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Specific Features of Cerebral Tumours in Children

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Abstract: ***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). Advances in molecular genetics have led to a shift from pure histopathological diagnosis to integrated diagnosis. For the first time, these new criteria were included in the WHO classification published in 2016 and has been further updated in the 2021 edition. Integrated diagnosis is based on molecular genomic similarities of the tumor subclasses, and it can better explain the differences in clinical courses of previously histopathologically identical entities. Important advances have also been made in pediatric neuro - oncology. A growing understanding of the molecular - genetic background of tumorigenesis has improved the diagnostic accuracy. Re - stratification of treatment protocols and the development of targeted therapies will significantly affect overall survival and quality of life. For some pediatric tumors, these advances have significantly improved therapeutic management and prognosis in certain tumor subgroups. Some therapeutic approaches also have serious long - term consequences. Therefore, optimized treatments are greatly needed. Here, we discuss the importance of multidisciplinary collaboration and the role of (pediatric) neurosurgery by briefly describing the most common childhood brain tumors and their currently recognized molecular subgroups.***

Keywords: pediatric neurosurgery; pediatric gliomas; medulloblastoma; ependymoma; targeted therapy; individualized tumor – treatment

1. Introduction

Brain tumors are the most common solid tumors in children and are associated with high mortality (1). 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) (2). Radiation exposure is the only environmental factor shown to be associated with an increased risk of brain tumor development (3).

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 (4). 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 (5). 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 (6).

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 (8). Here, we discuss the importance of multidisciplinary collaboration and the role of (pediatric) neurosurgery by briefly describing the most common childhood brain tumors and their currently recognized molecular subgroups.

2. 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.

3. Results and discussion

The Role of Neurosurgery

The extent of tumor resection remains the most important factor with respect to event free and overall survival in nearly all kinds of tumor types (9). Resection of a tumor - mass can provide immediate relief from tumor - related signs and symptoms, and improve longterm outcomes and survival. Additionally, the tissue obtained during surgery is used to provide a histopathological and molecular - genetic diagnosis. For this purpose, an adequate amount of tumor tissue must be sampled. Depending on the localization and histology, gross total resection (GTR) and minimum morbidity ensuring maximum quality of life, are the goal of the (pediatric) neurosurgeon (10). In case of significant remnant or recurring tumors, second look surgery, must be considered, if feasible and depending on tumor entity (11). The new management concepts of pediatric brain tumors underscore the importance of these second look surgeries and the removal of metastases. The surgical anatomy of pediatric brain tumors differs substantially from those in adult patients. Highly eloquent midline structures, such as the basal ganglia, brainstem, and cerebellum are most often involved. Intraventricular and suprasellar involvement are also common locations. The frequent involvement of midline structures and the posterior fossa explains a high rate of associated hydrocephalus. Primary treatment stratification therefore always includes hydrocephalus management if necessary. Shuntplacement or endoscopic third ventriculostomy are indicated if tumor resection does not resolve the CSF disorder (12). Maximally safe resection in these regions is demanding and requires a high expertise. Surgery by dedicated pediatric neurosurgeons ensures the better outcomes than interventions performed by inexperienced surgeons (13). The safety of the child should always be the focus. To achieve a maximum resection without harming the child, various tools are available to (pediatric) neurosurgeons. For surgical preparation, microsurgical instruments and a microscope are used. Depending on the location of the tumor and the preference of the (pediatric) neurosurgeon, neuronavigation can help plan the approach. The navigation also contributes to the extent of resection. Integration of additional fMRI information may also contribute to complete removal from a functional perspective (14). Intraoperative imaging methods can be used for tumor localization and to verify the extent of resection; examples include real - time ultrasoundand intraoperative MRI (15). Intraoperatively performed MRI images can also be fed into the navigation systems. As an additional tool, an endoscope can reach deeper or hidden areas without a large access route, thus improving resection results, such as in craniopharyngiomas (16). Both eloquent brain areas and cranial nerves can be detected and controlled by IONM. IONM can help preserve brain function and is indispensable in the resection of deeply located brain tumors, e. g., in the posterior fossa as well as of spinal cord tumors (17). This method has been demonstrated to be safe and reliable in children of all ages (18). Biopsy may be required when tumor resection is not feasible because of high morbidity or mortality, or when a specific entity, such as a diffuse intrinsic pontine glioma (DIPG), is suspected. For superficial tumors, an open biopsy is possible. For deep - seated tumors, a stereotactic procedure is most suitable, because it provides high safety with low morbidity (19). In certain tumors, e. g., neoadjuvant chemo - or radiation therapy can be an appropriate treatment after biopsy and tumor marker assessment and represents another interface of multidisciplinary collaboration (20).

Molecular Advances and Their Effects on Clinical Management

Integrated Diagnosis

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 (21). 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 (22). Some tumors are described in general terms. For accurate final integrative diagnosis, the molecular profile is needed to divide tumors into subgroups (23).

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 (24). 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 (25).

Medulloblastoma

Because medulloblastoma is the most common malignant brain tumor in children (26), many children with this brain tumor are also treated by general pediatricians. Therefore, familiarity with the broad clinical spectrum of this disease is important. Medulloblastoma belongs to the group of embryonal tumors and accounts for almost 10% of all pediatric brain tumors. Two age peaks can be observed, one at 3–4 years and the other between 8 and 10 years (27).

Glioma

Low - Grade Glioma

Approximately 30% of all pediatric brain tumors are LGGs. Most of them tend to grow slowly, and patients may have a long history of symptoms. Acute symptoms can also occur, owing to associated hydrocephalus or rapid growth of tumor cysts. The cerebellum is the most prevalent location (15%–

25% of all pediatric brain tumors), followed by the cerebral hemisphere (10%–15%), the basal ganglia (10%–15%), optic pathways (5%), and the brain stem (2%–4%). Approximately 15 to 20% of children with neurofibromatosis type 1 develop optic pathway/ hypothalamic glioma (28). LGGs consist of grade 1 and 2 tumors according to the WHO classification, and frequently show cerebellar localization. Pilocytic astrocytoma is the most common representative, but other astrocytic tumors, subependymal giant cell astrocytomas, pleomorphic xanthoastrocytomas, oligodendroglial tumors, and benign neuroepithelial tumors are also observed (29).

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Again, the (pediatric) neurosurgeon's role is to completely resect the tumor, if possible, because GTR may be curative for LGGs, particularly for pilocytic astrocytomas. The roles of radiation oncologists and pediatric oncologists are particularly important in cases of non - resectable tumors. Chemo - or radiation therapy may be applied, depending on the clinical course and patient age (31). For suspected LGG in highly eloquent locations, e. g., the supra - sellar region or incidental lesions, a wait - and - see approach may also be discussed, because rapid progression or malignant transformation are rarely seen (32). In a wait - and - see approach, close monitoring by the multidisciplinary team, including the general pediatrician, is recommended.

High - Grade Glioma and Midline Glioma

Children with HGG usually have a short history and are likely to have symptoms suggestive of increased ICP. These patients are also often admitted as emergencies, and diagnosis must be assessed as quickly as possible. According to the WHO, grade 3 and 4 tumors are high - grade gliomas (33). Histologically, they are often similar or identical to adult tumors, but their clinical course and molecular markers significantly differ from those in adults.

Ependymoma

In children, both cranial and spinal symptoms may be present, because pediatric ependymomas occur along the entire neuraxis and account for 10% of all pediatric brain tumors. Intracranial manifestation, particularly in the posterior fossa, is more frequent than spinal tumors in children. Ependymomas were previously considered one entity with different tumor grades. WHO grading continues to be used in recent and ongoing studies, but age - and location - specific risk - stratification according to biologically distinct subtypes, appears more adequate (34).

4. Conclusion

Important advances have been made in pediatric neuro - oncology during the past decade. A growing understanding of the molecular - genetic background of tumorigenesis has improved the diagnostic accuracy, e. g., with respect to prognosis and defining distinct tumor subgroups. Re - stratification of treatment protocols and the development of targeted therapies will significantly influence the overall survival and quality of life of our pediatric patients. Because the increasing number of subgroups interferes with the statistical power of clinical trials, multinational centralized research projects must be established. Hope exists for new alternative treatment options, such as targeted therapy or even individualized tumor treatment. Radiation therapy techniques have also significantly improved, and adverse effects are expected to be further decreased. Some tumor subgroups will no longer require irradiation. Certain subgroups of medulloblastomas and ependymomas can currently be successfully treated without radiation therapy. The need for tumor tissue biopsy will probably be replaced by refined MRI techniques, liquid biopsies, or NGS - based diagnostics in the future. Currently, however, (pediatric) neurosurgeons must ensure maximally safe tumor resection and sufficient tumor tissue acquisition for adequate molecular - histological classification and further research on targeted therapies.

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