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Paediatric Update

Gliomas

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INTRODUCTION

CENTRAL NERVOUS system (CNS) tumours are the most common solid neoplasms of childhood and account for 20% of all malignancies in this age group. Gliomas constitute 40–60% of all childhood primary brain tumours [1]. Low-grade astrocytomas are the most common neoplasms of childhood glial tumours [2]. Astrocytomas are seen more frequently in the supratentorial compartment, although the cerebellar hemispheres are also a common site for astrocytoma [3]. High-grade gliomas also predominantly arise in the supratentorial compartment, although brainstem gliomas are common malignancies arising in the infratentorial compartment. In this review we will discuss all histological types of paediatric gliomas including the different anatomical locations, treatment options and prognoses.

AETIOLOGY

The incidence for all paediatric brain tumours ranges between 2.4 and 3.5 per 100 000 children [4]. Glial tumours are classified histologically as astrocytoma, anaplastic astrocytoma (AA), subependymal giant cell astrocytoma, oligodendroglioma, ependymoma, choroid plexus, mixed glioma and glioblastoma multiforme (GBM).

The aetiology of the majority of childhood brain tumours remains obscure. However, children with phakomatoses such as neurofibromatosis and tuberous sclerosis are at higher risk of developing CNS tumours [2]. Approximately 35% of all children with optic pathway gliomas [5] and 70% of patients with intra-orbital glioma [6] have neurofibromatosis. Tuberous sclerosis is most commonly associated with cortical tubers and subependymal giant cell astrocytomas within the ventricular system.

A case-control study showed that relatives of children with CNS tumours are more likely to develop brain tumours or malignancies of the hematopoietic-lymphocytic systems compared with the general population [7]. Maternal exposure to nitrosamine-containing foods and drugs is another risk factor that increases the development of the astrocytoma [8]. A previous history of radiotherapy predisposes a child to developing meningioma, glioma or sarcoma later in life [9]. Classic examples include patients who received scalp irradiation for tinea capitis [10] and patients with acute lymphocytic leukaemia who received prophylactic radiation to the CNS [11].

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CLASSIFICATION AND HISTOPATHOLOGY

Bailey and Cushing were the first to separate epithelial tumours from neuronal and glial tumours [12]. Glial tumours are classified in a four-grade system, grade 1 being the most benign and grade 4 being the most malignant. It has also been proposed to grade gliomas on the basis of nuclear atypia, mitoses, endothelial cell proliferation and necrosis [13].

Optic pathway and diencephalic gliomas

Gliomas of chiasm, hypothalamus and thalamus constitute approximately 20% of all paediatric gliomas and are almost always low-grade [14]. Neoplasms of the thalamic region tend to be more aggressive than neoplasms in the hypothalamus, chiasm and optic pathway. Neoplastic symptoms usually last less than 1 year. The most common sign is increased intracranial pressure due to obstruction of the ventricles. Patients with tumours can present with hemiparesis, hemisensory loss, altered mental status, lateralising uncoordination, tremor, aphasia, dystonia and visual loss [2].

Pilocytic astrocytomas constitute the majority of hypothalamic gliomas. These tumours can invade the optic tracts and give both hypothalamic and visual signs and symptoms. Hypothalamic symptoms include failure to thrive, euphoria and hyperactivity and endocrine disorders such as diencephalic syndrome, obesity, diabetes insipidus, hypogonadism and precocious puberty [3].

Optic gliomas constitute 3–5% of all childhood intracranial tumours. Approximately 60–80% of optic pathway tumours involve the optic nerves, chiasm, and the optic tracts. These tumours can involve a single nerve or occur bilaterally or involve the whole chiasm [15]. The other 20–40% of optic gliomas occur in the prechiasmatic region [16]. 35–50% of children with optic gliomas are associated with neurofibromatosis [17]. Optic gliomas can be seen in patients between the ages of 9 months to 21 years. The common presenting symptom is diminished visual acuity.

Cerebral and posterior fossa low-grade gliomas

Nearly 25% of paediatric brain tumours involve the cerebral hemisphere with low-grade gliomas constituting the largest

group [18]. Low-grade gliomas are divided into four histological subgroups: pilocytic astrocytomas, fibrillary and protoplasmic astrocytomas, low-grade oligoastrocytomas and oligodendrogliomas. More recently, tumours such as gangliogliomas and pleomorphic xanthoastrocytomas have also been categorised as low-grade gliomas [3].

Astrocytomas are comprised of a moderately cellular background of astrocytes with little pleomorphism. The most common microscopic pattern is the fibrillary astrocytoma which most often occurs in the cerebellum, brainstem and hypothalamus. Pilocytic astrocytomas are considered grade I and are almost entirely found in the paediatric age group. They are characterised by long, spindle-shaped cells, eosinophilic cell bodies and endothelial proliferation [2]. They are mostly located in the cerebral hemispheres, optic pathways and hypothalamus. One of the other common low-grade gliomas is ganglioglioma which is often located in the temporal lobe and associated with seizures [19]. It is comprised of a non-pleomorphic astrocytoma background intermixed with ganglion cells. A pleomorphic xanthoastrocytoma is a superficially located astrocytoma which is frequently contiguous with the leptomeninges [20]. Astroblastomas are rare cerebral hemispheric tumours which follow an indolent course [21].

The dysembryoplastic neuroepithelial tumour and the desmoplastic infantile ganglioglioma have been recently subcategorised [22, 23]. These two tumours have limited growth potential and tend to occur in children less than 2 years of age. Desmoblastic infantile gangliogliomas are sharply demarcated tumours which may have dural attachment [24]. Clinical presentation of desmoblastic infantile gangliogliomas is highly dependent on its location. Intractable epilepsy is common with gliomas of temporal and frontal lobes [3]. Nonspecific headaches and focal neurological compromise are other common signs of temporal and frontal lobe gliomas.

Supratentorial malignant gliomas

Anaplastic astrocytoma and glioblastoma multiforme (GBM) constitute the majority of malignant gliomas and account for 6–10% of brain neoplasms in children [25]. A study of 50 paediatric supratentorial malignant gliomas showed that GBM has a lower frequency than AA in children. There was a high incidence of second malignant neoplasms, leptomeningeal spread and intratumoral haemorrhage. Child GBMs had a more favorable prognosis compared with adult GBMs [26]. Malignant gliomas predominantly occur in older children and teenagers. The most common predisposing factor is a previous low grade glial tumour [26–28]. The second most common predisposing factor is previous radiation therapy [29]. There is some clinical and genetic evidence that acute lymphocytic lymphoma and GBM can be seen either in the same patient or occur more commonly in some families. Some genetic disorders such as retinoblastoma and neurofibromatosis predispose patients to the occurrence of second CNS neoplasms.

AAs are characterised by increased cellularity, pleomorphism and mitotic figures whereas GBMs display haemorrhage, necrosis and fatty degenerative changes in addition to AA characteristics [13]. Gemistocytic astrocytomas are comprised of 50% or more plump astrocytes and they behave clinically as an anaplastic tumour. GBMs infiltrate the CNS through white matter tracts and corpus callosum [30]. Cell proliferation kinetics in gliomas using a double-label method such as bromodeoxy uridine (BUdR) index and iododeoxyuridine correlates well with malignancy potential [31].

Headaches, seizures and vomiting are the most common presenting symptoms of supratentorial malignant gliomas [2]. Focal motor or sensory deficits or signs related to the area of the cortical involvement are other common clinical findings. The duration of the symptoms is longer with supratentorial gliomas than with infratentorial gliomas.

Ependymomas

Ependymomas constitute 6% of all intracranial tumours in children and adults [32]. They typically occur at ages younger than 5 years [33]. The mean age of children with fourth ventricular ependymomas tends to be younger than children with ependymomas in other locations [34]. Supratentorial ependymomas are less frequently seen tumours than infratentorial ependymomas. Infratentorial ependymomas typically arise from the roof, floor and lateral recesses of the fourth ventricle. Supratentorial ependymomas arise from the ependymal lining of the lateral and third ventricles.

Low-grade ependymomas are cellular tumours with regular, round nuclei and sometimes cilia. Ependymal rosettes and perivascular pseudorosettes are diagnostic of low-grade ependymomas [2]. High-grade or malignant ependymomas have the typical features of ependymomas but also include pleomorphism, necrosis, mitosis and giant cells. They have an increased mitotic index and a dense cellularity which usually indicate a higher recurrence rate. They tend to occur more commonly in the supratentorial regions.

Nausea, vomiting and headaches are the most common nonspecific symptoms both in supratentorial and infratentorial ependymomas. Balance problems, neck stiffness and coordination problems are more common with infratentorial ependymomas whereas focal motor weakness, visual disturbances and seizures are more common with supratentorial ones [35].

Brainstem gliomas

Brainstem gliomas comprise 20% of all posterior fossa tumours of childhood and predominantly arise in the pons [36], typically involving the sixth and seventh cranial nerves associated with or without long tract signs [3]. When brainstem glioma involve the medulla they cause speech and swallowing difficulties. Hydrocephalus occurs approximately in one third of the patients at the time of diagnosis.

There are three subtypes of brainstem gliomas, the most common involving diffuse infiltrative lesions. Histologically, this subtype is predominantly low-grade but has discreet malignant areas [36]. The second subtype comprises 10% of cases and tends to arise in the cervicomedullary region and extend exophytically from the dorsal surface of the brainstem. Ataxia may be the earliest finding in these cases. The third subtype occurs in the high midbrain, involving the tectum [37]. Patients with this subtype mostly present with hydrocephalus and rarely with focal neurological findings. The second and the third subtypes are more likely to be histologically benign [38].

MOLECULAR BIOLOGY OF PAEDIATRIC BRAIN TUMOURS

Adult astrocytomas which progress from low-grade to high-grade show loss of the short arm of chromosome 17 in 40% of

AA and 30% of GBM cases [39]. However, most paediatric pilocytic astrocytomas do not contain 17p deletions [40]. These tumours rarely show deletion of 17q which includes the gene for type I neurofibromatosis [41]. It has been hypothesized that the protein product (neurofibramin) of the *NF1* gene functions as a tumour suppressor gene. The mutations of the *NF1* gene lead to increased cell proliferation and tumour formation [42]. Juvenile pilocytic astrocytomas show a high frequency of gains in chromosomes 7 and 8 [43] whereas diffuse fibrillary astrocytomas show none. Only 14% of paediatric astrocytomas of all grades and 16% of non-pilocytic astrocytomas have loss of heterozygosity (LOH) of 17p [44]. It has been also demonstrated that the incidence of *p53* mutation is statistically significantly lower in paediatric astrocytomas than the adult astrocytomas [45]. Very few of these tumours show LOH for chromosome 10 [46] and no amplification of epidermal growth factor receptor has been noted in any paediatric tumour. Chadduck and colleagues found multiple chromosome 1 and 7 abnormalities in paediatric malignant gliomas [47]. These results suggest different pathways leading to paediatric astrocytomas.

In contrast, brainstem gliomas resemble adult glioblastomas as LOH of chromosome 17p and 10 and *p53* mutations have been demonstrated in these tumours [48]. In ependymomas, loss of chromosome 22 is the most frequently detected abnormality [49]. Another study showed an association between SV40 viruses and ependymomas [50]. The SV40 large T antigen inactivates the two tumour suppressor genes, *p53* and the retinoblastoma susceptibility gene product ($p110^{rb}$), inducing tumour production [51, 52].

SIGNS AND SYMPTOMS

Tumours in the cerebral hemispheres produce symptoms referable to the involvement of the specific cortical region. Seizures are common in tumours arising from the temporal lobes or adjacent to the motor or sensorimotor cortex. The most common type of seizures are generalised tonic–clonic, simple and complex partial seizures. Low-grade tumours tend to present with seizures more commonly than the high-grade tumours.

Tumours of the optic chiasm or hypothalamus cause visual and behavioural disturbances, endocrinopathies and appetite and thirst dysregulation. Thalamic tumours cause tremor and increased tone in the contralateral side. Thalamic pain syndrome, common in adults, is rare in children. Although headaches are often nonfocal and generalised, focal headaches reliably indicate the malignant tumour location in up to 93% of patients [53].

Posterior fossa tumours cause headaches associated with nausea, vomiting and lethargy due to the increased intracranial pressure. This is due to the obstructive hydrocephalus caused by the tumours of the third ventricle, aqueduct of Sylvius and brainstem gliomas. Papilloedema can be a late neurological sign. Cerebellar astrocytomas cause truncal and/or limb ataxia and other coordination problems.

TREATMENT

Treatment, as in adults, of paediatric brain tumours consists of surgery, radiation and chemotherapy. In young children less than 3 years of age, chemotherapy is a feasible option which may produce a response or stabilisation of the tumour and potentially preclude use of radiotherapy.

Low-grade astrocytomas

The treatment of choice for low-grade cortical neoplasms is surgical resection [54]. Optimal treatment following partial resection is still controversial. Although a protocol was designed to randomise patients with subtotal resection of a low-grade glioma to observation versus radiotherapy, patient and/or physician bias precluded enrolment of adequate patient numbers to answer this question [3]. The Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) jointly decided to observe patients with totally resected low-grade cortical tumours with no further therapy.

In a study of 71 children with low-grade cerebral hemispheric gliomas, it was concluded that complete tumour resection provides the best opportunity for long-term progression free survival PFS [55]. Even with incomplete tumour resection, long-term PFS could be achieved. Poorer results were seen in the patients with tumours other than pilocytic astrocytoma. Although radiation therapy after incomplete resection appeared to increase the likelihood of long-term PFS, overall survival did not improve significantly. In addition, children who received radiation demonstrated a higher incidence of late cognitive and endocrine dysfunctions.

Although pilocytic astrocytomas are indolent low-grade glial neoplasms, they cause serious problems when they are located in deep structures or disseminate to the leptomeninges. Adjuvant chemotherapy can be used when surgery with or without radiation is inadequate. High-dose cyclophosphamide has shown significant benefit in treating pilocytic astrocytomas metastatic to the leptomeninges [56].

Management for optic pathway and hypothalamic/chiasmatic gliomas includes observation, surgery, irradiation and chemotherapy. Radiation has been standard therapy for progressive tumours at these sites. However, late effects of radiation such as endocrinopathy, vasculopathy, optic nerve damage, injury and radiation-induced second neoplasms, generated interest in using chemotherapy for these patients. This is especially true for the patients under the age of 5 years who are at more risk for long-term sequela from radiation therapy. Janss and associates showed that chemotherapy with vincristine plus antinomycin-D (AMD) could delay the radiotherapy and reduce radiation induced neurological morbidity but 60% of the children eventually relapsed [57]. In this study, 33% of the patients had neurofibromatosis-1 with more indolent disease.

Actinomycin-D, an antibiotic that binds to DNA and prevents transcription and vincristine, an alkaloid that inhibits mitoses by binding to microtubular proteins were used in combination to treat low-grade astrocytomas of the diencephalon. 62% of children with hypothalamic/chiasmatic gliomas showed regression or stabilisation of the disease. PFS was 3 years [58].

Nitrosoureas are alkylating agents that inhibit DNA and RNA synthesis. They are used in different combinations with other agents in the treatment of both low- and high-grade astrocytomas. Prados and associates added dibromodulcitol and 6-thioguanine into PCV (procarbazine plus CCNU plus vincristine) and treated 41 children with low-grade astrocytomas prior to radiation therapy. 38 children had either a response or stabilisation of the disease. Median time of the response was 2 years and toxicity was minimal [59].

Carboplatin is another alkylating agent which has been shown to have activity against low-grade gliomas, particularly

optic gliomas. 50 children with progressive optic glioma had a high response rate when treated with single agent carboplatin prior to radiotherapy [60]. Carboplatin was also used in combination with vincristine in both recurrent and newly diagnosed low-grade gliomas [61]. 12 of 23 children with recurrent disease showed a response with a duration ranging from 15–36 months. 5 children had stable disease. 23 of 37 children with newly diagnosed tumours showed a response which ranged between 18 and 35 months. 13 children had stable disease. Myelosuppression caused by carboplatin and vincristine neurotoxicity were the most common side-effects.

Chemotherapy of recurrent low-grade gliomas has been proven to produce relatively long-term disease stabilisation. Lefkowitz and associates used CCNU and vincristine in 6-week cycles for a maximum of eight cycles in children with recurrent high- and low-grade gliomas [62]. No benefit was seen for high-grade gliomas but 7 of 10 children with low-grade glioma responded. The most common toxicity observed was reversible bone marrow suppression.

High-grade astrocytomas

Children with high-grade astrocytomas have a better prognosis than adults, with a median survival ranging from 15–42 months and PFS between 7 and 18 months. Campbell and colleagues showed that the extent of resection at initial operation was significantly associated with PFS and overall survival [63]. In this study, the patients who underwent subtotal (< 90%) and near-total (90–99%) resection had median PFS of 5.5 and 11 months, and overall survivals of 10.5 and 25 months, respectively. The patients who had gross total resection had no disease progression during the follow-up period (84 months). All totally resected tumours were within the cerebral hemispheres. The prognosis is poorer for the deeply-seated lesions and subtotally resected hemispheric tumours even with the use of adjuvant therapy.

Radiotherapy alone causes long-lasting disease control in less than 25% of patients with complete resections and poorer control for patients with partially unresectable tumours. Alternative radiotherapy techniques such as brachytherapy and focused radiosurgery are currently being investigated. In a study done with high-activity ^{125}I brachytherapy in primary and recurrent paediatric brain tumours, the median survival was between 8 and 37 months for the newly diagnosed GBM patients and 7–21 months for recurrent GBM patients [64]. The main drawback was focal necrosis caused by the high radiation requiring re-operation.

BCNU (carmustine), CCNU (lomustine), procarbazine and vincristine are the most commonly used FDA approved chemotherapy agents for both newly diagnosed and recurrent malignant gliomas. In newly diagnosed glioblastoma multiforme, BCNU alone was as effective as combination therapies [65]. However, a subset of malignant glioma patients (anaplastic gliomas) showed a better survival when PCV was used compared with BCNU alone. The CCG demonstrated improved survival (46%) after gross total resection in children treated with radiation and adjuvant chemotherapy (CCNU plus vincristine plus prednisone) compared with radiation alone (18%) [18]. Another CCG study compared eight-drug-in-one-day therapy before and after radiotherapy with adjuvant chemotherapy during and following radiotherapy with CCNU and vincristine [66]. There was no difference in survival between the two groups but survival was still better than with radiation alone. Based on these two randomised studies, it was proposed to administer adjuvant chemotherapy routinely following radiation.

Currently, no conventional dose chemotherapy is effective for recurrent paediatric malignant gliomas. Finlay and associates showed greater than a 40% response rate in children with recurrent high-grade gliomas treated with high-dose carmustine, thiotepa and etoposide followed by autologous bone marrow rescue [66]. However, there was increased morbidity and mortality with this regimen. High-dose chemotherapy (thiotepa and cyclophosphamide) and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly diagnosed malignant glioma patients failed to show any benefit compared with the conventional therapies [67].

Topoisomerase I inhibitors may play roles in the treatment of brain tumours. They are potentially effective agents and are also radiosensitisers [68]. The Radiation Therapy Oncology Group (RTOG) and the CCG are both currently running phase I studies for malignant gliomas where topotecan is delivered intravenously (i.v.) daily 30–120 min prior to irradiation in order to maximise tumour drug concentrations at the time of the radiation treatment. Unfortunately, topotecan alone has been shown to be inactive against high-grade gliomas and brainstem tumours [69].

Cyclophosphamide, which is commonly used in the treatment of primitive neuroectodermal tumours, has shown modest activity against malignant gliomas [70–72]. A phase II study with thiotepa showed some stabilisation of malignant gliomas, ependymoma and brainstem glioma but no objective responses [73].

Brainstem gliomas

The diffuse pontine type gliomas are very resistant to chemotherapy and radiation therapy. Surgical intervention has no established role and radiotherapy is still the mainstay of treatment. The usual radiotherapy dose is 54 Gy given over 6 weeks [74]. Although clinical improvement is seen in approximately 75% of patients, median survival is less than 1 year. Hyperfractionated radiotherapy has been tested and it has been suggested that, at intermediate dose levels of 70.2 and 72 Gy it may show minimal, if not trivial, improved efficacy [75]. Different studies done with CCNU plus 5-FU [76], vincristine plus CCNU plus prednisone [77], cyclophosphamide plus cisplatin [78] and high-dose chemotherapy with stem cell rescue [79] showed no significant benefits. Future considerations include radiosensitisers, dosage intensification of the chemotherapeutic agents and potentially synergistic drug combinations.

Ependymomas

Radiotherapy is the standard intervention for totally resected ependymomas. Ependymomas display modest sensitivity to carboplatin and cisplatin [80]. Evans and associates randomised patients to receive or not to receive adjuvant chemotherapy (cisplatin plus lomustine plus prednisone) after surgery and craniospinal radiation, but failed to show any improved long-term outcome [81]. The POG study showed a response rate of 48% to cyclophosphamide and vincristine combination therapy [82]. A phase II study with combination of cyclophosphamide, cisplatin, vincristine and etoposide is currently under investigation in children with partially resected intracranial ependymomas [79].

Chemotherapy for infants

Infants have more biologically aggressive malignancies which make them more resistant to therapy. In addition, they suffer from cognitive deficits, the long-term effects of radiation therapy if they start at very young ages [83]. Because of this, POG evaluated 200 children less than 3 years of age who had malignant brain tumours (of all histological types) [82]. These children were treated postoperatively with cyclophosphamide, vincristine alternating with cisplatin and etoposide followed by delayed radiation. 39 of 102 evaluable children showed complete or partial responses. The best responses were achieved in malignant gliomas (60%), choroid plexus carcinoma (60%), medulloblastoma (48%) and ependymoma (48%).

The CCG did another study using eight-drugs-in-one-day chemotherapy (cisplatin, cyclophosphamide, vincristine, hydroxyurea, procarbazine, methylprednisone, cytosine arabinoside and CCNU), all given in the same day prior to radiation [84]. 7 of 25 patients responded with a response rate and 3-year PFS was lower than the POG study.

CONCLUSION

Paediatric gliomas comprise a broad spectrum of tumours which occur at different sites, demonstrate different histologies and have biologically distinct behaviour. Progress has been made in the treatment of virtually all of these tumours with the exception of brainstem gliomas and glioblastoma multiforme. It is critical that children with these tumours be referred to centres actively invested in the care of children with brain tumours. Nihilism with regard to the effectiveness of treatment of children (and adults) with brain tumours is very pervasive and only through referral to centres committed to the investigation and treatment of children with these neoplasms will progress be made.

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