CURRENT TOPIC

Clinical management of brain stem glioma

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Brain and spinal tumours in childhood (0–15 years) account for 20–25% of childhood cancer, affecting one in 2500 children. In the UK, this means that about 350 new cases are diagnosed each year, of which 55% and 50% survive five and 10 years, respectively.¹ For those who are survivors, about 60% have cognitive deficits and 20–30% have difficulties with mobility and chronic pain.² Deaths from this group of tumours in England and Wales account for the loss of over 10 000 life years each year (C Stiller, personal communication, 1995).¹

Within the group of brain and spinal tumours there are a number of well defined categories with characteristic clinical presentations, biological behaviour, and suitability for specific treatment approaches. These factors combine to predict a range of outcomes from the highly curable tumours (> 80% 10 year survival rate) such as germinoma and cerebellar astrocytoma, through to the virtually incurable brain stem glioma.¹ Age at presentation is also a crucial factor affecting both prognosis and treatment selection, especially for those who develop tumours early in life before the brain has completed growth and development.³

Brain stem gliomas account for about 10% of all brain and spinal tumours.¹ The selection of brain stem glioma for this article was prompted by difficulties surrounding its clinical diagnosis, both professional and lay uncertainty about optimal surgical management, ineffectiveness of non-surgical treatment, clinical difficulties with good palliative care, and a historical lack of clear guidance about optimal referral patterns to children's cancer centres, where appropriate resources have already been centralised for children's cancers of other organs.^{4–5} We define the brain stem as extending from the midbrain (tectal plate) to the medullary cervical junction (fig 1A). Therefore, brain stem glioma is a term describing a collection of anatomically related tumours with characteristic appearances on computed tomography (CT) and magnetic resonance imaging (MRI) scans. Because they are frequently not biopsied, "glioma" is used as a "catch all" term unless a histological diagnosis has been made.

Establishing the diagnosis

The ready availability of modern neuroimaging makes confirmation of the clinical diagnosis of

a brain stem tumour in a child very simple as long as the need for such imaging is identified by correct attention to the presenting clinical features. Diagnosis by MRI gives clear definition of the site, extent and direction of growth, as well as the nature of the tumour—for example, focal, diffuse, solid, or cystic (fig 1B and C).⁶

Symptoms at presentation relate to the level of the lesion in the brain stem (midbrain, pons, or medulla) and the rate and direction of growth of the tumour. Late diagnosis by a general practitioner, paediatrician, or other specialist may be a problem if there is a lack of appreciation of the importance of symptoms and signs,^{7–8} and can lead to enhanced distress for the child and parents.

Most cases of posterior cranial fossa tumour in children present predominantly with features of raised intracranial pressure, and focal neurological symptoms take second place. However, in most cases of brain stem glioma the converse applies. Common presenting symptoms are those of cranial nerve dysfunction producing any or all of the following: eye movement disturbance, diplopia, facial weakness, facial sensory loss, dysphagia, and dysarthria.⁹ These might initially suggest disturbance of a single cranial nerve and lead to an erroneous diagnosis such as benign squint, Bell's palsy, or other postviral syndromes. The appearance of such symptoms without obvious cause should always be taken seriously and be pursued by referral to a paediatric neurologist or paediatric neurosurgeon, or by definitive investigation using MRI.

Other symptoms might include weakness and/or ataxia of one or more limbs signifying involvement of the corticospinal pathways and cerebellar connections, respectively. Headache and vomiting can occur, although clinically raised intracranial pressure and papilloedema are relatively unusual, except in later stages of disease progression. A fluctuating course is common and can give rise to confusion with inflammatory pathologies.¹⁰ Similarly, changes in mood and behaviour recognised by the family are common and can precede more obvious neurological features. It is not uncommon for these to be attributed to life events, which can distract the family and doctors from the more specific symptoms when they develop. More prolonged histories (several weeks to several months) indicate slower growing tumours.

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Figure 1 (A) Line drawing of brain stem showing the ventricular system as the shaded area, the boundaries of the midbrain (MB), pons (P), medulla (MD), and cervicomedullary junction (C/MD). (B) Magnetic resonance imaging (MRI) scan showing transverse view of diffuse pontine glioma. (C) MRI scan showing sagittal view of focal pontine glioma.

Faster growing tumours can precipitate dramatic neurological deterioration over a few days to weeks. In younger children (< 3 years old) failure to thrive, often associated with

unexplained vomiting, may be mistaken for a gastrointestinal or nutritional problem. The motor symptoms can then be regarded incorrectly as developmental delay secondary to the poor state of nutrition and a further delay in diagnosis follows.

The exceptions to the above patterns of presentation are tumours of the tectal plate of the midbrain and dorsally exophytic growths of the medulla, both of which produce raised intracranial pressure caused by hydrocephalus as the major symptom.

NEUROFIBROMATOSIS TYPE 1

Patients with neurofibromatosis type 1 (NF-1) have a predisposition to develop astrocytic tumours, which most commonly occur in the region of the hypothalamus/optic chiasm. They can also occur, less frequently, in the brain stem.¹¹ They can be confused with unidentified bright objects on MRI, which can enlarge and recede during childhood and adolescence. Treatment with radiotherapy may be associated with enhanced neurotoxicity. A cautious approach is recommended, reserving radiotherapy for patients with troublesome symptoms that are clearly linked to tumour progression.^{12 13}

The role of surgery

GENERAL

As with all central nervous system tumours in childhood the role of surgery is directed at the control of raised intracranial pressure, the provision of tissue for accurate histological diagnosis, and the physical reduction of tumour burden with the intention of improving focal neurological dysfunction. The actual role of surgery relates to the site of the lesion and its gross morphological characteristics as judged on MRI. Detailed gross morphological classification of brain stem tumours is now possible with both CT¹⁴ and MRI.^{6 15} Subgroups identified by site and imaging characteristics require specific management (table 1; fig 1). Whenever tumour debulking is being considered the neurosurgeon needs to consider the risks and benefits as regards operative mortality and worsening neurological disability.

MIDBRAIN TUMOURS

Focal tumours of the tectal plate are often small and produce hydrocephalus with or without midbrain eye signs. They are usually low grade astrocytomas and surgery is restricted to control of the hydrocephalus, preferably by neuroendoscopic third ventriculostomy,¹⁷ rather than by insertion of a ventricular shunt, to avoid the morbidity associated with the latter.¹⁸ Although typically indolent,¹⁹ careful follow up with annual MRI is required because a number will progress,²⁰ at which time open surgery to establish a firm diagnosis and to reduce tumour bulk is indicated.

The occasional tumour will be large at presentation, spanning the pineal region and midbrain. Estimation of serum concentrations of α fetoprotein, β human chorionic gonadotrophin, and placental alkaline phosphatase

Table 1 Consensus for surgical management of brain stem tumours (UK paediatric neurosurgical group)¹⁶

Anatomical site/ imaging characteristics	Probable pathology	Surgical management
Midbrain		
Tectal plate	Low grade astrocytoma, exclude non-germinomatous germ cell tumours by measuring tumour markers	Observe/cerebrospinal fluid diversion if necessary, consider debulking if tumour progresses
Other	As for Pons	As for Pons
Pons		
Diffuse	High grade astrocytoma	No biopsy proceed to radiotherapy
Focal solid/cystic	Low/high grade astrocytoma	Drain cysts/debulk solid component DXT depending upon severity of neurological signs
Exophytic	Low/high grade astrocytoma	Debulk
Medulla	As for Pons	Neurological, results of surgery poor
Cervico-medullary	Low grade astrocytoma	Radical removal

DXT, dual x ray therapy.

will detect the small numbers that are non-germinomatous germ cell tumours. It is crucial that these tumours are identified correctly because their treatment is specific and often highly effective.²¹ Biopsy may be feasible at the time of neuroendoscopic third ventriculostomy. For the remainder, which are usually low grade astrocytomas or gangliogliomas, open surgery is indicated.

Focal tumours of the tegmentum are usually low grade astrocytomas or gangliogliomas and should be resected.²² Diffuse tumours confined to the tegmentum are rare and should undergo image guided stereotactic biopsy.

PONTINE AND MEDULLARY TUMOURS

Diffuse tumours

These are by far the most common brain stem tumour and most are high grade. Surgery of any sort, beyond that occasionally needed to relieve hydrocephalus, is not indicated, because the typical appearances on MRI are characteristic and reduction in tumour bulk only adds to the child's misery.²³ Although biopsy can be performed safely by image guided stereotaxy,²⁴ there is currently no indication for such a procedure in children with a short history and typical MR appearances, because it currently will not alter management strategy.²⁵ This view might change if biological or imaging²⁶⁻²⁸ markers are identified that can predict more precisely the sensitivity of the tumour to treatment or other biological characteristics that are important for planning treatment (such as risk of metastasis).

Focal tumours

These are either solid or partially cystic, have an aspect abutting on the fourth ventricle and are not associated with alteration in speech or swallowing. This is especially so in those with a long clinical history, which are usually low grade astrocytomas or gangliogliomas. Surgery with a view to resection should be considered. Complete removal is not possible. The residuum might not progress, justifying an expectant policy after surgery. In contrast, if the history is short, there are bulbar symptoms, and the tumour is solid and placed low in the brain stem, the morbidity of intervention is likely to be high and resection best avoided.

DORSALLY EXOPHYTIC TUMOURS

These are low grade astrocytomas or gangliogliomas that have grown out of the brain stem into the fourth ventricle. The symptoms are slowly progressive and usually include features of raised intracranial pressure. Partial resection is indicated and long term remission without the need for adjuvant treatment is the rule.^{20 22}

CERVICO-MEDULLARY TUMOURS

These are essentially very rostral intrinsic spinal cord tumours and are amenable to radical resection.²⁹

The role of radiotherapy

Most brain stem gliomas transiently respond to radiotherapy as judged by the alleviation of neurological symptoms and evidence for improved duration of survival in patients given higher doses (> 50 Gy *v* < 50 Gy) of radiotherapy.^{30 31} For those with diffuse characteristics located within the pons, the duration of response is brief and progressive symptoms can be expected at a median of about nine months after diagnosis.^{32 33} The clinical aims of radiotherapy range from palliation of neurological symptoms in diffuse intrinsic tumours to eradication of the tumour residuum after subtotal resection of focal tumours. In symptomatic patients, radiotherapy should start as quickly as possible. The current UK children's cancer study group (UKCCSG) protocol for brain stem glioma recommends radiotherapy to start within one week of diagnosis (E Bouffet, personal communication, 1998). However, the recent report of the Royal College of Radiologists has identified that as a result of shortage of linear accelerators and radiotherapy funding the more usual time interval is three to four weeks.^{27 34} Steroids might be able to control life threatening symptoms for a brief period but longer lasting benefits can only be expected when radiotherapy has been completed. Symptomatic improvement does not always occur during radiotherapy because some patients, particularly those with NF-1, might experience considerable neurological deterioration.^{12 13} This is thought to be related to the radiation treatment and in some cases is associated with the development of a necrotic cyst within the tumour.³⁵ Those with localised and histologically benign disease might have a longer lasting response, with a 50% five year survival rate.³⁶

RADIOOTHERAPY DOSE PRESCRIPTION

The optimal target volume and dose/fractionation schedule is poorly defined in the literature. As a general principle, the treatment volume of the radiation field should encompass all the site(s) of disease with a defined margin to allow for non-imageable tumour spread into adjacent brain (1 cm for low grade and 2 cm for high grade tumours). The dose and fractionation schedule dictates the balance between tumoricidal efficacy and the risks of normal tissue damage. Higher total doses produce greater control rates, more frequent and smaller fractions being less damaging to normal tissues. Conventional radiation

Table 2 Societe Internationale d'Oncologie Pediatrique (SIOP) brain tumour committee: tumour response criteria⁴⁵

Complete response
No radiological evidence of tumour on contrast enhanced computed tomography or magnetic resonance imaging scan
Partial response
Greater than 50% reduction of the product of two maximum perpendicular diameters of the tumour. No radiological evidence of tumour progression at primary site or other sites or the appearance of unequivocal malignant cells in the cerebrospinal fluid (CSF)
Objective response/minor response
Between 50% and 25% reduction of the product of two maximum perpendicular diameters. No radiological evidence of tumour progression at primary site or other sites or the appearance of unequivocal malignant cells in the CSF
Stable disease
Less than 25% reduction of the product of two maximum perpendicular diameters of the tumour. No radiological evidence of tumour progression at primary site or other sites or the appearance of unequivocal malignant cells in the CSF
Tumour progression
Radiological evidence of tumour progression or the appearance of unequivocal malignant cells in the CSF

schedules give daily fractions five days out of seven, usually for up to six weeks in total. More frequent, smaller fractions can be given, usually twice each day with no treatment gaps and, therefore, permit a higher cumulative dose to be given over a shorter time—so called hyperfractionation.

Brain stem tumours are localised tumours and are treated with parallel opposed fields, using a linear accelerator, the child lying face down in a mask to ensure accuracy and reproducibility in each treatment fraction. Five to ten per cent of patients relapse at margins of radiation fields, suggesting unrecognised local infiltration. Whole brain irradiation is considered unnecessary.³³ The dose of radiation required to control disease has been studied intensively. Doses of radiation > 50 Gy are associated with improved survival compared with lower doses.³¹ Studies of hyperfractionated radiotherapy with doses up to 72 Gy have been shown to be safe and acceptable but have not been shown to improve cure rates. The median time to progression in these studies ranged from seven to 11 months from diagnosis.^{32 37–40}

TOXICITY DURING AND AFTER TREATMENT

For most children and their family the course of radiotherapy should present few difficulties because the treatment is painless and well tolerated. Very young children (3 years) might require daily anaesthetics but older children seldom require sedation as long as the initial planning process is coordinated smoothly. Clear explanations through play therapy, training videos, and departmental visits before treatment ensure good cooperation in most cases. Hair loss in the radiation fields is inevitable, as is hypopituitarism causing growth hormone deficiency. Radiation brain necrosis is rare (< 2%) but can be difficult to distinguish from recurrence unless scanning directed at estimating tissue metabolism is used (for example, thallium or single photon emission computerised tomography (SPECT) scanning).⁴¹

The role of chemotherapy

There is no standard chemotherapy regimen for this group of tumours because none has been shown to improve survival. Most trials of

chemotherapy have concentrated upon the typical diffuse intrinsic brain stem glioma. Population based reports have not demonstrated any trend of improvement in survival over the past two to three decades.^{42–44} Phase 2 studies of single and multiple agents, in conventional doses and high dose with stem cell/bone marrow rescue, have been conducted. There have been difficulties assessing tumour response because the diffuse imaging characteristics prevent clear definitions of tumour margins for response assessment (table 2). Positron emission tomography (PET) and SPECT can identify the metabolic status of glial tissue. Such techniques, when they become more widely available, might provide more precise ways of determining tumour response to treatment as well as other biological characteristics of the tumour that help select optimal treatment approaches.^{26–28}

A recent literature review of single agent phase 2 studies that have included patients with brain stem gliomas has identified trials of cisplatin,^{46–48} carboplatin,^{49–52} iproplatin,⁵⁰ oral etoposide,^{53 54} cyclophosphamide,⁵⁵ ifosfamide,⁵⁶ 1-(s-chlorethyl)-3-(2,6, dioxo-3-piperidyl)-1-nitrosourea (PCNU),⁵⁷ thiopeta,⁵⁸ methotrexate,⁵⁹ topotecan,⁶⁰ β interferon,⁶¹ temozolomide,⁶² and aridylbenzoquinone.⁶³ Conventional response criteria would require a 30% “partial response” rate (table 2) to establish that the drug had activity. None of these trials identified more than a 20% response rate, the highest being with oral etoposide, although this was based upon two studies where only 15 patients were studied in total. A similar literature review of phase 2 trials of drug combinations including cisplatin/cytarabine/etoposide,⁶⁴ cisplatin/cyclophosphamide,⁶⁵ mustine/vincristine/procarbazine/prednisolone,⁶⁶ and thiopeta/etoposide given in high dose with autologous bone marrow rescue,⁶⁷ failed to identify any of these combinations as being capable of producing a measurable sustained responses. The current UKCCSG brain stem glioma study is investigating tamoxifen, given in parallel with radiotherapy and at high dose (120 mg/m²/day) continuously in newly diagnosed patients with diffuse intrinsic brain stem glioma. Tamoxifen in this study is being used in doses aimed at inhibiting glioma cell proliferation by an antimitotic effect rather through its actions on oestrogen receptors^{68 69} (conventional anti-oestrogen doses in adults with breast cancer are 20 mg daily).

For the focal brain stem tumours where biopsy or resection is attempted and histological classification is available, the use of chemotherapy should be dictated by current trials for specific histological type. High grade astrocytomas are currently being investigated by the UKCCSG with a series of single agent phase 2 studies seeking a drug with any demonstrable activity. Patients with low grade astrocytomas should be entered in the Societe Internationale d'Oncologie Pediatrique (SIOP)/UKCCSG low grade glioma study. This study is investigating carboplatin and vincristine in patients under the age of 5 years if surgical resection is

not possible, if there is evidence of progressive disease, or if there are severe symptoms (DA Walker and R Taylor, UK study coordinators). Radiotherapy in the young group of patients is reserved for patients whose tumours subsequently progress. In children over 5 years, radiotherapy is recommended initially, with chemotherapy being offered for subsequent tumour progression.

Symptom care

Where palliation is the main aim of treatment, measures that are useful in addition to radiotherapy include the use of corticosteroids and analgesia, surgical relief of hydrocephalus, management of bulbar impairment, physical rehabilitation, and social and emotional support

STEROIDS

The presenting symptoms of raised intracranial pressure and, to a lesser degree, neurological symptoms, are in most cases effectively relieved by dexamethasone. Although this is reassuring to the child, their family, and their doctors, prolonged treatment leads inevitably to a progressive Cushing's syndrome and distressing alterations in mood. Furthermore, steroids can substantially impair neurological rehabilitation. The optimal use of steroids has been studied infrequently although they are used extensively.^{70 71} It is our practice to use dexamethasone (maximum dose 10 mg/m²/day), together with an antacid to prevent dyspepsia. We try to use the minimum dose that is effective for as short a period of time as possible. Dexamethasone might be necessary during radiotherapy while awaiting clinical response or to treat radiation induced oedema. By using short repeated courses of dexamethasone (lasting three to five days), we are able to review their benefit for the child in conjunction with the parents. It is our experience that in the absence of symptoms of raised intracranial pressure (headaches and vomiting), the improvement in neurological symptoms is seldom sufficient to justify the side effects. If dexamethasone has been continued during radiotherapy, we aim to stop it subsequently in all patients and only restart it to control symptoms of raised intracranial pressure, or if there is evidence of delayed radiation induced neurotoxicity. With this approach we have avoided severe steroidal side effects in most of our patients.

HYDROCEPHALUS

Symptomatic hydrocephalus requiring surgical drainage is unusual at presentation in the common diffuse pontine glioma but is frequently a feature of midbrain tumours. Wherever possible, neuroendoscopic third ventriculostomy should be used to avoid the morbidity associated with ventricular shunts. If a shunt has been placed initially then subsequent malfunction can usually be treated by neuroendoscopic third ventriculostomy.⁷² Neurosurgeons who are not familiar with neuroendoscopic third ventriculostomy should be prepared to involve a colleague who is suitably trained and equipped. When the disease is advancing, sur-

gical interventions require careful consideration, the overall objectives of palliative care should be central to the discussion.

BULBAR IMPAIRMENT

Patients with speech, swallowing, and breathing difficulties will require support by means of alternative methods of communication, nasogastric tube feeding, or percutaneous endoscopic gastrostomy; unusually, tracheostomy is indicated. Families will need the appropriate specialist nursing care and instruction in dealing with these circumstances in the community.⁷³

ANALGESIA

Apart from headache as a result of raised intracranial pressure, pain is a relatively infrequent complication of brain stem glioma. Standard approaches to palliative pain control using careful pain assessment together with child and family support and the analgesic ladder are successful in controlling pain for most children.^{74 75}

NEUROLOGICAL DISABILITY

Patients should be assessed early throughout treatment. Plans should be made for rehabilitation to run in parallel with other antitumour treatments. Special arrangements should be made for the rehabilitation programme to be deliverable at home, in school, and in hospital.⁷⁶

CHILD AND FAMILY INFORMATION SUPPORT

Patients and families coming to terms with brain stem tumours pose a real challenge. The scene for success or failure is often set at the outset by the approach taken by the individual who "breaks the bad news". The "right from the start principles" should be followed.⁷⁷ The neurosurgical options are often discussed early on. The use of phrases such as "inoperable tumour" is likely to bias the rest of the emotional management strongly towards frustration and failure. It is crucial that the neurosurgeon takes time to explain the rationale behind the surgical decisions and, in the case of diffuse pontine glioma, helps the family to understand that surgery is not "impossible" but "unhelpful". Neurosurgeons dealing with these cases must accept the need for a child and family centred approach or pass the case to a specialist paediatric neurosurgery colleague who understands that the paediatrics is as important as the neurosurgery. Families appreciate an early introduction to the concept of the paediatric neuro-oncology team and its links to national and international trials groups such as the UKCCSG and SIOP.⁵ These organisations provide a network of paediatric specialists through whom alternative opinions can be sought in the knowledge that they are linked to recognised children's cancer centres.

Conclusion

This group of tumours are among the most difficult of paediatric cancers to treat because of difficulties in diagnosis, lack of effective treatments, and a historical lack of consensus

between specialists. It is hoped that the anatomical classification of these tumours with modern imaging, coupled with the development of a national network of children's brain tumour centres,⁵ and the launch of strategies for testing new agents and specific recommendations for supportive care should reassure families that they are receiving optimal standards of care and provide hope that new treatments will be tested as soon as they are discovered.

The views expressed in this article have resulted from extensive discussions with colleagues from the kids neuro-oncology workshop (KNOWS) at the University Hospital, Nottingham, the UKCCSG brain tumour and radiotherapy committees, the UK paediatric neurosurgical group of the Society of British Neurological Surgeons, and the brain tumour committee of the Society Internationale d'Oncologie Pédiatrique (SIOP). We would like to acknowledge the assistance of Dr T Parker and Mr D Sokal of the Department of Human Morphology, Faculty Health Sciences, University of Nottingham in the preparation of fig 1.

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