Clinical Pediatric Brain Tumors

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Contributor: Katharina Lutz , Stephanie T. Jünger , Martina Messing-Jünger

Brain tumors are the most common solid tumors in children and are associated with high mortality. The most common childhood brain tumors are grouped as low-grade gliomas (LGG), high grade gliomas (HGG), ependymomas, and embryonal tumors, according to the World Health Organization (WHO).

pediatric neurosurgery | pediatric gliomas | medulloblastoma | ependymoma

1. Introduction

Brain tumors are the most common solid tumors in children and are associated with high mortality [1][2]. The most common childhood brain tumors are classified as low-grade gliomas (LGG), high grade gliomas (HGG), ependymomas, and embryonal tumors according to the World Health Organization (WHO) [3][4][5][6][7]. Radiation exposure is the only environmental factor shown to be associated with an increased risk of brain tumor development [1].

Various brain tumor registries (such as the National Program of Cancer Registries [NPCR] and the Surveillance, Epidemiology, and End Results [SEER] Registry) provide population-based data from patients with central nervous system tumors. These data can be used to analyze brain tumors on the basis of histology, location, age, survival, clinical features, and other characteristics [8][9]. According to combined data analysis, from 2008 to 2017, the incidence rates for malignant brain tumors and other central nervous system (CNS) tumors in children and adolescents increased from 0.5% to 0.7% per year, whereas those in all other age groups decreased [8]. Malignant brain tumors are observed more frequently from 1 to 4 years of age. Low-grade brain tumors are common until infancy and further increase in incidence until adolescence. The 5-year relative survival rate for malignant brain tumors is 77% on average in children younger than 14 years of age and 81% in those 15–19 years of age. The 5-year relative survival of patients with non-malignant brain tumors is almost 100% (98 and 99%) in both age groups [8].

Advances in molecular genetics have led to a shift from a pure histopathological diagnosis to integrated diagnosis, which was first included in the WHO classification published in 2016 [6] and further updated in the 2021 edition [7]. Integrated diagnosis is based on molecular genomic similarities of tumor subclasses, which can better explain the different clinical courses of previously identical histopathological entities. This new subclassification may ideally reveal new therapeutic targets for individual tumor therapies.

In the past decade, many advances have been made in diagnostics, molecular genetic pathology, surgical techniques, and non-surgical therapeutic methods. For several pediatric tumors (e.g., medulloblastoma and LGG), these advances have significantly improved therapeutic management and prognosis in certain subgroups. For other tumors (e.g., HGG), the prognosis remains dismal despite these advances. Several therapeutic approaches also have serious long-term consequences. Thus, optimized treatment and development of new therapeutic methods are greatly needed. In particular, advances in molecular biology have moved the field toward the goal of an individualized therapy. For some tumors, these innovations have already influenced treatment modalities; for other tumors, promising therapeutic agents remain to be developed [2].

2. 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.

3. 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.

4. Clinical Approach and Therapy

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].

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