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Primary Brain Tumours – Everything a Medical Student Needs to Know

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ABSTRACT

A brain tumour is an illness that inspires fear and foreboding in the general population. They can strike at any age and can often have devastating consequences. They are however relatively uncommon and perhaps this is why many undergraduate medical students do not have much in depth teaching in this area. In this review, we will consider all that an undergraduate student needs to know to have a good understanding of this complex and varied pathology.

What are brain tumours and how common are they?

Primary brain tumours can be defined as benign or malignant growths that arise in intracranial tissue. As a group, they are heterogeneous, varying from benign tumours which can be removed with surgical resection through to inoperable malignant lesions which have a very poor prognosis. They are relatively uncommon, accounting for only 2% of adult tumours. In the UK around 4,400 people are diagnosed with a primary brain tumour annually and this translates to an overall annual incidence of around 7 per 100,000.[1] Although brain tumours affect all ages and both sexes, they do become more common as people age, rising in incidence from the age of 30 onwards[1] with the incidence peaking at the age of 65 to 79 years.[2] The incidence of brain tumours is slightly higher in men than women, with men having a life-time relative risk of 0.65% as opposed to 0.5% for women.[2] However, women have a higher incidence of meningioma than males.[1] Despite their rare incidence, primary brain tumours have a relatively high mortality rate, being the leading cause of cancer death in children and the third leading cause in young adults aged 15 to 34.[3] Tumours need to be classified pathologically, and staged, as this will determine the treatment that will be of most benefit to the patient. Up to half of brain tumours are benign, however the most common malignant primary brain tumour is glioblastoma multiforme (GBM) which has a poor prognosis.[2,3] In this review, we shall explore the presentation of primary brain tumours, their investigation, diagnosis and treatment options. We shall then consider the outcomes for patients with these tumours following optimal treatment.

Presenting features: History and Examination

Brain tumours present with signs and symptoms primarily due to three factors: mass effect, parenchymal infiltration and tissue destruction.[3] Headache due to mass effect is the most common presenting feature[3] occurring in 23 to 56% of adults[4] and in 41%

of paediatric cases.[5] There are certain characteristics of a headache which must immediately raise the suspicion of a sinister cause such as a brain tumour. If the headache is associated with nausea and vomiting (the second commonest presenting feature in children) then the suspicion of a brain tumour must be considered. There can be worsening of the headache at different times of the day, with a typical worsening of symptoms first thing in the morning and during the night. At night the patient may complain of being awoken by the pain. This is due to decreased respiration during REM sleep, which then leads to an increase in blood carbon dioxide levels. The resultant cerebral vasodilatation further increases intracranial pressure exacerbating headache symptoms. Certain actions such as coughing or straining also exacerbate the headache from a brain tumour. A new onset of headaches in later life or a changing intensity or character of headache can also signify the presence of an intracranial tumour.[3] Patients may present with seizures. Indeed the incidence of seizures is as high as one third of all patients in certain tumours such as gliomas (particularly low grade gliomas).[3] In younger adults new onset seizures carry a 1.2% risk of being associated with an intracranial tumour and this rises further to 2.3% in the over 65s.[4] Other symptoms which commonly occur with brain tumours include confusion, dysphasia, motor weakness, personality change and memory loss.[5] In the history of presenting complaint, these red flag symptoms should help distinguish a sinister headache due to raised intracranial pressure (ICP) from much more common benign headaches.

A general examination should be performed, with particular attention paid to the neurological exam and the examination of the cranial nerves. Visual fields should be assessed to look for bitemporal hemianopia often found in pituitary gland tumours. It is important to assess the optic discs by fundoscopy. This can provide valuable information as to the level of intracranial pressure. Particular attention should be paid to whether papilloedema (swelling of the optic disc) is present or not. Additionally the presence of retinal venous pulsation as the veins turn into the disc should be assessed, as when present, this indicates normal intracranial pressure. Although this is normally evident in around 90% of the population, it may be absent in 10% of the population.[6] Focal neurological deficits nay be present when there is raised intracranial pressure due to a tumour. It is difficult however for doctors to decide when to investigate potential symptoms of a brain tumour further.[4] Nevertheless, further investigation must then proceed if several of these symptoms are present, if there are clinical signs of raised intracranial pressure or there is a strong suspicion of an underlying tumour.

Investigations

Investigation is necessary to confirm the presence of an intracranial tumour and specify its location and radiological features as this can assist in diagnosis of the lesion. MRI scanning is the scan of choice for primary diagnosis of a brain tumour. The administration of intravenous Gadolinium contrast enhances some lesions such as glioblastoma multiforme. MRI can also provide other useful features aside from T1 and T2 weighted images. For example, MR spectroscopy can provide metabolic and biochemical information regarding suspected tumours. The levels of choline (a marker of cell membrane turnover), lactate and lipid are elevated in high grade gliomas

compared to normal brain tissue. Also, the neuronal marker N-acetylaspartate (NAA) typically decreases in malignant tissue.[7]

CT scanning provides an alternative imaging modality and will typically reveal a mass lesion. However, mass lesion sin the posterior fossa in particular may not be readily identifiable, as it is difficult to obtain an artefact free image of this area.[3] Additionally, this imaging modality exposes the patient to ionising radiation.[3] Imaging outside the CNS is unnecessary since CNS primary tumours do not tend to metastasise due to the blood brain barrier. Only occasional case reports of primary CNS tumour metastasis outwith the CNS have been reported and these generally involve disruption of the blood brain barrier as in patients with ventriculoperitoneal shunts.[8] However, certain primary brain tumours such as primitive neuroectodermal tumours (e.g. medulloblastomas) can spread via the subarachnoid space and an MRI scan of the spine should be undertaken to exclude such eventualities.[3] When a tumour is identified by MRI, it can then be biopsied to obtain a definite tissue diagnosis, so as to better inform the MDT as to how best to proceed with treatment.

Pathology and classification of Brain Tumours

In order to discover the exact pathology underlying a brain tumour, it is essential that it is biopsied and sent for analysis to an experienced neuropathologist. This biopsy can be done via a stereotactic technique, which allows tissue to be sampled from the lesion in a relatively safe way. This deploys a co-ordinate system based on scans, which allows the surgeon to access the tumour for biopsy in a minimally invasive approach. The other alternative is that a biopsy is performed as part of the debulking or excision of a tumour.

Broadly speaking, brain tumours can be classified as either gliomas or non-gliomas. These are either tumours of the glial cells of the brain or tumours of the other intracranial cells. The vast majority of lesions in adults tend to be supratentorial (above the tentorium cerebelli) and 86% of these falls into the category of gliomas. This includes astrocytomas, oligodendrogliomas and ependymomas.

1. Gliomas

Astrocytomas are the most common type of glioma and are graded according to the WHO scale of grades one to four. Grade 1 astrocytomas include pilocytic astrocytomas which are benign. Grade 2 astrocytomas are low grade infiltrating tumours. Grade 3 anaplastic astrocytomas exhibit mitoses. Finally, the grade 4 glioblastoma multiforme (GBM)[3] is the most aggressive primary brain tumour in humans and has a median survival of 14 months following diagnosis even if given optimal therapy.[9] GBM can arise as a first presentation or a secondary presentation to a lower grade astrocytoma. The gliomas most commonly encountered in adults are neoplasms of astrocytic or oligodenrocytic lineage. Mixed tumours also occur, the most common of which is termed anaplastic oligoastrocytoma.[10] In US studies, glioblastomas formed around 50% of these tumours. This was followed by oligodendrogliomas (9.2%), other astrocytomas (9.1%) and ependymomas (5.6%).[3]

2. Non-Gliomas

Non-gliomas form the remainder of brain tumours. This includes meningiomas, which arise from the meninges and compress the brain thereby creating a mass effect. With an incidence of around 2 per 100,000,[11] over 90% of these tumours are benign and are therefore potentially curable through resection. Loss of chromosome 22 is a characteristic genetic feature of these tumours.[3]

Pituitary adenomas also fall into the category of non-gliomas and are either functioning or non-functioning. If functioning, they may secrete hormones causing endocrine disturbance. The clinical manifestation of the tumour depends on the hormone secretion. Sexual dysfunction and galactorrhoea occur in prolactinoma. A "buffalo hump", "moon face", acne, weight gain, hypertension and diabetes mellitus occur in Cushing's disease (ACTH hypersecretion). Acromegaly can result from an over-secretion of growth hormone with the typical changes that occurs with soft tissue growth in adult sufferers. Rarely, other secreting pituitary tumours such as TSHomas occur. Non-functioning pituitary tumours may exert a mass effect due to their proximity to the optic chiasm and can cause visual disturbance such as bitemporal hemianopia.[12]

Medulloblastomas are primitive neuroectodermal tumours which are rare in adulthood but much more common in children, accounting for 20% of childhood brain tumours.[13] These tumours are generally located in the cerebellum and therefore present with signs of cerebellar dysfunction. They can involve the 4th ventricle and lead to the development of hydrocephalus.[3,13] With the correct initial treatment of medulloblastoma, long-term survival may be achieved in around 40-60% of all patients.[13] These tumours can however spread in the subarachnoid space to involve other parts of the CNS.

Primary CNS lymphoma is another tumour within the grouping of non-gliomas. These constitute 2-3% of total brain tumours in people of normal immunity. Patients with immunodeficiency are at an increased risk of developing this form of cancer.[3,14]

Treating Brain Tumours

The options for treatment of a brain tumour depend on several factors. The location, type of tumour and overall health of the patient must be taken into consideration when formulating a treatment strategy. We will now consider the treatment options in 4 main categories:

1. Surgery

The first line of treatment in brain tumours is usually a surgical approach. The goals of surgery are as follows: (i) to obtain a histological diagnosis, (ii) reduce the mass of the tumour whilst preventing iatrogenic neurological deficit as effectively as possible and (iii) to treat hydrocephalus if present.[3] Surgery can be curative for most benign tumours whilst debulking improves prognosis for malignant tumours provided the tumour is not infiltrating essential areas of the brain such as language areas. If this approach is not possible, simple biopsy is the second option and modern stereotactic

approaches mean that this is now possible, even in neurologically critical areas of the brain, where attempting a resection would lead to death or a major neurological deficit.[3] Problems can arise with higher grade tumours in ensuring that as much of the tumour is removed as is possible. Novel approaches include photodynamic techniques such as fluorescence image guided surgical resection (FIGS). Photosensitizers administered pre-operatively accumulate selectively in the tumour. The visible tumour is then surgically removed under white light before a blue light longpass filter is then used to allow the surgeon to visualise and remove as much of the remaining residual tumour as possible. The more of the tumour resected, the better the prognosis. This technique therefore offers more effective treatment to patients with high grade tumours.[15] Excision of at least 98% of a GBM improves life expectancy by a median of 4.2 months compared with patients who have 2% or more of residual tumour remaining post operatively.[14]

2. Radiotherapy

Radiotherapy provides another option in brain tumours. External beam radiotherapy remains an important tool either in addition to surgery or, in some cases, as an alternative.[16] In certain tumours it can be curative and in the majority of cases it will prolong survival.[3] There are various different approaches with this therapy. Whole brain radiotherapy is used in certain tumours like medulloblastoma and primary CNS lymphomas.[3,14] "Involved field" radiotherapy is used in other tumours such as gliomas. Stereotactic radiosurgery is another method of radiotherapy, which delivers a large dose of radiation to the tumour in one dose, based on imaging that has accurately outlined the lesion. This technique is therefore useful in well-defined tumours such as meningiomas.[17] Another form of radiotherapy used in brain tumours is stereotactic radiotherapy, which carefully targets the radiation towards the tumour tissue, but also exploits the different radiosensitivities of neoplastic cells compared to normal brain cells via the process of fractionation.[3]

3. Chemotherapy

Chemotherapy is increasingly being used in the treatment of primary brain malignancies. The most commonly used agent is temozolamide, an alkylating agent which has good penetration of the blood brain barrier thereby allowing access to brain tissue.[18] Certain regimens in combination with radiotherapy have shown a survival benefit in gliomas compared to controls.[17] Chemotherapy can be used also in the treatment of oligodendrogliomas.[18]

4. Other therapies

Other treatments are beneficial in brain tumours such as corticosteroids to reduce mass effect and thus help to alleviate symptoms and improve the quality of life. Anticonvulsant therapy can be used in patients with seizures. Clinically apparent DVT or pulmonary embolism occurs in around 20-30% of patients with brain tumours.[3] This is perhaps due to the release of thromboplastins when brain tissue is injured.[3] In these patients, anticoagulants can be used to prevent further thrombotic events.[3]

Outcome and Prognosis

Outcome depends very much on the type of brain tumour. Benign tumours, such as meningiomas and pituitary adenomas, can be excised and are thus amenable to cure with an excellent prognosis. Astrocytomas, however, particularly higher grade tumours, are much more aggressive and therefore survival in the long-term is less likely. Median survival times (MST) vary with the grade of the tumour: the higher the grade, the poorer the prognosis. According to a Swiss study, pilocytic astrocytomas (WHO grade 1) have a very good prognosis, with 96% of patients surviving ten years. Grade 2 astrocytomas have a MST of around 5.6 years, while grade 3 anaplastic astrocytomas have a MST of 1.6 years. Grade 4 glioblastoma multiforme had a mean survival time of only 4 months in this study.[18] Oligodendrogliomas generally have a better prognosis, with a MST of 11.6 years for WHO grade 2, and 3.5 years for WHO grade 3.[19] Medulloblastoma outcome depends, among other factors such as whether there has been spread within the CNS to the spine. Non-disseminated medulloblastoma carries a relatively good long-term prognosis in children with a 5-year survival of 80%. This compares favourably to survival rates in adults which are around 50 to 60%.[20] In ependymoma, survival rates vary depending on whether the tumour is differentiated or anaplastic. Overall, in a retrospective study of the disease, survival was 57% and 46% at 5 and 7 years respectively following diagnosis.[21]

Conclusion

Brain tumours come in many varieties, with varying prognoses and management options. In this review I have tried to provide an overview of the different pathology that is included under the term of brain tumours. This is an area of much research and hopefully further developments will provide improved outcomes for patients and new techniques to improve morbidity and mortality from even the most aggressive tumours.

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