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Brain tumours in children

Brain tumours are the most common site for solid tumours in childhood. A small peak in incidence of brain tumours in early childhood drops to a minimum in teenage years. Most childhood brain tumours (70-80%) are infratentorial (glial tumours, medulloblastoma) or in the midline (germ cell tumours, craniopharyngioma). Glial tumours in children are more frequently low-grade.[1]

Brain tumours generally have a better outcome in children than in adults but children with brain tumours are frequently unwell for months prior to diagnosis and a prolonged period between symptom onset and diagnosis is associated with increased morbidity.[2]

How common are brain tumours in children? (Epidemiology)[3]

- Brain tumours account for a quarter of all childhood cancers, affecting 1 in 2400 children under the age of 16 annually in the UK. More children die of brain tumours than any other cancer.[4]
- The largest subgroup is astrocytoma. Astrocytomas are diagnosed throughout childhood. Most astrocytomas are diagnosed as 'low-grade'.
- The second most common subgroup is the intracranial and intraspinal embryonal tumours (19% of all childhood brain and CNS tumours). Most of these are primitive neuroectodermal tumours (PNETs) and about 73% are medulloblastomas. PNETs occur most frequently in younger children.
- About 10% of childhood brain and CNS tumours are ependymoma and choroid plexus tumours. The incidence is highest in 1-year-old children.

Causes of brain tumours in children (aetiology)

- The underlying cause of brain tumours is unknown. However, some tumours are more common with certain illnesses - eg, astrocytomas are seen with increased frequency in neurofibromatosis and haemangioblastomas are more prevalent in patients with von Hippel-Lindau disease.
- This suggests a genetic link and mutations in several genes have been proposed - including the retinoblastoma gene (RB1), neurofibromatosis genes (NF1 and NF2) and tuberous sclerosis gene (TSC1), which function as tumour suppressor genes.[5] However, most cases of brain tumours are sporadic.
- Previous cranial irradiation also increases the risk of brain tumours - eg, meningeal leukaemia.[6]

Classification[7]

There are over 100 different histological subtypes of brain tumours:

- Gliomas (gliomas are graded according to whether they are slow-growing (low-grade) or fast-growing (high-grade); grade 1 is the slowest-growing type and grade 4 is the fastest-growing):
    - Astrocytic tumour: low-grade astrocytoma, anaplastic astrocytoma, glioblastoma multiforme.
    - Oligodendroglioma: benign or anaplastic.
    - Ependymoma: benign or anaplastic.
    - Mixed glioma: astrocytoma and oligodendroglioma.
    - Ganglioglioma: benign or anaplastic.
    - Choroid plexus tumour: papilloma or carcinoma.
- PNETs: supratentorial primitive neuroectodermal tumours, medulloblastoma, pineoblastoma.
- Congenital: teratoma, craniopharyngioma.

- Pineal tumours: germinoma, endodermal sinus tumour, embryonal cell carcinoma, choriocarcinoma, pineocytoma or pineoblastoma.
- Very rare tumours: primary CNS lymphoma.
- Benign tumours (more common in adults): meningioma, acoustic neuroma, pituitary tumour.

Localisation and frequency of childhood brain tumours

- Hemispheric: glioma.
- Midline: chiasmal gliomas, craniopharyngiomas, pineal region tumours.
- Posterior fossa: brainstem gliomas, medulloblastomas, ependymomas, cerebellar astrocytomas.

Symptoms of brain tumours in children (presentation)[8] [9]

- Intracranial tumours:
    - Headache, nausea and vomiting, abnormalities of gait and co-ordination, and papilloedema.
    - Headaches are usually recurrent, frequent and gradually worsening.[10]
    - Headaches may be worse on waking, indicating raised intracranial pressure. Headaches are more common with infratentorial lesions.
- Children aged under 4 years with intracranial tumours:
    - Macrocephaly, nausea and vomiting, irritability and lethargy.
    - Children under the age of 2 years tend to have nonspecific presentation with vomiting, lethargy, failure to thrive and irritability. They may develop macrocephaly, hyperreflexia and cranial nerve palsies.

- Children with an intracranial tumour and neurofibromatosis:
    - Reduced visual acuity, exophthalmia and optic atrophy.
- Posterior fossa tumours:
    - Nausea and vomiting, headache, abnormal gait and co-ordination, and papilloedema.
    - The presentation of infratentorial tumours relates to blockage of the CSF flow, leading to hydrocephalus. Common signs and symptoms include morning headache, vomiting (may be the only symptom of an ependymoma), ataxic gait with unsteadiness, double vision and papilloedema.
    - Brainstem tumours may also present with facial or ocular muscle palsies and hemiparesis.
- Supratentorial tumours:
    - Unspecified symptoms and signs of raised intracranial pressure, seizures and papilloedema.
- Central brain tumours:
    - Headache, abnormal eye movements, squint, and nausea and vomiting.
- Brainstem tumours:
    - Abnormal gait and co-ordination, cranial nerve palsies, pyramidal signs, headache and squint.

- Other neurological features related to tumour location (eg, frontal lobe tumours are associated with personality change and occipital lobe tumours are associated with visual deficits). Other symptoms relating to type or location of brain tumour include:

    - Chiasmal tumours - visual field defects and hydrocephalus.
    - Craniopharyngiomas - short stature, visual field defects, hormonal abnormalities and hydrocephalus.
    - Pineal tumours - impaired upgaze, impaired accommodation and hydrocephalus.
    - Infratentorial tumours: features may include seizures, visual problems, headaches, muscle paralysis, respiratory changes, increased intracranial pressure, poor co-ordination and heating loss..

- Other features included weight loss, growth failure and precocious puberty. Symptoms of raised intracranial pressure were absent in more than half of children with brain tumours.

Diagnosing brain tumours in children (investigations)

Important information
NB: consider a very urgent referral (for an appointment within 48 hours) for suspected brain or CNS cancer in children and young people with newly abnormal cerebellar or other central neurological function.[11]

- MRI and CT:
    - MRI is the preferred modality of imaging, as it provides better images and there is no radiation involved.[8]
    - However, compared to CT scanning it takes longer and the child may need sedating, as they are required to remain still for the entire procedure.
    - Usually contrast is also given to detect areas of damage to the blood brain barrier and highlight the extent of oedema around the tumour.
    - MRI will provide detailed information regarding the tumour size, location, extent, surrounding oedema and presence of hydrocephalus.
- Biopsy - often excision biopsy.
- Other investigations will depend on individual presentation but may include hearing tests and pituitary function tests.
- CSF analysis can reveal increased levels of human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) in pineal tumours and raised serial polyamines in recurrence of medulloblastoma before radiological detectable recurrence. However, lumbar puncture and CSF evaluation generally have little to add in the diagnosis of childhood brain tumours.

Management of brain tumours in children

Treatment will be determined by the tumour type and location as well as the age of the child. Treatment may involve surgery, chemotherapy and radiotherapy.[8]

Management also includes treatment of complications (eg, raised intracranial pressure, hydrocephalus, seizures, pituitary hormone deficiencies), support for the child and their family and addressing any associated psychological and educational difficulties.

Surgical resection

- Surgical resection is very important and recent data suggest that complete total resection, especially of gliomas, should always be the aim and is associated with improved survival in children.[12]
- However, complete resection of the tumour is often not achievable as the margins of most tumours are indistinct. This means that during surgical resection it becomes difficult to determine whether abnormal or normal tissue is being resected. Resection also allows for a biopsy to be taken which in some types of brain tumour alters therapy.
- Biopsy may be performed beforehand and usually direct open biopsy is preferred at the time of surgery although, for basal ganglia and brainstem lesions, stereotactic biopsies are taken.
- Hydrocephalus is common postoperatively and therefore at the time of surgery an external ventricular drain or ventriculoperitoneal shunt is inserted which will be removed a few days later once the CSF clears.
- Very young children (under the age of 2 years) require radical resection as radiotherapy is delayed until they are older, as it will damage local normal tissue which is still developing. This is usually followed by chemotherapy.

Radiotherapy

- This is provided in low doses and to very localised areas to avoid damage to surrounding normal brain tissue. There are various techniques that can be used, eg, gamma knife (used for slow-growing lesions) and interstitial seeds which are implanted during surgery.

Chemotherapy

- There are various chemotherapy regimens in use, depending on histological subtype and stage of the individual brain tumour.

Follow-up after treatment

Children have regular reviews with MRI scans. The frequency and duration of follow up will depend on multiple factors, including histological subtype and initial treatment success.

Complications of brain tumours in children

- Intellectual decline - a recent study of 120 young patients with primary brain tumours showed a decline in sustained attention span and reaction times. This appeared to be caused by multiple factors including local tumour effects, surgery and radiotherapy. More recently, guidance on detecting and monitoring cognitive decline has been proposed.[13]
- Growth hormone deficiency is common (thyroid hormone deficiency is less common).
- Neurological handicap may occur and be permanent.
- Increased risk of a second brain tumour 10-20 years down the line due to irradiation (eg, developing meningioma or sarcoma) - risk is increased if the brain is irradiated at a very young age.[14] [15]
- Reduced bone mineral density of multifactorial origin.[16]
- Cavernomas presenting as haemorrhagic lesions are increasingly being associated with CNS irradiation.[17]

Prognosis[3]

Earlier diagnosis of brain tumours in children and young adults improves long-term outcomes.[8]

A UK report in 2019 reported that 5-year survival from CNS tumours was lower for children (74%) than for teenagers and young adults (78%).

- The survival gap in favour of teenagers and young adults was wider for ependymoma (children 71%, teenagers and young adults 88%), medulloblastoma (children 65%, teenagers and young adults 75%) and for mixed and unspecified gliomas (children 44%, teenagers and young adults 64%).
- Survival exceeded 90% in both children and teenagers and young adults for pilocytic astrocytoma, craniopharyngioma and neuronal and mixed neuronal glial tumours.
- For astrocytomas other than pilocytic astrocytoma, children had higher survival (66%) than teenagers and young adults (50%).

The spectrum of CNS tumours is different between young children, older children, adolescents and young adults, and a simple comparison of survival between CNS tumours in children and teenagers and young adults misses much relevant detail. Even within a single tumour type, there may be marked morphological and biological differences with age.

Further reading

- Brain Tumours in Children Toolkit; Royal College of General Practitioners (2016)
- Ostrom QT, Adel Fahmideh M, Cote DJ, et al; Risk factors for childhood and adult primary brain tumors. Neuro Oncol. 2019 Nov 4;21(11):1357-1375. doi: 10.1093/neuonc/noz123.

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Originally Published: 20/11/2023	Next review date: 21/06/2023	Document ID: doc_1883

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