brainstem, optic tracts, and hypothalamus. Some tumours such as high- grade gliomas, and medulloblastomas have a high recurrence rate, despite 'gross tumour resection'. This may be due to local tumour invasion or to concurrent metastasis as seen in medulloblastomas, and ependymomas [28,29,31].

Several paediatric brain tumours are diagnosed solely based on radiological and clinical appearance in the absence of biopsy. These tumours may be complicated with hydrocephalus which may need to be treated without tumour resection or biopsy. These include classical diffuse intrinsic brainstem glioma (DIPG), classic tectal glioma, bifocal tumour (pertaining always to germinomas), optic pathway glioma (especially when associated with neurofibromatosis type 1), and subependymal giant cell astrocytoma (when associated with tuberous sclerosis) [3,25,29].

Thus, over the years, various chemo-radiation adjuvant treatments have evolved [32,33]. Certain tumours are extremely sensitive to adjuvant treatments. Weighing the risks and benefits of the various treatments (including surgery, chemotherapy, and radiation therapy), the better judgment for some tumours is to treat mainly by chemotherapy and/ or radiation therapy, while surgery (if at all) is applied for diagnosis only. A good example of this is treating germ cell tumours with chemotherapeutic agents. These typical midline lesions occur either in the suprasellar area or in the pineal region. These tumours are extremely sensitive to chemotherapy and radiation [26,27-32]. Over the last few years, their diagnosis and treatment have shifted from surgical resection to diagnosis based on serum (or CSF) marker. Only if all biomarkers are negative is there an indication for a biopsy [12]. However, when presenting with obstructive hydrocephalus from aqueductal compression, these patients are treated by an endoscopic third ventriculostomy (ETV) and endoscopic biopsy [3,25,28,29].

Chemotherapy and radiation therapy are the most commonly non-operative treatment options for paediatric brain tumours. In general, radiation is

deferred as long as possible due to concerns of longterm sequelae, except in children > 3 years old with a high-grade tum our or an incompletely resected low-grade tumour [34-38]. For many childhood CNS tumours, radiation therapy plays an essential role in treatment, because chemotherapy or surgery cannot eliminate all the cancer cells [34]. Despite the beneficial effect of radiation therapy, there are potential, mostly long-term complications. The developing immature brain is vulnerable to radiation, particularly the white matter [9]. Neurocognitive decline, neuroendocrinopathy, cranial neuropathy, retinopathy, vasculopathy (including secondary moya moya disease), myelopathy, and spinal growth disturbance are all secondary to injury to the developing brain, spine, and adjacent structures [33]. Cavernous hemangiomas secondary to microvascular injury may occur. Secondary tumours (such as meningiomas, high- grade gliomas and thyroid carcinoma) occur due to various genetic insults and may occur many years after the radiation therapy. The risk of secondary tumours may be higher among syndromic children, such as those with neurofibromatosis and nevoid basal cell carcinoma syndrome.

Radiation therapy (RT) represents an integral component in the treatment of many paediatric brain tumours [34,35].Advances have emerged within paediatric radiation oncology that aim to optimize the therapeutic ratio improving disease control while limiting RT-related toxicity. These include innovations in treatment planning and execution with MRI simulation, as well as increasingly sophisticated radiation delivery techniques. Advanced RT techniques, including photon-based RT such as intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), as well as particle beam therapy and stereotactic RT, have afforded an array of options to dramatically reduce radiation exposure of uninvolved normal tissues while treating target volumes. Along with advances in image guidance of radiation treatments, novel RT approaches are being implemented in ongoing and future prospective randomized clinical trials [35-38]. When RT is indicated, the intent and target varies depending on several factors [35-39]. Among patients with embryonal brain tumours, such as those with medulloblastoma, adjuvant RT is recommended in the setting following resection, generally targeting the entire craniospinal axis as well as a boost to the tumour bed [15].The aim of craniospinal irradiation (CSI) in this context is to eradicate microscopic disease elsewhere in the CNS, given the propensity for seeding via CSF by embryonal tumours.[15]

For patients with high-grade tumours that are unresectable, such as the diffuse intrinsic pontine glioma (DIPG), RT remains the only therapeutic option available to delay progression and death. Thus, with a range of adjuvant, definitive, and palliative indications, RT plays an important role in the treatment of most childhood brain tumours.

Adjuvant chemotherapy like RT has become part of the protocol for most adult brain tumours, and in some paediatric tumours too. Since in the very young population, radiation therapy is associated with complications, the need to add adequate chemotherapy is even stronger. Chemotherapy may be used as a neoadjuvant treatment before surgery [25,33] especially in high-risk surgical patients such as infants harboring huge tumours as well as children with choroid plexus carcinomas. A group of patients in which chemotherapy has become a rightful alternative to surgical intervention is the case with tuberous sclerosis-associated subependymal giant cell astrocytomas (SEGAs). These tumours respond favorably to mTOR inhibitors (such as Rapamycin and Everolimus), with about 40% of patients having reduction in tumour volume by at least 50% over 6 months. mTOR has other positive effects on tuberous sclerosis patients, improving their seizures, renal tumors, rash, and even cognition, thus becoming a disease altering drug [34-36].

Chemotherapy with carboplatin and vincristine or 6-thioguanine, procarbazine, lomustine, and

vincristine is used before and has been shown to delay the need for radiotherapy when used in patients with high-grade glioma. Numerous chemotherapy regimens have been studied in children, and most provide modest benefit when combined with radiotherapy, but none has proven to be vastly superior [37-38].

Prognosis

Survival rates in paediatric brain tumours are dependent on histological grade, age at presentation, tumour site, the extent of resection, and use of adjuvant therapy. Overall, survival declines with increasing sequential histological grade and decreased extent of resection, with tumour grade and extent of resection being the most significant predictors of survival. Tumour site is also important in prognosis, largely as it is based on the ability for resection, with brainstem tumours having the worst rates of survival and cerebellar tumours having the best survival rates. Regarding patients' age, mortality increases with increasing age, except for children < 1-year old, who have the lowest survival rates [8,12,39].

CONCLUSION

Paediatric brain tumours represent a non-homogenous group of tumours, whose clinical and biological characteristics vary widely. Malignant brain tumours are the second most common form of cancers in children and thus one the leading cause of cancer mortality. The aetiology is unknown. Physical, chemical, and infectious agents have been implicated in tumourigenesis. They present with clinical features of raised intracranial pressure and dysfunction of the part of the brain involved. Multimodality therapy and multidisciplinary approach for these tumours consisting of neurosurgical resection, radiation therapy, and systemic chemotherapy or targeted agents is the mainstay of management. Neurosurgical resection alone may afford excellent outcomes for many benign or low-grade tumours that are accessible surgically, while combination approaches including surgery, radiation therapy, and chemotherapy are indicated for aggressive malignant tumours to achieve optimal outcomes.

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