Review Article

Recent Advances in Childhood Brain Tumours

GCF Chan

Abstract

Brain tumours are the second commonest form of childhood malignancy. In Hong Kong, around 25 to 40 children below 15 years are diagnosed to have various types of brain tumours each year. But the term "brain tumour" in fact includes a heterogeneous group of tumours and their classification, diagnostic criteria, treatment modalities and outcome have undergone major changes in the past 2 decades. In this review, the objectives are to provide brief and update information on various developments in these areas. These will include: 1) the recent consensus in the classification of childhood brain tumours; 2) the current epidemiology of children with brain tumours, both locally and aboard; 3) the current hypotheses on the pathogenesis of some common paediatric brain tumours; 4) the common presenting features of the commonest types of childhood brain tumours locally; 5) the current diagnostic and therapeutic approaches and lastly; 6) the commonly encountered long-term sequelae among paediatric brain tumours survivors. In summary, many common forms of childhood brain tumours found locally can be cured nowadays. Current challenge is to further improve the outcome in those with poor outcome and minimise therapy related toxicity in those with good prognosis.

Key words

Brain tumours; Children

Classification of Childhood Brain Tumour

The classification of brain tumours has been constantly revised over times and the latest update version was the WHO classification year 2000 version.1 The basis of most classifications was primarily based on the histological characteristics with some consideration on the genetic background and embryonal origin. It has been quite confusing for paediatricians or even oncologists to comprehend totally due to several problems with the proposed classification system. First, it is quite complicated and many of the tumour types are not commonly seen in paediatric age group (i.e. most of the meningioma, intracranial mesenchymal and haematopoietic neoplasms). Secondly, there are overlaps in the terminology due to historical reason. For example, neuroblastoma found in the adrenal and sympathetic ganglions region is a very distinct disease entity in terms of origin, genetic aberration and clinical behaviour as compare to neuroblastoma in the supratentorial region or in the olfactory region. Thirdly, there are detailed subclassifications of some tumour types (i.e. 15 subclassifications for meningioma and 4 subclassifications for ependymoma and medulloblastoma each) and many of which do not carry any actual or definite differences in terms of clinical behaviour and treatment outcome.

Clinically, another simplified version of classification has been proposed primarily for coding purposes so easier data accrual and analysis can be performed in a population bases. This is known as International Classification of
Childhood Cancer (ICCC-3) and it classifies the common childhood brain tumours into a grouping of astrocytoma, other glioma, ependymoma, primitive neuroectodermal tumour (PNET), and miscellaneous intracranial & intraspinal tumours. This approach has also been adopted by the SEER (Surveillance, Epidemiology & End Result) for data collection and analysis purpose.

Some WHO classifications information can also applies with clinical relevance in paediatric brain tumours, for example, astrocytomas can further be classified according to their histological features into grade I to IV (grade I, pilocytic astrocytoma; grade II, low grade glioma; grade III, anaplastic astrocytoma; grade IV, glioblastoma multiforme) and this has remarkable correlation with the clinical aggressiveness and outcome.

PNET of the central nervous system (CNS) should also be clearly separated from the peripheral PNET. Peripheral PNET is closely related to Ewing’s sarcoma (EWS) and majority of them shares the t(11;22) abnormality and expresses Mic-2 antigen. EWS usually arises from the bone and peripheral PNET arises from soft tissues all around the body. In contrary, PNET of the CNS comprises a group of embryonic tumours arising from different parts of the brain. Histologically, they are quite similar to each other but they can be differentiated from each other by location. For example, medulloblastoma arises from the vermis of the cerebellum, supratentorial PNET arises from the cerebral hemisphere, pineoblastoma arises from the pineal gland, etc. However, recent microarray study showed that CNS PNETs have distinct gene expression profiles and therefore the differences do not lie on the location alone. Among the "miscellaneous intracranial tumour", germ cell tumours are the one that we should pay more attention to due to its relative high incidence locally. Germ cell tumours can further be divided into germinomatous and non-germinomatous groups. The non-germinomatous group includes yolk sac tumour (ectodermal sinus tract tumour), choriocarcinoma, embryonal carcinoma, benign and malignant teratoma and mixed type. It is important to differentiate them for their clinical behaviour especially in terms of response to treatment and prognosis.

Epidemiology of Paediatric Brain Tumour

In most countries and ethnic group, brain tumour is the second commonest group of childhood malignancy. But there are variations in the relative incidence of different tumours types. This can be due to either referral bias or difference in the classification method. Ethnic difference has also been described such as the higher incidence of germ cell tumour in the Japanese population. There is so far no population-based data on the incidence of different types of brain tumours in Chinese children found in the indexed English literature. Based on the Hong Kong Paediatric Haematology/Oncology Study Group (HKPHOSG) and Hong Kong Cancer Registry (HKCR) database from Jan 1999 to Dec 2003, there were a total of 131 children with brain tumours diagnosed in Hong Kong (GCF Chan, HKPHOSG Annual Workshop Report 2004). Based on the estimated mid-year children population (<15 years) of 1.1 millions by 2001 population census and excluding one patient originally coming from outside Hong Kong and 5 children older than 15-year-old (n=126). The annual incidence of brain tumours for Chinese Children in Hong Kong is 22.9/million children/year. The comparison of histological types with the Western population can be found in Figure 1. Similar to Japan, we have a much higher incidence of germ cell tumours in the brain than the Western population. The slight smaller incidence in the astrocytoma and higher incidence in the PNET group can be either due to the change in histological classification over the past 2 decades or to a genuine ethnic variation. This can be confirmed when our database became large enough for further verification.

The most common histological type of brain tumours in children remains to be astrocytomas as shown in different reported series. They can be further subdivided into different grades (i.e. Grade I to IV) and different locations (i.e. cerebral, brainstem). The relative frequency of each subtype in our patients’ cohort is shown in Figure 2. Concerning about the location of all the brain tumours, around 40-50% of the childhood brain tumours are originated from infratentorial territory and medulloblastoma is the commonest form of tumour arising from this region. Other relatively common infratentorial brain tumours in childhood include juvenile pilocytic astrocytoma, ependymoma and brain stem glioma. More than 95% of brain stem gliomas are high-grade astrocytoma and locate mainly in the pontine region. Germ cell tumours mainly arise from the mid line.
structures of the brain in particularly over the pineal region. Whereas ependymoma characteristically arising from the para-ventricular areas along the whole CNS system. All these characteristics are similar to what have been described in the Western literature.

Current Understanding of the Pathogenesis

The amount of knowledge about brain tumour biology increased exponentially over the past decade. The advances in molecular biological technology facilitated this development. Great amount of translational research findings have been generated but consistent correlation with clinical observations still requires the verification of large prospective studies. Due to the heterogeneity of the tumour types, it will not be surprised to see different models being postulated. Astrocytoma and medulloblastoma will be cited here as an example to illustrate some of these hypotheses.
Recently established genetic profiles of various grades of astrocytoma suggested an association between the biological behaviour with the events in genetic aberrations such as activation of oncogenes and inactivation of putative tumour suppressor genes. Activation of multiple oncogenes such as \( EGFR \) (epidermal growth factor receptor or \( c-erB1 \)), \( PDGFRA \) (platelet derived growth factor receptor alpha) genes in the same tumour are associated with high-grade characteristics with rapidly progressed clinical course. On the other hand, loss of heterozygosity at certain loci on chromosomes 10 (i.e. \( PTEN/MMAC-1 \), phosphate and tension analog/mutated in multiple advanced cancers-1 at 10q23) and 17 (i.e. p53 gene at 17p13.1) leading to loss of proliferation regulation has been linked to the progression of anaplastic astrocytoma to glioblastoma multiforme.

For medulloblastoma, loss of chromosome 17p distal to TP53 and isochromosome 17q is the commonest cytogenetic abnormality. Familial linkage studies identified association between nevoid basal cell carcinoma syndrome (NCCCS, also known as Gorlin syndrome) and the development of medulloblastoma. NBCCS is caused by a gemline mutation of a putative gemline tumour suppressor gene on chromosome 9q31. The gene involved is known as Patched (\( Ptc \)), which is a transmembrane receptor for the secreted ligand Sonic Hegehog (SHH) intracellular signaling pathway. So far, the desmoplastic variant of medulloblastoma that accounts for 10-20% of sporadic medulloblastoma cases is also characterised by mutations in the \( Ptc \) pathway. Interestingly, we have a much lower incidence of this particular type of medulloblastoma locally (1.5%, 2/131). Another condition that is prone to the development of medulloblastoma is Rubinstein-Taybi syndrome (RTS). RTS is associated with microdeletions on chromosome 16p13.3 in which is the gene responsible for the production of human CREB (cAMP response element) binding protein or CBP (CREB binding protein). CBP is a transcriptional co-activator that functions in many signal transduction pathways. It interacts with SHH signaling pathway mentioned above as a co-activator of \( Gli \) (Glioblastoma-1) family of transcription factor, in particularly \( Gli-1 \). Another familial condition known as Turcot syndrome, which results from mutation of APC or DNA mismatch repair genes are also associated with the development of medulloblastoma.

To summarise the current understanding on the genetic background of the 2 commonest types of childhood brain tumours, a diverse genetic mechanism has been identified. This information can help us to understand more about their pathogenesis or even prognostic significance. The known chromosomal or genetic aberrations associated with either good or bad clinical outcomes are listed in Table 1. The various inherited syndrome associated with the development of brain tumours are listed in Table 2.

### Pattern Recognition of Common Presenting Features of Childhood Brain Tumours

In general, presenting symptoms of brain tumours are closely related to the topographic location of the lesions, such as long tract sign for patients with tumour affecting the cortical spinal tract, different forms of visual field defect for optic tract tumour, etc. This is mainly the pattern for supratentorial tumours affecting the different parts of the cerebral hemisphere. Supratentorial astrocytoma and

<table>
<thead>
<tr>
<th>Types of tumours</th>
<th>Poor prognosis factors</th>
<th>Good prognostic factors</th>
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<tr>
<td>High grade astrocytomas</td>
<td>Mutated or over-expression of ( P53 ) \</td>
<td>-1p*, -19q* \</td>
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<tr>
<td></td>
<td>Over-expression of ( MIG-1 ) \</td>
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<tr>
<td>Medulloblastoma &amp; PNET</td>
<td>Over-expression of ( c-Myc ) \</td>
<td>Over-expression of ( Trk-C ) \</td>
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<td></td>
<td>Over-expression of ( ErbB-2 \ &amp; \ ErbB-4 ) \</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>+1q \</td>
<td>+7, +9, +18, -3, -6, -15 \</td>
</tr>
<tr>
<td>Meningioma</td>
<td>LOH: -1p, -10q, -14q \ Del ( CDKN2A ) (9p21) \</td>
<td>Over-expression of ( E-cadherin ) \</td>
</tr>
</tbody>
</table>

Abbreviations: + gain of chromosome, - loss of chromosome, Del: deletion, LOH: loss of heterozygosity

* Good prognostic correlation found in adults patients but no such association found in paediatric patients.

(Information adopted from the 10th International Symposium on Paediatric Neuro-Oncology, London, June 9-12, 2002.)
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene (chromosome)</th>
<th>Encoded protein (expression)</th>
<th>Gene dysfunction (function)</th>
<th>Brain tumours commonly found</th>
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<tr>
<td>Neurofibromatosis I</td>
<td>NF-1 (17q11.2)</td>
<td>Neurofibromin</td>
<td>Tumour suppressive gene</td>
<td>- Optic glioma</td>
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<td></td>
<td></td>
<td></td>
<td>- Low grade glioma</td>
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<tr>
<td>Neurofibromatosis II</td>
<td>NF-2 (22q11.2)</td>
<td>Merlin or Schwannomin</td>
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<td>- Meningioma</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- Acoustic neuroma</td>
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<tr>
<td>Turcot syndrome (associated with colonic cancer with polyposis in the colon)</td>
<td>APC (5q21)</td>
<td>Adenomatous polyposis coli (APC) protein</td>
<td>Disrupted Wnt signaling results in increase c-Myc &amp; cyclin D expression (oncogenes)</td>
<td>- Medulloblastoma</td>
</tr>
<tr>
<td>Turcot syndrome (associated with colonic cancer with no polyposis in the colon, HNPPC)</td>
<td>hMLH1 / hPMS2 proteins</td>
<td>DNA mismatch repair genes and cause microsatellite instability</td>
<td></td>
<td>- Glioblastoma</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 (9q34) / TSC2 (16p13.3)</td>
<td>Hamartin / Tuberin</td>
<td>Tumour suppressor gene</td>
<td>- Astrocytoma</td>
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<td>- Ependymoma</td>
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<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>VHL</td>
<td>VHL<em>9p &amp; pVHL</em>19</td>
<td>Cell cycle and angiogenesis control</td>
<td>- Haemangioblastoma</td>
</tr>
<tr>
<td>Cowden syndrome (Lhermitte-Duclos disease)</td>
<td>PTEN (10q23.3)</td>
<td>PTEN/MMAC-1 protein</td>
<td>Tumour suppressive gene</td>
<td>- Dysplastic gangliocytoma of cerebellum</td>
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<td>- Meningioma</td>
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<td>Li-Fraumeni syndrome</td>
<td>p53 (17p13.1)</td>
<td>p53 protein</td>
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<td>- Astrocytoma</td>
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<td>- Medulloblastoma</td>
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<td>- Choroids plexus carcinoma</td>
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<td></td>
<td>- Ependymoma</td>
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<tr>
<td>Gorlin syndrome</td>
<td>Ptc (9q31)</td>
<td>Ptc transmembrane receptor</td>
<td>Tumour suppressive gene</td>
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<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>-16p13.3</td>
<td>CBP</td>
<td>Tumour suppressive gene</td>
<td>- Medulloblastoma</td>
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<tr>
<td>Familial retinoblastoma syndrome</td>
<td>Rb (13q14)</td>
<td>pRb</td>
<td>Tumour suppressive gene</td>
<td>- Retinoblastoma</td>
</tr>
<tr>
<td>Families with increase melanoma &amp; brain tumours</td>
<td>INK4 (9p21) / (p16 &amp; p19ARF) proteins</td>
<td>Tumour suppressive gene</td>
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<tr>
<td>Pallister-Hall syndrome</td>
<td>Gli3 (7p13)</td>
<td>Transcription factor</td>
<td>- Hypothalamic hamartoma</td>
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(Information adopted from the 10th International Symposium on Paediatric Neuro-Oncology, London, June 9-12, 2002.)
ependymoma are the common groups of tumour present this way. Seizure as a whole is uncommon in children with brain tumours. It accounts for <5% of the presenting symptoms of brain tumours in our children. When it occurs, it is most commonly associated with low-grade astrocytoma or oligodendroglioma in the supratentorial region, and temporal lobe seems to be the commonest site in our local experience.

Tumours arise from the infratentorial region particularly at the vermis of the cerebellum region often present with symptoms of increase intracranial pressure. That is because of the forward expansion of the mass often compresses the narrow 4th ventricle anteriorly and induce obstructive hydrocephalus. Interestingly, the headache and vomiting can occur rather subtly. Affected child may complaint of headache upon waking up in the morning with or without vomiting. The symptoms can often be relieved after vomiting and the recurrence of symptoms may take several days or even week. There may not be any symptoms in between attack. Observative parents or teachers may be able to pick up deterioration in handwriting or gait occasionally in older children. Frequent headache, vomiting, trunkal ataxia or even cranial nerves deficit (mainly 6th and 7th cranial nerve) are symptoms related to more advanced disease. The non-specific initial signs and symptoms provide explanation why brain tumours in this region often present late. In contrary, brainstem glioma seldom presents with sign of obstructive hydrocephalus. A triad of symptoms namely multiple cranial nerves deficit (>90% occurs in the pons therefore mainly affects 5th, 6th, 7th & 8th); long tract sign (involvement of the corticospinal tract) and ataxia (involvement of the cerebellar tract) and without sign of increase intracranial pressure are strongly suggestive of pontine glioma.

Another characteristic pattern of presentation is related to the germ cell tumour. Since it is mainly arising from mid line, in particularly at the pineal and hypothalamic region, endocrine disturbances such as precocious puberty, diabetes insipidus may be the initial symptoms. Headache and vomiting due to obstructive hydrocephalus of the 3rd ventricle or chiasmatic visual field defect may be noted in more advanced stage. Diencephalic symptoms (wasting despite good appetite) and Giallastic seizure (inappropriate laughter episodes) are relatively uncommon but is characteristically associated with either germ cell or other types of tumour (i.e. hypothalamic hamatoma) arising from the mid line region of the brain. Some suprasellar tumour such as craniopharyngioma often has a long presenting history due to its benign nature. Growth failure due to hypopituitarism is one of the common presenting features with visual field defect. Of interest, the visual field defect does not necessary presents as bitemporal hemianopia (chiasmatic involvement) and a minority of patient may have other form of visual field defect such as unilateral homonymous hemianopsia due to the involvement of the optic tract posteriorly.

Current Diagnostic and Treatment Modalities

Diagnostic Modalities

With the advances of the imaging techniques, CT scan and MRI scan are now the 2 main tools in the diagnosis of brain tumours in children. In general, MRI can provide a more details and thorough assessment of the brain parenchyma but it takes a longer time to capture the information. Adequate and longer sedation may be necessary for young children. There are no more roles for some of the older forms of imaging such pneumagram and myelogram in the modern paediatric oncology service. They have been totally replaced by either CT or MRI scans by now.

While it is relatively satisfactory for either CT scan or MRI to provide diagnostic information, there are problems at time to differentiate the residual tumour from post-treatment scarring or inflamed tissues. Newer build-in modalities such as MR spectroscopy may be helpful in this aspect. Especially the multi-voxels MR spectroscopy may be theoretically helpful even for small size lesions. But it remains to be an investigatory tool at the moment and still could not produce reliable finding in periventricular areas. Positron Emission Tomography (PET) can assess the functional status of a tumour by checking its glucose isotopes uptake. It is quite sensitive and can provide additional information to the conventional CT or MRI imaging. However, false positive findings do exist and it does not provide spatial relationship between the lesions and normal brain structure. Proper correlation with conventional imaging is therefore mandatory. Currently, a newer modality, which combines the CT scan and PET scan via digital technology that can solve the anatomical correlation problem but the resolution of the CT scan appears to be less refined in this setting.

However, the gold standard of confirming the diagnosis remains to be histological examination. Therefore biopsy is required in most situations. The exception will be brainstem glioma. It is because >90% of them are high grade astrocytoma which diffusely involves the pontine area,
surgical biopsy of the pontine area carries high morbidity and mortality and the result will not alter the prognosis of this group of patients. Another example is non-germinomatous germ cell tumour with elevated serum αFP or β-HCG secretion; actual benefit of biopsy remains controversial in this setting.

**Treatments Modalities**

Surgery, radiation therapy and chemotherapy are the 3 main forms of therapeutic modalities and whether they have to be applied singly or in combination depending on the type and stage of the brain tumours. For medulloblastoma, except for a few localised completely excised tumours which may be treated with surgery and radiation therapy alone, combination of surgery/radiation therapy/chemotherapy are often time indicated. For the chemotherapy regimen, by using cisplatinum, CCNU and vincristine on 6 weekly basis for 8 cycles, an 86% 5-year-event free survival has been achieved for standard risk group of patients. But craniospinal irradiation upfront with weekly vincristine is another key element of this regimen. Latest result suggested that reduced dose radiation therapy could achieve similar result. It appears that cisplatinum-based chemotherapy with upfront radiation therapy produced similar results in our local patient cohort as well, a 83% 4-year-event free survival has been recorded so far (HKPHOSG 2004 workshop). For those with high-risk features which includes: 1) more than 1.5 cm residual tumour volume after surgery and 2) those with leptomeningeal metastasis, megatherapy followed by autologous marrow transplant rescue has been shown to produce a reasonably good result. Children <3-year-old is another poor risk group for radiation therapy has to be applied singly or in combination depending on the histological subtypes. In general, with the exception of malignant teratoma, GCT is chemosensitive. In recent years, platinum based chemotherapy remains questionable; recently temozolamide was found to induce response in a quarter of patients tested. There is a strong association between the status of the DNA repair enzyme O6-methyl-guanine-DNA-methyl-transferase (MGMT) and the outcome of response. Another novel modality is by using by using tumour lysate challenged autologous activated T-cells or dendritic cells as tumour vaccine. This remains to be an experimental approach and has to be conducted on a clinical trial basis.

For gliomas, low-grade tumours (Grade I & II) are treated with surgery alone. Grade I glioma such as pilocytic astrocytoma has a very good long-term survival of >90% if it is completely excised. However, when it located in the unresectable area such as the optic chiasma or thalamic area, the long term outcome is guarded. The role of chemotherapy and RT on unresectable low-grade gliomas, though controversial, has been tested with some encouraging preliminary results in recent years. For high-grade tumours, the survival remains dismal up to the current moment. Basically surgical excision is the main form of treatment follows by local high dose RT. The long-term survivors are rarity if there is any. The estimated median survival of anaplastic astrocytoma and glioblastoma multiforme are usually measured in months. The role of chemotherapy remains questionable; recently temozolamide did not produce any good evidence of response. Another novel modality is by using by using tumour lysate challenged autologous activated T-cells or dendritic cells as tumour vaccine. This remains to be an experimental approach and has to be conducted on a clinical trial basis.

For ependymoma, the role of chemotherapy remains controversial. The main form of treatment is surgery and local RT. The outcome is highly correlated with the presence of residual disease after surgery or not. In our limited experience, we found that supratentorial tumours that were completely excised, the long-term survival can reach 70-80% but for those with residual disease or with...
surgically inaccessible tumour, the survival rate would be much lower. We adopted the combination approach of using surgery + local RT + chemotherapy locally.

Despite being a benign tumour, craniopharyngioma has a high recurrence rate with significant long-term consequence in children.\textsuperscript{50,51} After either surgery or RT alone, close to 30\% will relapse. Current thought is to avoid overzealous intention in excising the tumour surgically.\textsuperscript{52} Additional therapy includes repeated surgery or intralesional chemotherapy if there is a cystic cavity inside the tumour.\textsuperscript{53} If the size of the tumour remains small, ablative RT in the form of gamma or X-knife can be attempted.

Common Long-term Sequelae of Paediatric Brain Tumours Survivors

As the survival rate of children with brain tumours improved over the past decade, a number of long-term complications either associated with the initial effect of the disease or as a consequence of the treatment.

Defect in cognitive function in the forms of short-term memory, abstract thinking, calculation and other high intellectual function are relatively common in childhood brain tumour survivors. The cause may be multifactorial. Study demonstrated that the baseline intelligent assessments of children with medulloblastoma prior to the commencement of treatment were already lower than the control group.\textsuperscript{54} That means the effects of the local tumour infiltration; its associated hydrocephalus or direct pressure effect may already have an impact on the brain function. The other confounding factor is high dose cranial irradiation. It has been shown to have an adverse effect on a developing brain. Children were found to have lower IQ score and poorer school performance than the age matched control.\textsuperscript{54,55} The effect of systemic chemotherapy and chronic hospitalisation on IQ score is less clear. However, cis-platinum, carboplatinum and ifosfamide had all been shown to have neurotoxicity. High frequency hearing impairment is a common finding of children receiving platinum based chemotherapy. In case of medulloblastoma, the booster radiation field targeted at the posterior fossa also inadvertently hit on the part of temporal lobe and inner ear canal, which may make the hearing impairment worse.\textsuperscript{56,57}

Permanent multiple endocrine deficiency in form of hypopituitarism and diabetes insipidus is a common finding of germ cell tumours and craniopharyngioma. The defect is partly or wholly caused by the tumour. The subsequent radiation therapy targets at the tumour bed will further ablate whatever residual function left. Proper assessment pre- and post-therapy will guide the replacement strategy. Partial endocrine defect may occur sometimes in patients receiving whole brain cranial irradiation with radiation dose of more than 3000 cGy.\textsuperscript{58}

Residual motor impairment and inco-ordination is a common finding of childhood brain tumours in particularly those affecting the cerebellum. In contrary, epilepsy is commoner in supratentorial tumours. Patients with large tumour, incompletely resected tumour or after extensive surgery are at a greater risk of developing epilepsy.\textsuperscript{59} Chronic subdural haematoma can occur as a consequence of excessive shunting within a short period of time leading to excessive negative pressure intracranially.\textsuperscript{60} It can be managed conservatively if it is mild or change to a low-pressure shunt system or to ventricular-atrium shunt. Recent trends is to avoid installing permanent VP shunt in children with resectable brain tumours, an external shunt can be used during the acute phase instead. While mild degree of leukomalacia can commonly be detected in brain tumour survivors using newer mode of MRI examination,\textsuperscript{61} severe radio-necrosis and leucomalacia is uncommon but does occur and carry significant morbidity.\textsuperscript{62}

Summary

Brain tumours, being the second commonest group of childhood malignancy, is a heterogeneous group of disease. Though with a complicated histological classification systems currently, it can be simplified into several key groups in paediatric population. The diagnosis of brain tumours in children are often delayed due to their subtle clinical signs and symptoms and lack of awareness of the relative non-specific presenting patterns. With the advances in the diagnostic tools and treatment modalities, the prognosis of many childhood brain tumours (such as medulloblastoma, germ cell tumour) improved drastically over the past decade. Some tumour types such as high-grade glioma remains to be a therapeutic challenge for both adult and paediatric oncologists. The understanding of the pathogenesis of brain tumours by the recent advances in molecular biology may help us to look for possible novel and targeted treatment modality. This may hopefully improve the treatment outcome of those poor risk brain tumours and minimise the treatment-induced complications of those good risk brain tumours in the future.
References


