Posterior fossa tumours in children – an overview of diagnosis and management

The posterior fossa is the commonest site of primary intracranial tumours in children. The commonest neoplasms are pilocytic astrocytoma, medulloblastoma, ependymoma and brain stem glioma. In children over one year old, over two thirds of intracranial tumours arise from the cerebellum or brainstem, compared with 15% in adults. Survival rates of some of these lesions has improved markedly over the last twenty years, due to advances in surgical techniques, chemotherapy, delivery of radiotherapy and, more recently, an improved understanding of tumour biology. These tumours remain the focus of intense research aimed not just at prolonging survival, but also at minimising the impact of treatment on growth, cognitive development and long-term quality of life.

Clinical presentation

Posterior fossa tumours often present with clinical manifestations of hydrocephalus and raised intracranial pressure. More aggressive tumours present with a shorter history. The most prevalent symptoms include headache, nausea and vomiting. In young children headache is reflected in irritability and a desire not to be handled. Vomiting, usually an early morning phenomenon, may also be related to irritation of the lower fourth ventricular floor, at the area postrema, by the tumour. The hyperventilation associated with vomiting often transiently improves the headache. Raising intracranial pressure may also cause drowsiness, neck stiffness, sixth nerve palsy and visual disturbances. Papilloedema is common in patients presenting with longstanding progressive symptoms. Aggressive brain stem tumours often present with pyramidal tract signs together with disorders of ocular motility and diplopia. A head tilt may be a reflection of tonsillar herniation or a fourth nerve palsy related to a diffuse brainstem tumour. Young children with progressive hydrocephalus demonstrate macrocephaly with fullness of the fontanelles and increased separation of calvarial sutures. Ataxia arises from vermal and cerebellar hemisphere involvement, brainstem dysfunction and chronic hydrocephalus.

Headache is an uncommon complaint in early childhood; early referral and imaging is warranted. Similarly, early investigation of other symptoms allows rapid diagnosis and prompt initiation of treatment.

Pilocytic astrocytoma

Cerebellar astrocytomas are the most frequent posterior fossa tumours in children, accounting for up to 35% of these lesions. Peak age is 5 to 13 years; approximately half arise in the midline and half from the cerebellar hemispheres. They are circumscribed, discrete, slow-growing lesions, often associated with cysts within and around the tumour.

On computed tomography (CT), pilocytic astrocytomas are large cystic lesions arising from the cerebellar vermis or hemisphere. The solid components are hypodense and enhance avidly on contrast administration. On T1-weighted magnetic resonance imaging (MRI), the solid component tends to be iso- to hypointense on comparison with grey matter; heterogeneity is due to microcystic and necrotic areas. It is hyperintense on T2-weighted images (Figure 1A and B). The solid and mural components enhance prominently (Figure 1C). Enhancement of the cyst wall suggests tumour infiltration of the capsule.

Histologically these tumours are characterised by a biphasic pattern. This consists of compacted bipolar cells with Rosenthal fibres, and loose multipolar cells with microcysts and eosinophilic granular bodies, which form globular aggregates within astrocytic processes. Their slow growth permits development of regressive changes, such as hyalinised vessels, calcification, necrosis, lymphocytic infiltration and cysts. In this context, necrosis carries no prognostic significance. Rarely pilocytic astrocytomas seed the neuraxis, although this tends to occur with hypothalamic, rather than posterior fossa, primary tumours. In these cases the primary tumour may still demonstrate a low proliferation index; such tumours generally respond well to chemotherapy and radiotherapy, and long-term survival is still possible.

Pilocytic astrocytomas maintain their WHO grade I status for years; they only rarely show malignant transformation, and they should then be termed anaplastic pilocytic astrocytomas, rather than glioblastomas. Even then, their prognosis is not uniformly poor. Reported cases had undergone previous radiotherapy, and this was likely relevant to their transformation.

A large percentage of pilocytic astrocytomas, particularly those arising within the cerebellar hemisphere, have demonstrated alterations in the BRAF gene, which is essential for growth signalling through mitogen-associated protein kinase (MAPK) pathways. These alterations have not been clearly associated with outcome. p16 deletions are commoner in primary tumours. In these cases the primary tumour may still demonstrate a low proliferation index; such tumours generally respond well to chemotherapy and radiotherapy, and long-term survival is still possible.

Resection is the treatment of choice for well-circumscribed lesions (Figure 1D) and the factor most strongly associated with outcome is the...
extent of surgical removal.\cite{6,7} Gross total resection leads to over 90% long-term survival.\cite{7}

Cerebellar pilocytic astrocytomas are generally resectable and adjuvant therapy is not indicated. Those arising from the brainstem, however, are often not completely resectable and require adjuvant chemotherapy, usually including carboplatin and vincristine, and consideration of radiotherapy at progression. A clinical trial of BRAF and MAPK pathway inhibitors, such as AZD6244, is underway.\cite{8}

Another trial, using the antiangiogenic agents bevacizumab and linalidomide, has already shown some promise in Phase I and II trials.\cite{9}

A recent study has reported long-term follow up, to a mean of 18.4 years, for 101 children with benign posterior fossa astrocytomas.\cite{6}

Complete resection, confirmed radiologically, was achieved in half the patients; only three of these recurred. 26 of 50 residual tumours progressed, at a mean of 30 months; the others demonstrated spontaneous regression or growth arrest. 60% of recurrences or progression occurred within two years, and only one beyond eight years of the original surgery. The interval to progression was shorter for subtotal resections, solid tumours and involvement of brainstem or cerebellar peduncle. The authors conclude that gross total resection should not be aggressively pursued when the tumour invades critical structures.

**Medulloblastoma**

Medulloblastoma is a primitive neuroectodermal tumour (PNET) occurring in the cerebellum. It is the most common malignant brain tumour in children and represents 30% of posterior fossa tumours. It is classified as WHO grade 4 and has a propensity to leptomeningeal dissemination. The annual incidence is 6.5 per million children.\cite{10}

10% of cases are diagnosed in infancy. 75% occur in the midline; cerebellar location is associated with older age and desmoplastic histology.\cite{11}

Medulloblastoma is typically a midline enhancing homogeneous posterior fossa mass on CT. The mass is hypointense on T1 and T2-weighted images; it enhances heterogeneously on gadolinium administration. Cystic components may be present (Figure 2A and B). The characteristic high cell density is reflected in

**Figure 1:** Pilocytic astrocytoma. T2-weighted axial (A) and post-contrast sagittal (B) images of two posterior fossa pilocytic astrocytomas, demonstrating solid and cystic components; the close relationship of the tumour in (B) to the tectum (\*) is evident on the axial post-contrast image in (C). Post-operative midline post-contrast MRI in (D) confirms gross total resection of the tumour in (B) and (C).

**Figure 2:** Medulloblastoma. Sagittal post-contrast (A) and axial T2 (B) images, showing typical posterior fossa medulloblastoma. Both demonstrate heterogeneous nature of the tumour. Obstruction of the aqueduct and secondary obstructive hydrocephalus is evident in (A). (C) demonstrates a nodular medulloblastoma in an infant with the typical ‘bunch of grapes’ appearance. (D) is an intra-operative photomicrograph obtained during resection of a posterior fossa medulloblastoma – \(t\) represents residual tumour around the cavity; the fourth ventricular floor \(f\) is exposed and free of tumour; the arrow points to the dilated caudal end of the aqueduct after decompression.
5%). The desmoplastic variant is characterised by pale nodular areas within a reticulin network; this is commoner in older children and is associated with a better prognosis. The large cell and anaplastic variants are associated with a poor prognosis. Extensive investigation into the genetic differences in medulloblastoma over the last ten years has led to further classification into distinct molecular variants. Current clinical medulloblastoma trials are still based on histological classification. Genetic typing however is not far from clinical use and is likely to improve prognostication and risk stratification, as well as allow tailored therapeutic approaches.

Medulloblastomas arise from aberrant proliferation of granule neuron precursor cells that go on to constitute the external granular layer of the cerebellum. The different signalling pathways involved in this complex process have led to the identification of four molecular subgroups.\(^{13}\) Wnt signalling has an important role in neural stem cell proliferation in the normal cerebellum.\(^{14}\) This pathway, originally identified in mutant wingless fruit flies, is fundamental to neural tube patterning. Tumours involving Wnt pathway anomalies are more likely to arise in younger children, demonstrate classic histology tend to be located within the fourth ventricle and are associated with a very good prognosis; their nuclei stain positively for β catenin.\(^{15}\) The sonic hedgehog (Shh) signalling pathway regulates progenitor cell proliferation in the external granular layer; medulloblastomas associated with Shh signalling abnormalities tend to arise within the cerebellar hemisphere and are more likely to occur in infants or older children; their prognosis is intermediate.\(^{16}\) Abnormalities in these pathways are not simply related to mutations in expressed genes, but also to epigenetic changes leading to abnormal expression of tumour suppressor genes, including promoter inactivation by DNA methylation, histone modification and gene silencing by nonprotein-coding micro RNAs.\(^{17}\) There are two additional non-Wnt, non-Shh subtypes; both tend to be either classic or large cell / anaplastic tumours, frequently with metastases at presentation and c-myc amplification. Group 3 have a poor and Group 4 an intermediate prognosis.\(^{18}\)

Following resection, (Figure 2D) further adjuvant treatment of medulloblastoma depends on whether they are classified as standard or high risk. Staging requires MRI of the brain and spine, without and with contrast. CSF from the lumbar region is also required; this is obtained two weeks post-operatively to avoid false positive cytology early after resection, and is more sensitive than ventricular CSF.\(^{19}\) High risk patients include all children under three as well as those with positive CSF macrometastases on MRI implying tumour dissemination and > 1.5cm of residual tumour visible on post-contrast MRI within 24 to 72 hours of surgery. Children older than three with anaplastic histology or c-myc amplification are also considered high risk.

Children over three at standard risk undergo cranio spinal irradiation (23.4 Gy), commenced within 40 days of surgery with a posterior fossa boost to a total dose of 54-55.8 Gy. This is combined with weekly concurrent chemotherapy. Hyperfractionation does not lead to an improvement in overall or progression free survival.\(^{20}\) Based on this regimen, five year event-free survival is up to 80%.\(^{21}\) Historically the five year progression-free survival for children with high risk disease is 40%.\(^{22}\) Recent studies have focused on improving prognosis in this group using multimodality treatments.\(^{23}\) High risk patients are treated with 36 Gy to the craniospinal axis followed by a posterior fossa boost to 54 to 56 Gy. Studies have evaluated the use of hyperfractionated radiotherapy, including posterior fossa boosts to 60 Gy and myeloablative courses of chemotherapy followed by peripheral blood stem cell rescue, yielding five year progression free survival of up to 73%.\(^{24}\)

The neurocognitive sequelae of radiotherapy are more severe in young children. In infants and children under three, repeated cycles of chemotherapy have been used after surgery in an attempt to prevent progression until they become eligible for radiotherapy: Outcomes from early studies were poor, encouraging the introduction of high dose chemotherapy regimens.\(^{25}\) It is likely that such studies were affected by multiple tumour biological factors which directly affected survival; infants with desmoplastic variants, for example, consistently showed better outcomes than all the others.\(^{26}\)

Figure 3: (A) post-contrast MR image demonstrating an epidermoidoma in the cerebellopontine angle (asterisk); the tumour is hypointense and does not enhance; the brainstem is distorted and rotated to the right; (B) FLAIR image demonstrating a diffuse hyper-intense lesion consistent with a pontine glioma. (C) and (D) post-contrast axial and sagittal MR images of posterior fossa ATRT; the tumour is large and diffuse, involving the cerebellum and brainstem and extends superiorly through the tentorial incisura.
Ependymoma
Ependymoma is the third most common paediatric brain tumour, over 50% of cases arise in children under five years of age.24 Infratentorial ependymomas arise from the floor or roof of the fourth ventricle and grow into the ventricular lumen. They have a propensity to extend through the foramen of Luschka into the cerebellopontine cistern and around the brainstem (Figure 3A), as well as down through the foramen magnum. The extent of surgical resection is a major determinant of outcome. In historical series, five-year overall survival for ependymoma has ranged from 50 to 64%.25 However institutions with gross total resection rates of up to 82% have reported five-year overall survival figures of 87.3% and 62.1% for ependymomas and malignant ependymomas respectively.26 Infratentorial ependymomas in children are classified as WHO grade 2 or 3, grade 1 being reserved only for subependymoma and myxopapillary ependymoma.2 They are well-delineated soft, heterogeneous tumours, often with cystic, necrotic and haemorrhagic elements. Histologically they are characterised by a more rarely anaplastic rosettes. The latter consists of tumour cells concentrically organised around a lumen.2 Ependymomas stain positively with GFAP, NCAM and EAM. Multiple chromosomal anomalies have been identified in ependymomas. Anomalies on chromosome 22q have been reported in 26 to 71% of ependymomas.27 Chromosome 1q gain has been found in up to 22% of childhood ependymomas, and is associated with posterior fossa location, anaplastic features and a poor prognosis.28 A recent study identified gains at chromosome 1q, high tumour cell density and high mitotic count as defining features of a high risk subgroup in infratentorial ependymoma.29

On CT, ependymomas are iso- or hypodense lesions. Punctate calcification is detectable in up to 50% of cases. They enhance heterogenously on contrast administration.30 On MRI, they are iso- to hypointense on T1-weighted sequences and hypointense on T2. Calcification, cysts, areas of necrosis and micro-haemorrhages cause heterogeneity within the tumour mass on enhanced and non-enhanced sequences. Leptomeningeal dissemination at presentation is less common than in medulloblastoma, full spinal MRI at diagnosis is imperative as part of the staging process.31

Despite several multi-institutional studies, mostly including platinum-based agents, no single chemotherapeutic regimen has demonstrated significant survival benefit for ependymoma.32,33 The role of chemotherapy alongside postoperative radiotherapy remains unclear. In a recent single-institution study conformal radiotherapy, administered immediately after surgery, led to better overall survival rates up to 85% at five years, compared to earlier studies with up to 73% at five years.34 This may be partly attributable to the high rate of gross total resection in this study. Radiotherapy was confined to the tumour bed and a 10 mm margin, and was also administered, for the first time, to children under three years; children under 18 months received 54 Gy rather than the standard dose of 54.4 Gy. The seven-year local control rate was 87%. Among the patients with differentiated ependymoma treated with gross total resection and 59.4 Gy, there were very few local failures. The low frequency of side effects from limited volume irradiation has also encouraged this group to recommend repeated surgery and re-irradiation for children presenting with local recurrence.35

Brainstem tumours
Brainstem gliomas account for 10 to 20% of all CNS tumours in children.3 They are broadly classified into diffuse or focal. Focal brainstem tumours are well-circumscribed masses that may be intrinsic, exophytic or cervicomедullary.36,37 Diffuse intrinsic pontine gliomas are high grade fibrillary astrocytomas with median overall and progression-free survival of up to eleven and nine months respectively (Figure 3B).38 They present with a short history, often exacerbated by cranial nerve palsies and ataxia. Hydrocephalus occurs late. They are diagnosed radiologically and when typical, do not require biopsy. They are hypointense on T2- and hypointense on T1-weighted images, with ill-defined boundaries and diffuse enlargement of the brainstem. They generally do not enhance with contrast. Surgical resection has no role in these tumours. Despite several clinical trials over the last fifteen years, based on various chemotherapeutic agents and radiotherapy delivery techniques, there has been no improvement in clinical outcome.

Focal gliomas are discrete solid or cystic tumours, in diameter, and are commonly low grade astrocytomas. In a recent large retrospective study of focal brainstem gliomas, following 52 children over a mean of ten years, the survival rate was 88% at five years and 90% at ten years; 36.5% underwent gross or near total resection. The authors recommend that surgery should be pursued if the tumour is considered accessible and the family understands the risks of new neurological deficit. In other situations, the authors recommend stereotactic biopsy, followed by radiation for clinical or image-based progression.39

Atypical teratoid/rhabdoid tumour (ATRT)
ATRT is a malignant WHO grade IV tumour with a poor prognosis, occurring typically in children under two years of age. Approximately 15% of children under 36 months with a malignant brain tumour have an ATRT.40 First described in 1987, it is histologically difficult to differentiate from medulloblastoma or PNET. About half arise in the posterior fossa. Due to their high growth, presentation is often rapid, with macrocephaly and progressive neurological deficit. Up to 20% present with disseminated disease.41 Radiologically, posterior fossa ATRTs often invade the cerebellopontine angle and enhance brightly on contrast administration. They are hyperdense on CT, with ill-defined wispy margins. On MRI, the tumour is heterogeneous due to areas of haemorrhage, necrosis and cyst formation (Figure 3C and D).42

Histologically ATRT consists of sheets of rhabdoid cells within a background of epithelial, mesenchymal or neuroectodermal cells.43 Mitotic labelling typically shows indices of 50 to 100.44 These tumours characteristically demonstrate mutation or inactivation of the INI1 gene on chromosome 22q.11.2 This is also abnormal in rhabdoid tumours outside the central nervous system, including the renal and extra-renal forms. Although the exact function of this gene is unknown, it is a component of an ATP-dependent chromatin remodelling complex and is involved in the regulation of transcription. The presence of an INI1 mutation in a tumour resembling PNET, even without sheets of rhabdoid cells, is still sufficient to secure the diagnosis of ATRT.45

Treatment of ATRT consists of combinations of surgery, multi-agent chemotherapy and radiotherapy. Median overall survival for a large cohort was 17.3 months.46 Patients with gross total resection had longer survival than subtotal resection or biopsy. Survival for children under three years old who also had radiotherapy was 15.8 months, compared to 7.9 months for those who did not.47 Variability in chemotherapy regimens, in conjunction with the small numbers of cases involved, has made it difficult to establish the comparative efficacy of different agents. Intrathecal chemotherapy has been shown to be of benefit in some patients.48

REFERENCES
If it is the case that “Medicine is fundamentally narrative”, as suggested by Kathleen Montgomery Hunter in Doctors’ Stories. The narrative structure of medical knowledge (Princeton University Press, 1991:5), then the kinship of medical practice with the verbal and visual narratives encountered respectively in literature and art is obvious.

In focusing on brain disease as portrayed in novels, theatre, and film, the editors of this volume have at their disposal a potentially limitless resource for discussion (on theatre, and film, the editors of this volume have at their disposal a potentially limitless resource for discussion). It is not the case that “listeners are rejected through citation of “stranger-than-fiction” type cases in the medical literature, and Dieugue contends that intuitive conceptions of memory may feed in to scientific understanding and vice versa, a notion which may be at odds with principles of neuropsychological research.

David Perkin gives examples of movement disorders whose recovery can be slow and is independent of other factors such as age, gender, and socioeconomic status. He suggests that there is some evidence to support the hypothesis that the brain has the capacity to reorganize itself after injury, and that this process may be facilitated by physical therapy and other forms of rehabilitation.

It is also important to recognize that the medical profession has a responsibility to ensure that patients are informed about their condition and the treatment options available to them. This can be achieved through patient education programs and the use of visual aids such as videos and diagrams. Moreover, doctors should be mindful of the potential for patient emotions to influence treatment decisions, and should strive to create a supportive and non-judgmental environment in which patients can express their fears and concerns.

Finally, it is essential to recognize that the medical profession has a role to play in promoting public health and preventing disease. This can be achieved through the provision of preventive care, such as vaccinations and screenings, and through education programs that promote healthy lifestyles. By doing so, doctors can help to reduce the burden of disease on society and improve the overall health of the population.