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CLINICAL ASPECTS AND DIAGNOSIS OF BRAIN TUMOUR IN CHILDREN

Arben Preza[1] and Alketa Hoxha[2]
[1]University Hospital Centre "Mother Teresa", Tirana, Albania
[2]Obstetric-Gynecological University Hospital "Koço Gliozheni", Tirana, Albania

Abstract: Primary central nervous system (CNS) tumors are the 2nd most common cancer and the leading cause of cancer-related death in children [1,2]. Survivors may suffer significant long-term morbidity as a result of the tumor and/or the therapy given [3–6]. In general, therapy may consist of surgery, chemotherapy and/or radiation depending on the underlying diagnosis. Over time, there has been gradual improvement in survival of children with CNS tumors. To ensure an optimum treatment strategy in the management of children with brain tumors, a multidisciplinary team of specialized clinicians is mandatory. The disciplines involved must be coordinated at regular intervals. Each individual discipline has its area of expertise and performs its assigned role. However, decisions are often made and supported collectively by several or even all the involved disciplines. The exact treatment approach to treating children with brain tumors is described in the following. Initially, the pediatrician frequently has the leading role. In cases of suspected brain tumors, a specialist (pediatric neurologist and/or (pediatric) neurosurgeon) should be consulted from the beginning of treatment.
Keywords: Pediatric brain tumours, morphology, diagnostics.

Introduction

Primary central nervous system (CNS) tumors are the 2nd most common cancer and the leading cause of cancer-related death in children [1,2]. Survivors may suffer significant long-term morbidity as a result of the tumor and/or the therapy given [3–6]. In general, therapy may consist of surgery, chemotherapy and/or radiation depending on the underlying diagnosis. Over time, there has been gradual improvement in survival of children with CNS tumors [7]. This is related to improved diagnostics, enhanced neurosurgical technique and multimodal therapies. Despite this, a significant portion of patients succumb to their disease and improvements are needed not only with regard to survival but as well with regard to quality of outcome. In order to interpret national outcome data, one must have an understanding of the therapy given. This context is crucial to understanding fluctuations or improvements over time. When possible, children should be offered enrollment into a clinical trial, however this is not always possible either due to paucity of trial availability, limited spaces for early phase trials or family refusal to participate. Canadian data suggests that only

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a minority of children with CNS tumors enroll on a clinical trial with the most common reason cited being absence of a clinical trial available [8]. In certain tumors, the molecular drivers have been well described including medulloblastoma [9], pediatric low grade glioma (pLGG) [10], ependymoma (EPN) and atypical teratoid rhabdoid tumor (ATRT). These have been found to have clear implications for outcome; however, clinical trials are just now examining alternative therapies based on molecular subgroup. Historically, patients with one histological diagnosis (i.e. medulloblastoma) have all been treated homogeneously. Targeted inhibitors are also under study in a variety of tumors, though adoption of use outside of clinical trials has been limited in most tumors. In many cases, this molecular information impacts prognosis and trial eligibility, but does not yet alter clinical management in the absence of a trial.

Material And Methods

The literature search was performed on PubMed, Medline and Google scholar, chosen because they are reliable and easy to read. ‘Neurogenic bladder’, ‘disc herniation’, ‘disc prolapse’, ‘disc protrusion’, ‘cauda equina syndrome’, ‘treatment’, ‘surgery’ and ‘urodynamic’ were used as keywords, either alone or in combination using ‘AND’ or ‘OR’, to focus the search on the topic without excluding relevant papers. The reference lists of the articles retrieved were examined to capture any other potentially relevant article. The search was restricted to articles published between 2000 and 2022 to acquire all the scientific knowledge about neurologic bladder, which grew fast in this period. Seventy-nine papers were found, but only 39 were reviewed and summarized. The excluded papers were judged neither pertinent nor very useful.

Results

Clinical Assessment/Symptoms

In medicine, children cannot simply be considered small adults, and a specialized multidisciplinary team is mandatory to manage all treatment related aspects in children with CNS tumors [1]. Pediatric brain tumor related symptoms and signs can be unspecific, thus delaying diagnosis. Therefore, several brain tumor awareness programs have been initiated [10,11]. In infants and young children, not only the tumor itself but also an associated hydrocephalus can significantly impair neurodevelopment and have severe long-term sequelae. Neurological signs and symptoms in pediatric brain tumors can be different compared to adult patients. It is recommended that pediatric patients should be seen by a pediatric neurologist and/or neurosurgeon with extensive experience in pediatric neuro-

oncology (ideally by a pediatric neurosurgeon). No clinical correlation exists between tumor type and symptoms. Clinical and radiological tumor presentations vary significantly and are dependent on the age of the child and the tumor growth patterns [12]. Children with brain tumors may present with focal symptoms [1]. These symptoms depend on the exact location of the tumor and the adjacent structures. Motor and sensory deficits may occur, for example, if the central cortex or corticospinal tracts are affected. A language deficit can result from impairment of the language centers or the connections of these regions (frontoparietotemporal left-sided tumors, e.g., Broca's, Wernicke's, or fasciculus arcuatus). Cerebellar tumors often result in ataxia, fine motor dysfunction, and balance disorders. However, cranial nerve deficits may also be observed, and, depending on the extent of brainstem impairment, respiratory and circulatory disorders may also
occur [13]. Focal symptoms may be accompanied by further symptoms due to increased intracranial pressure (ICP). The increased intracerebral pressure might be caused by the tumor mass or concomitant hydrocephalus. Again, the symptoms often differ among age groups. For example, signs of elevated ICP in infants may manifest as a tense fontanel, sunset phenomenon, and vomiting. In addition, non-specific symptoms, such as macrocephaly, irritability, failure to thrive, or loss of developmental milestones, can be signs of increased ICP caused by a brain tumor or associated hydrocephalus. In older children, high ICP may present with headache, nausea and vomiting, anisocoria, impaired vision, and decreased vigilance [1]. For a subset of tumors growing in the suprasellar region, signs of endocrine dysfunction should also warrant suspicion.

In addition, attention should be drawn to family history and a possible syndromic disease. Several syndromes with elevated risk of developing a brain tumor during childhood, such as neurofibromatosis type 1 (NF-1) and type 2 (NF-2), tuberous sclerosis, Li-Fraumeni syndrome, and Gorlin syndrome [1]. Seizures can be directly induced by a supratentorial brain tumor [13] or a high ICP due to associated hydrocephalus. In infants, failure to thrive may be the only sign of a brain tumor. Whenever a child presents with neurologic symptoms, acute ICP should always be considered, and immediate admission to a specialized clinic should be sought, because any delay in diagnosis and treatment is potentially life-threatening.

Diagnostics

After the clinical examination and detailed anamnesis by the general pediatrician and/or pediatric neurologist, and possibly a (pediatric) neurosurgeon, any subtle suspicion of a pediatric brain tumor should be investigated with sliced imaging as early as possible. The

diagnostic gold standard for a suspected brain tumor is magnetic resonance imaging MRI [14]. A larger mass can also be seen in computed tomography (CT) scans. CT is justified in emergencies, such as a comatose child presenting with dilated pupils who requires immediate surgery. However, because of its radiation exposure and limited diagnostic value, CT should be used in children only in emergency settings or when an MRI is not feasible. In the case of eloquent neighboring regions, functional MRI (fMRI) can be applied to reveal the involvement of important brain areas. Special approaches, such as diffusion studies, can be used to determine tumor type [15,16]. The MR spectroscopy (MRS) can additionally contribute to the differentiation of the tumor entity [17]. Some of the tumors (e.g., medulloblastoma, pilocytic astrocytoma, or ependymomas) are associated with leptomeningeal or intrinsic dissemination. If suspected, to confirm the diagnosis, an MRI of the entire neuroaxis should be acquired. Furthermore, cerebrospinal fluid (CSF) samples can be obtained through lumbar puncture to determine leptomeningeal spreading after exclusion of a potential risk of brain herniation [18,19]. In cases of suspected germ cell tumors, the assessment of serum and CSF tumor markers is crucial for the initial treatment stratification [20]. Because most brain tumors are associated with elevated ICP or may involve optic structures, ophthalmological assessment is recommended. In suprasellar midline tumors, additional hormonal status determination is advisable. Because of the importance of rapid and complete work up, a pediatric neurologist, pediatric oncologist and/or (pediatric) neurosurgeon should be involved immediately after hospital admission. This multidisciplinary management at the beginning of treatment ensures immediate and appropriate treatment according to the existing protocols available for most of the tumor entities.

Discussion

To ensure an optimum treatment strategy in the management of children with brain tumors, a multidisciplinary team of specialized clinicians is mandatory. The disciplines involved must be coordinated at regular intervals. Each individual discipline has its area of expertise and performs its assigned role. However, decisions are often made and supported collectively by several or even all the involved disciplines. The exact treatment approach to treating children with brain tumors is described in the following. Initially, the pediatrician frequently has the leading role. In cases of suspected brain tumors, a specialist (pediatric neurologist and/or (pediatric) neurosurgeon) should be consulted from the beginning of treatment. If signs of elevated ICP are present, the immediate involvement of a (pediatric) neurosurgeon is

mandatory, to enable early emergency interventions and avoid unnecessary delays. After neuroimaging, discussion with a neuroradiologist is necessary to narrow down the most likely differential diagnosis. The subsequent approach depends on the symptoms and the suspected diagnosis of the child. If the suspicion of elevated ICP is confirmed on imaging, emergency intervention has to be considered because of the associated life-threatening risks. Therapy includes optimized body positioning (e.g., neck elevation at 30_ to avoid jugular vein compression), short-term hyperventilation [21], administration of steroids [22] and hyperosmolar therapy (e.g., mannitol, or hypertonic saline) [21], and more invasive procedures, such as the insertion of an external ventricular drain, insertion of an Ommaya reservoir for serial puncture, endoscopic ventriculostomy, or emergency tumor resection. In the absence of elevated ICP, subsequent procedures are decided jointly by collaborators from different disciplines. As a rule, an internal multidisciplinary discussion among a pediatrician, pediatric neurologist, pediatric oncologist, radiation oncologist, (pediatric) neurosurgeon, and nursing staff [23] is important. The group composition may vary and must be adapted to each individual case. In the further course, other disciplines will be added to the multidisciplinary team. A multidisciplinary neuro-oncology group also includes a (neuro-) psychologist and/or physiotherapist. The leading department is defined, and subsequently performs coordination tasks and serves as direct contact for the family. Often, pediatric oncology or pediatric neurology is the clear leading department choice. However, neurosurgery may be chosen, depending on the individual situation. The possible suspected diagnosis is discussed, and the further procedure are determined step by step as follows. The (pediatric) neurosurgeon indicates the possible surgical procedures, e.g., whether a tumor resection is possible or whether a biopsy can instead be attempted from a surgical view-point. Depending on the suspected diagnosis, the pediatric oncologist emphasizes the extent of resection. Several scenarios can be collaboratively reviewed. Inclusion in ongoing clinical studies must be considered by the oncologist. The (neuro-) psychologist might already better address fears and psychological issues, and support the family. After multidisciplinary discussion, the family should be informed of all possible consequences of the disease. The first joint conversation with the family is usually conducted by a member of one of the disciplines, and complementary information is provided by the other specialists. The family is introduced to all the involved disciplines and is carefully

guided through the conversation with the help of a (neuro-) psychologist. Together, the multidisciplinary team can best provide all important information to the family and the

patient. Children must be included in this communication in an age appropriate manner. They tend to feel guilty about their parents' confusion or sadness, and can better cope with situations when they know the underlying reasons. This knowledge also minimizes anxiety and stress. Sometimes showing images of the tumors to patients is helpful, even if they are young. Depending on the situation, the further procedure is then be discussed in more detail with the parents alone. The (pediatric) neurosurgeon explains and illustrates the possible surgery. Questions can be answered in detail. The presentation of needed postoperative therapies may also be important. Here, depending on the psychological condition of the family, the information must be coordinated. The presence of a (neuro-) psychologist is particularly important, so that the family can be supported from the beginning of the process, and any fears will be made apparent to the (neuro-) psychologist and can be considered.

The initial consultation also sets the time schedule. The subsequent procedures and the difficult conditions for the family are clarified, including surgery, postoperative surveillance in the intensive care unit, waiting for the pathology results, and planning the further adjuvant treatments (e.g., chemo- and radiation therapy), if needed. Possible neurological deficits, necessary therapies (physiotherapy, speech therapy, and occupational therapy), and, if needed, neurological rehabilitation should also be discussed. This meetings at the beginning of the process, addressing all contingencies, can help families feel that they are not left alone. In these discussions, the function of each discipline (particularly surgical, adjuvant, and supportive) acting together in the multidisciplinary treatment team must be explained. Recurring joint meetings with physicians and therapists, as well as nursing staff, are part of the care of these children and families. After the family is briefed, the timing of surgery is determined. The timing depends on the urgency of the operation (e.g., signs of elevated ICP) and the optimal conditions required in the operating theater. The optimal team consists of at least an experienced neurosurgical team (ideally including a pediatric neurosurgeon), and a pediatric anesthesiologist with experience in neuro- as well as pediatric anesthesia [22], and a neurophysiologist for intraoperative neurophysiological monitoring (IONM) [24]. Total venous anesthesia (TIVA) is preferred, not only in surgeries under IONM. In suprasellar lesions, additional hydrocortisone stress prophylaxis is needed [22]. Intraoperative cooperation among a (pediatric) neurosurgeon, pediatric oncologist, and neuropathologist is also essential. The tumor tissue is made available to the neuropathologist for intraoperative histopathological analysis. The neuropathologist must be available during surgery for preliminary frozen section diagnosis, which can be discussed in direct telephone consultation

with the (pediatric) neurosurgeon and consequently influences the course of the operation [25]. Notably, the intraoperative diagnosis is not a final diagnosis but merely indicative. For definitive histopathological and molecular diagnosis, a larger total amount of tissue may be required. In most countries, a final reference pathology is obligatory. After frozen section diagnosis, if resection is difficult because of anatomical conditions, a pediatric oncologist may be consulted during surgery to determine whether more radical resection might be particularly important. Immediate postoperative care should be provided by an experienced team of pediatric and neurosurgical intensivists. Close monitoring is performed in the pediatric intensive care unit for the safety of the patient. If the clinical course is stable, the patient can be transferred to the leading discipline's normal ward the next day. Mobilization is usually accomplished with the assistance of physical therapy. Evaluation is performed to identify even the smallest neurological deficits to initiate the most effective therapy (physiotherapy, speech therapy, and/or occupational therapy). Regular wound checks are performed by a (pediatric) neurosurgeon. Contrast MRI is typically performed in the first 72 hours after surgery to assess the resection status and rule out CSF circulation disorders or possible complications. A resectable tumor remnant should always be discussed for second look surgery by the multidisciplinary team [26,27]: Tumor entities respond differently to adjuvant therapies. For chemosensitive tumors, a pediatric oncologist may offer therapy. If residual tumor is seen on MRI, tumor re-resection must be discussed if the tumor does not respond well to chemotherapy. A radiation oncologist may also recommend re-resection. For example, for residual tumors near eloquent brain regions, tumor volume reduction should be considered, to decrease the radiation dose and spare the eloquent areas. Radiation oncologist and pediatric oncologists often work together and jointly monitor the further course of therapy, according to tumor entity and the response to therapy. Depending on the age of the child, a time-saving therapy with chemotherapeutic agents can be performed first, so that radiation therapy is not started until the child's brain is more mature [28]. Another collaborative decision is whether chemotherapy should be administered concomitantly with radiation therapy. When intrathecal administration of chemotherapy is required, the indication for an Ommaya reservoir should be made by a pediatric oncologist and a (pediatric) neurosurgeon. Until discharge, the involved disciplines discuss new developments and prepare the family as best as possible for the prognosis. Rehabilitation needs are evaluated, including aspects of (neuro-) psychology, physiotherapy, speech therapy, and ergotherapy. The recommended adjuvant treatments are explained to the family and, if

necessary, integrated into the course of the intended rehabilitation or scheduled as a separate inpatient or outpatient stay. To optimize the quality of treatment, follow-up examinations (imaging and clinical) are often performed in collaboration among several disciplines (e.g., pediatric oncology, radiation oncology, and (pediatric) neurosurgery, with the involvement of (neuro-psychology). For all major aspects, the case is re-presented to the tumor board and the best possible treatment options can be re-evaluated. Contacting the general treating pediatrician directly may be helpful to organize further follow-up after discharge. He plays a critical role in supporting the families (e.g., with any decision-making), and good collaboration with the pediatric oncologist is very helpful. (Neuro-) Psychological care must be provided for not only acute situations, but also long-term consequences. The diagnosis of a brain tumor can cause stress for children and their families. The therapies required may also induce stress. For example, chemotherapy can cause neurocognitive and neuropsychological late effects, even 10 years after treatment. Risk factors, such as lower physical activity, have been identified and can aid in determining the therapeutic approach. Various strategies can be applied to counteract the effects of stress. Psychological support plays a central role, as does physical activity. Post-traumatic stress disorder is also increasingly found in parents of children with brain tumors, which in turn also affects the children [29]. The main goal of psychological care during hospitalization is to prevent psychological stress and to initiate supportive therapy at an early stage to improve quality of life and functioning [29].

Conclusion

Growing insight into the genetic and epigenetic background of childhood CNS tumors has changed the histology-based classification of CNS tumors and led to the definition of new tumor classifications and subtypes, as reflected by the regularly updated tumor classifications of the WHO. Diagnosis includes various investigative information and is presented as an integrated diagnosis, which combines tissue-based histological and molecular diagnosis and is quantified in a layered report with histological diagnosis, CNS WHO grade, and molecular information. Some tumors are described in general terms. For accurate final integrative diagnosis, the molecular profile is needed to divide tumors into subgroups. New molecular methods have improved the understanding of certain brain tumor groups. Previously, tumors thought to be of embryonic origin were classified as primitive neuroectodermal tumors. However, DNA methylation profiling has revealed that tumors within that former classification belonged to entirely different brain tumor groups. This new classification can explain the observed differences in clinical courses, and enables more appropriate therapy to

be applied. The classification of tumor types into further subgroups can enable more individualized therapy overall. On the one hand, more accurate prognostication of tumors is possible, so that the therapy can be adapted accordingly. For tumors with better prognosis, for example, a de-escalation of the therapy regime can be evaluated. Second, the molecular-genetic markers provide a basis for the development of new tumor-specific agents to improve tumor control and overall outcome.

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