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Approach to Brain Tumors in Children

Developed by Chelsea Howie and Dr. Bruce Crooks for PedsCases.com.
May 30, 2020

Introduction:

Hi everyone! My name is Chelsea Howie and I am a medical student at Dalhousie University Medical School. Today I will be discussing an approach to brain tumors in children. Before we get started, I would like to thank Dr. Bruce Crooks, a Pediatric Hematologist/Oncologist at the IWK Children's Hospital for his help in developing this podcast.

Clinical Case

Let's start with a clinical case. You are a clinical clerk doing your emergency medicine rotation at the local children's hospital. Charlie is an 8-year-old boy who has been complaining of intermittent headache for 2-3 months. They have seen a doctor in a walk-in clinic twice in the last few months, who reassured the family that everything was fine. When you ask about other symptoms, you discover that for the past week, he has vomited, usually in the morning, and his parents have noticed him having troubles with balance - bumping into walls and furniture which is uncharacteristic of him. He's also had difficulty going up and down stairs, needing to hold the handrail. You perform a neurological examination. Charlie has some unsteadiness walking heel-to-toe and loses his balance when trying to stand on his left leg alone. The cranial nerve exam reveals horizontal diplopia and what you believe to be an abducens (or a 6th) nerve palsy, as he has a right esotropia. The rest of the examination is unremarkable. What are your thoughts about Charlie's problems?

The objectives of this podcast are:

1. To delineate the epidemiology and etiology of brain tumors in children
2. To recognize the clinical presentation of brain tumors in children, including key findings on the history and physical exams, and differential diagnoses
3. To review the initial management and mainstays of treatment for common types of brain tumors in children

4. To discuss the short & long-term sequelae for children and youth after treatment for brain tumors

Introduction

Central nervous system, or CNS tumours represent 19% of cancers in children aged 0-14 (1). These are the most common solid tumors of childhood and are the most common cause of deaths from childhood cancer in the developed world. Children experience significant morbidity and mortality from CNS tumors, due both to the presence of the primary tumor as well as to short- and long-term side effects from various treatment modalities including surgery, chemotherapy and radiotherapy (2). As a result of new molecular and genetic testing, there is better understandings of the pathology of brain tumors. Similarly, evolving clinical research continues to shape diagnosis and treatment for affected children (3).

Epidemiology/Etiology

There are more than 100 different histological subtypes of brain tumors, grouped by cell of origin, and the incidences of which varies with subtype, patient sex, and age (4,5). Tumors are also grouped by clinical behaviour from low-grade to high-grade. Gliomas, which arise from glial cells, are the most common brain tumors, with low grade astrocytomas having the highest incidence in this group. Embryonal tumors are the next commonest group, with the most common of these being medulloblastomas at approximately 11%. Medulloblastomas are the most common *malignant* tumor across all age groups (5).

Approximately 57% of all brain tumor cases occur in males, particularly medulloblastomas (5). Younger children, aged 0-5, have higher incidences of embryonal tumors such as medulloblastomas, whereas glial tumors such as astrocytomas and glioblastomas are more common in older children, aged 9-11 (5,6).

There are multiple etiological factors which may influence the development of brain tumors in children. These include but are not limited to: familial cancer syndromes such as neurofibromatosis, Li Fraumeni syndrome or tuberous sclerosis, previous exposure to therapeutic ionizing radiation, older parental age, and congenital nervous system abnormalities (4).

Clinical Presentations

Children with CNS tumours often present due to the physical effects of a tumour mass on the structures of the brain itself. Symptoms are usually new neurological signs or may be due to hydrocephalus. As such these symptoms can be very diverse. Headache is the most common symptom. This finding is often a part of a slowly developing triad of

headache, nausea & vomiting, and ataxia, or unsteadiness, which is usually due to hydrocephalus. This is a buildup of cerebral spinal fluid due to obstruction of the normal drainage channels by the tumor, and is often seen in tumors within the midbrain structures, or posterior fossa. In infants and younger children (under 4), who are not yet walking or are unable to verbalize, common signs include macrocephaly, vomiting, irritability, and lethargy. Other signs and symptoms of a new brain tumor, depending on anatomic location, could include visual complaints, onset of weakness, regression of developmental milestones, and failure to thrive. Understandably, these signs and symptoms in isolation may not immediately raise alarm for presence of a brain tumor, and, need to be evaluated alongside other features on careful physical examination, and neuroimaging (6,7). The differential diagnoses for a brain tumor in a child often include common conditions such as tension or migraine headaches or non-specific infections. Less common conditions may include a brain abscess, non-malignant hydrocephalus, intracranial hemorrhage and arteriovenous malformations.
In terms of general *historical* findings, the history could include a progressive decline in school performance, change in mood, or personality in older children, or regression of developmental milestones in younger children. A careful neurological examination is of utmost importance in evaluating a new brain tumor. Let's go through possible exam findings, step by step. A more rapid presentation could be an acute decrease in level of consciousness. Cranial nerve examination may reveal various visual field deficits, double vision, papilledema, nystagmus, gaze paralysis, facial weakness, hearing deficits, and drooling or difficulty swallowing. Examination of peripheral motor function could show unilateral or bilateral weakness, with or without muscle wasting, pronator drift, changes in tone due to atrophy, and early handedness. Sensory examination can show deficits in a focal distribution. Evaluation of cerebellar function and coordination can reveal abnormality or asymmetry of finger or toe tapping, or rapid repetitive movements. There may be over or undershooting of finger-to-nose testing, otherwise known as dysmetria. There may be a broad-based, unsteady, or ataxic gait, difficulty performing tandem gait, and balance abnormalities, which may be unilateral or bilateral. Reflex testing is important, and may reveal hyper, or hypo-reflexia. Clinicians should also look for clonus and abnormal plantar reflexes. Combining neurological findings should point to the anatomical site of a tumour. Lastly, a thorough examination of the skin may help to indicate an underlying diagnosis. Neurocutaneous findings such as café au lait spots, neurofibromas, and axillary freckling are suggestive of neurofibromatosis, whereas shagreen patches, facial angiomas, and ash leaf macules are more indicative of tuberous sclerosis, for example (6,7).

Neuroimaging is a crucial part of solidifying the diagnosis. In the emergency setting, a CT is often used as a first-line scan, as it is more widely available, is fast, and may not require sedation. MRI with contrast enhancement, however, is the standard of care for children with a suspected CNS tumor. For children with known brain tumors, serial MRI's are used to track response to therapy and evaluate for tumor growth or recurrence (6).

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Let's go back to our case and review Charlie's presentation. He presented with a long-standing history of intermittent headaches, and more recently developed episodes of vomiting and trouble with coordination and balance. He has a handful of concerning signs on exam, including a cranial nerve deficit. You also note that he does not have any neurocutaneous findings suggestive of neurofibromatosis or tuberous sclerosis. You request a head CT, which reveals a mass in the posterior fossa. What are your next steps?

Management & Treatment

Breaking the news of any cancer to a family is always a difficult discussion. Giving this news to families should be done respectfully and tactfully by experienced professionals, following the general principles of breaking bad news. This is best done in a quiet and private location, asking them their current impression and level of knowledge, providing information in small pieces, answering any questions simply and honestly and providing the opportunity for follow up. It is important to note that a definitive diagnosis cannot be given to the patient and family until the tumor tissue is examined by pathology, following either surgical resection, or biopsy. Thus, discussion of diagnosis and the plan going forward should be led by a multidisciplinary team, including neurosurgery, oncology, and radiotherapy alongside strong supportive care including nursing and social work (6).

Due to the diversity in types and grades of pediatric brain tumors, the management and treatment strategies vary greatly. Generally, a consultation to neurosurgery is the initial step in managing and treating newly diagnosed brain tumors. A detailed assessment including appropriate MRI imaging is essential. This should be supported by appropriate bloodwork to prepare the patient for surgery. If a germ cell tumour is suspected, this should also include the tumour markers alpha fetoprotein, or AFP, and beta-HCG. Workup may also include a lumbar puncture to look for disseminated disease in the CSF (6).

Neurosurgical intervention can be for diagnostic and/or therapeutic purposes. Depending on the size and location of the tumor, a biopsy may be taken, or a partial or complete resection may occur. Complete resection may be curative in cases of low-grade tumors. Adjuvant treatments such as chemotherapy, radiation, and biologic therapy may be delivered based on the diagnosis, presence of residual tumor, and evidence of metastases (6).

Clinical review and surveillance neuro-imaging in children who have completed treatments is vital since the number of children who will have recurrences or residual disease is not insignificant. This is dependent on a number of factors including age, histological tumor type, and type and intensity of past therapies (6).

Looking back at the case, an urgent referral to neurosurgery is essential. The degree to which the tumor can be resected, and the definitive treatment plan would be determined by the multidisciplinary brain tumour team often alongside other professionals in the

setting of tumor boards or rounds. Charlie receives the appropriate pre-operative and operative care. His biopsies reveal a low grade, pilocytic astrocytoma in the posterior fossa, which was unable to be resected completely. In Charlie's case, even though he had residual disease, the brain tumour team decided that close observation would be the most appropriate initial management plan since some low-grade gliomas do not regrow, even if there is residual disease. If there was subsequent recurrence, chemotherapy was planned as the next recommended treatment. Due to its long-term side effects, radiotherapy was reserved for tumour that was non-responsive to chemotherapy, and was unresectable.

Short & Long-Term Sequelae

Any intervention or treatment may have side effects. Acute side effects may be related to any of the interventions that the child undergoes. Headache remains a common complaint post-surgically. Adverse effects of chemotherapy may include nausea, vomiting, fatigue and hair loss. There may also be myelosuppression, neuropathies, hearing and renal damage, depending on the chemotherapy agents used. Nausea, vomiting, and fatigue are common adverse effects of cranial radiation. Any child with a brain tumor can also experience seizures. Many of these effects can be managed well with medications (6).

Long-term morbidity and mortality are likewise consequences of treatments. Increasing numbers of long-term survivors have chronic health problems related to their treatments, or to their original tumours, some of which require long-term follow up and monitoring from health professionals. Previous treatment with chemotherapy comes with the risk of later developing secondary malignancies. Depending on the type of chemotherapy, organ function, including cardiac, renal, hepatic, and pulmonary, may be compromised. For both males and females, fertility and gonadal function may be decreased or lost. High frequency hearing loss is a common phenomenon in children who have received platinum-based chemotherapy such as cisplatin (8).

Radiation therapy often has the most significant impact in terms of long-term effects on children. Neurocognition is most commonly affected, and the risk of this is higher in children who receive cranial or craniospinal radiation at younger ages. In general, we try to avoid radiation completely in children under the age of three years. Tumor location and radiation dose are other important factors in the development of neurocognitive injury. These children often experience learning and memory difficulties, and as such may require educational and other supports within the school system. Radiation that affects the hypothalamus-pituitary axis can lead to development of endocrinopathies, such as hypopituitarism, hypothyroidism, growth hormone deficiency, and diabetes insipidus. Neurovascular disease, such as Moyamoya disease, can also occur and can increase the risk for future strokes (6,9).

All patients, regardless of age, tumor type or location, and treatments are at risk for psychosocial effects, such as depression. Screening by the family physician,

pediatrician, and neuro-oncologist for depression and other mental health illnesses is encouraged. It is also important to inquire about the family dynamic, as sibling and peer relationships may be disrupted (6).

Conclusion

Let's review a few of the important points discussed in this podcast:

- The subtypes and severity of brain tumors are extremely diverse, with gliomas being the most common type in children of all ages, and medulloblastoma being the most common malignant tumour. There are many possible risk factors for development.
- A common triad of signs and symptoms for a brain tumor include headache, nausea and/or vomiting, and gait imbalance. All signs and symptoms need to be considered within the context of the clinical presentation, including a thorough history, detailed physical exam, and neuro-imaging.
- Although variable, surgery, chemotherapy and radiation are mainstays of treatment for brain tumors in children. In some cases, surgery may be curative alone, whereas others require combination therapies.
- All involved health professionals should be aware and screening for the short and long-term effects post-treatment.

Let's re-visit our case for the last time. Now on your pediatrics rotation, you request to continue following Charlie through his course. Unfortunately, Charlie's tumour did continue to grow, and it was felt that a subsequent surgery put him at unacceptable risk of neurological damage. Charlie and his family are preparing for him to start treatment with chemotherapy, which will last for about 18 months. Alongside the oncologist, you discuss the schedule of treatments and include the possible acute and long-term effects of these therapies with the family, who give their consent. They are worried about how he will fare in school, his ability to have children in the future, and how this may affect the family unit as a whole. You provide the family with various resources, including local and online support groups, and refer them to social worker, school services and Child Life who work within the pediatric oncology team. They are happy with this, and Charlie's treatment plan is initiated.

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