Enayet *Egypt J Neurosurg* (2021) 36:33
https://doi.org/10.1186/s41984-021-00130-0

Egyptian Journal
of Neurosurgery

REVIEW Open Access

Brain tumors in the first two years of life

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Abstract

Background: Brain tumors in the first years of life are frequently encountered recently with the advancement in neuroimaging, neurosurgery and neuroanethesia where early diagnosis of these lesions became available even before birth. Their management is challenging where the surgery is technically demanding, radiotherapy is omitted in this age because of its late sequelae and chemotherapy role may be beneficial, but it is limited also by its side effects and neurotoxicity. The aim of this article is to review the current literature about the brain tumors in the first two years of life, their diagnosis and treatment.

Main body: Brain tumors in the first two years of life encompass mainly fetal/congenital tumors and infantile tumors. They account for 1.4–18% of cases of pediatric brain tumor, and most of them are diagnosed in the first year of life. The main histopathologies diagnosed are glial tumors, choroid plexus tumors, medulloblastoma and other embryonal tumors, teratoma and ependymoma. They are mainly supratentorial. Large head and bulging fontanelles are the main presenting symptoms and signs secondary to increased intracranial pressure secondary to large tumors or associated hydrocephalus. Prenatal and postnatal ultrasonography represents the initial imaging step in the diagnosis that should be complemented by MRI and CT brain. The main and first line of treatment of infantile brain tumors is surgical excision as the prognosis is directly related to the extent of resection besides surgery offers specimens for histopathological diagnosis and adjuvant chemotherapy is given for residual irresectable cases and malignant tumors with the main aim to delay radiotherapy beyond the age of three years.

Conclusion: Brain tumors in the first two years of life are a challenging group of different histopathological entities with underlying specific molecular characterization and genetic predispositions. They have aggressive behavior and general poor prognosis with limited options of management. Individualized multidisciplinary management for each case is needed, and future studies for therapeutic medications targeting underlying molecular biology may improve their outcome.

Keywords: Infantile brain tumors, Congenital brain tumors, Embryonal tumors

Introduction

Brain tumors in the first years of life are frequently encountered recently with the advancement in neuroimaging, neurosurgery and neuroanethesia where early diagnosis of these lesions became available even before birth, and their safe resection can be attempted with an accepted outcome. However, the occurrence of brain tumors in these early years of life is a challenging situation for both neurosurgeon and pediatric oncologist, and the neurosurgeon is confronted with an infant who has a limited blood volume and harbors a mostly malignant large lesion that must be resected or maximally debulked because of the age limitations of chemotherapy and brain irradiation, while the pediatric oncologist is faced with a very young child who must receive an adjuvant therapy with its immediate and remote complications. Children irradiation was clearly found to be correlated with delayed mental sequelae and endocrinopathies besides the high carcinogenic risk that was found to be higher with very early exposure in life and it may persist throughout life. Chemotherapy neurotoxicity and its associations with the development

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of leukoencephalopathies have been reported. These tumors have poor prognosis and more aggressive behavior that made them with their challenging management a special entity in the field of pediatric neurosurgery. The aim of this article is to review the current literature about the brain tumors in the first two years of life, their diagnosis and treatment.

Main text

Definitions, incidence and epidemiology

Brain tumors in the first two years of life encompass mainly fetal/congenital tumors and infantile tumors. Congenital tumors are not a universally accepted term and lacks clear definition, and it refers mainly to those tumors that are developed in the intrauterine life and are detected in utero [1] or early neonatal period and some consider them as definitely, probably and possibly congenital based on whether they occur at birth, within the first week of life or within the first six months of life [2], while some had extended these periods to be definitely congenital if diagnosed at birth or the first two weeks, probable if detected during the first year and possibly congenital when diagnosed beyond the first year when symptoms can be traced back to the first year of life [3] also some authors had pointed to tumors that may be congenital but presented later in infancy as teratomas or medulloblastomas [4, 5]. Infantile tumors in different series also are described to be in the first year of life only [6–10], while others extend this period to two years [11–13] and because these tumors are usually diagnosed late after prolonged period of symptoms so some authors add cases below three years [4, 14–16] considering all these tumors to start in the infantile period but diagnosed later so they were considered to be the same entity.

Brain tumors in infancy and early childhood, once thought to be rare, have been discovered more frequently in the last decades which may be related to advancement in imaging techniques and prenatal ultrasound [17], and they account for 1.4–18% of cases of pediatric brain tumor [4, 5, 7, 8, 13, 18–21], and most of them are diagnosed in the first year of life.

The incidence of different histological types was found to be heterogeneous within different series, and this was correlated with racial factors [22] where the most common tumor in Europe, USA, Canada, Mexico, Argentina, Japan and the Far East was astrocytoma [15]. Choroid plexus tumors were the most common in Egyptian and Indian series [22, 23]. Medulloblastoma was the commonest in Saudi Arabia [24], and primitive neuroectodermal tumor is the most common in series from Germany [15].

Histopathology and location

Being a rare entity, most of series in the literature about brain tumors in early life are relatively small and this can explain the heterogenicity between different studies in the literature about the commonest diagnosed histopathology and also these series were varied in their study groups where some were focusing on neonatal period or first year of life where others had extended their research to include all children below three years of life, so astrocytoma was the commonest in some [11, 13, 25], medulloblastoma in others [8, 26, 27], other investigators described choroid plexus tumors to be more common [22, 23, 28] and teratoma was named by others to represent about third of the diagnosed congenital tumors [21, 29, 30]. Primitive neuroectodermal tumors(PNET) account for the majority of pathological diagnoses in some other series [4, 6, 31].

Di Rocco et al. had previously listed the ten most common brain tumors in infancy that were, in a descending order, astrocytoma, medulloblastoma, ependymoma, choroid plexus papilloma, primitive neuroectodermal tumor (PNET), teratoma, sarcoma, meningioma, ganglioglioma and neuroblastoma [32]. While in a recent review, teratoma was found to be the most common congenital tumor followed by gliomas and choroid plexus papillomas, while embryonal tumors including medulloblastomas and atypical teratoid/rhabdoid tumors (ATRTs) are less frequent [33]. Ependymoma is another subtype that is diagnosed also in infants [34] although its incidence is higher under the age of four years [33]. Pinealoblastomas and craniopharyngiomas are other tumors that are encountered more rarely in this age group [25, 35].

The relation between the age and histopathalogy was pointed to in an epidemiological study that examined 75 case of brain tumors under the age of three years, and the author concluded that the most common tumors in the first year of life was PNET, while in the second year astrocytomas and ependymomas were most common and astrocytoma was the most frequent diagnosed pathology during the third year of life [15], and it was found that the histological heterogenicity from malignant to benign tumors was higher in neonates and infants compared to older children.

Tumors in this age group are predominantly supratentorial [10, 13, 22, 31, 36], and although some reported that supratentorial location is the commonest in the first year, then the ratio of supratentorial to infratentorial locations tends to be reversed in the second year and third year of life [37], the pooled data from most of other studies showed a higher tendency for supratentorial location in the first two or three years of life. However, there is nearly almost a consensus that brain tumors occurring

infratentorial in this age group are malignant in contrast to supratentorial location where benign tumors predominate [6, 31, 38].

Most of these tumors were found to occupy midline structures than to be laterally located where cerebellar vermis and fourth ventricles below the tentorium and chiasmatic / hypothalamic region above the tentorium were the most topographic locations reported [37]. It was suggested that this finding is mostly related to the fact that most neuroectodermal tumors in very young children arise from phylogenetically older structures of the central nervous [39]. In studies where lateralized tumors were more common than midline ones entailed higher number of choroid plexus tumors that occupied lateral ventricles mainly [22].

Cytogenetics and molecular pathways

The occurrence of brain tumors in infants sheds light on the fact that there is a minimal time of exposure to any exogenous factors that predispose to oncogenesis process, and thus, there may be a possible role of genetic predisposition in the causation of these tumors. Although chromosomal abnormalities detected in pediatric brain tumors may be non-specific, they are different from those detected in brain tumors in adults. The most common abnormality in medulloblastoma (in about 60–70%) is the total or partial loss of chromosome 17 [40]. Deletions involving 17p and absence of c-myc or N-myc amplifications have been reported in cerebral PNETs [41]. Deletions in chromosome 1 are found in childhood astrocytoma [42]. There is a high incidence of monosomy 22 associated with atypical teratoid/rhabdoid tumor [43].

Epigenetics is gaining a great concern in pediatric brain tumor pathogenesis, and although the existence of certain epigenetic features in infants is still unknown, it represent an important field of study for its diagnostic and therapeutic implications where several studies have revealed that a specific miRNA signature or DNA methylation profile could help distinguish a tumor subgroup with a consequent peculiar therapeutic approach in pediatric brain tumors as the specific miRNA expression that was detected in an atypical teratoid/rhabdoid tumor (ATRT), an ependymoma, medulloblastoma, and both low and high grade astrocytomas [44, 45], besides many studies on molecular pathways in choroid plexus tumors that showed a great understanding of its biology and the potential druggable targets in these tumors especially choroid plexus carcinoma of infants [46].

Clinical presentations

Large head and bulging fontanelles are the main presenting symptoms and signs secondary to increased intracranial pressure secondary to large tumors or associated hydrocephalus [6, 13, 27, 36]. The manifestations sometimes are non-specific owing to open fontanelles and non-fused sutures which permits skull expansion which makes detection of positive signs in the new born and young children is and many infants with manifestations of failure to thrive, vomiting, irritability, and delayed milestones are subjected to delayed diagnosis [16, 33, 47].

Some cases especially in the second year of life may present with focal neurological manifestations as weakness, cranial nerve affections or seizures [16, 30].

Suprasellar hypothalamic gliomas in this age may present with precocious puberty or diencephalic syndrome [13].

Some reports referred to presentations related to rapidly growing tumors before labor that lead to severe macrocranium with difficult or premature labor, dystocia or even still birth mainly intracranial teratomas, primitive neuroectodermal tumors (PNETs) and glioblastomas [48, 49].

Hemorrhage in the tumors is another presentation in this age group, and it was reported to be the initial presentation in 3–18% of cases. Congenital brain tumors were reported to have a high tendency to bleed intratumorally especially astrocytoma, medulloblastoma and PNET [50, 51]. It was suggested that imposing a rapidly changing pressure forces on the head of the neonate during delivery may be responsible for hemorrhage and as a result of repeated bleeds the space occupying effect of the tumor is enlarged [51]. So when a spontaneous intracranial hemorrhage is found, an underlying neoplasm should always be excluded [2].

Tumors in the neonatal and infantile periods are often a part of a familial syndrome or associated with congenital anomalies. In a review done by Wakai et al. [49], 11.5% of neonatal brain tumors had associated anomalies of various nonspecific types. Teratomas was reported to be associated with hydrocephalus, cleft lip and palate, proptosis, and anencephaly [29, 33]. Some tumors are parts of familial syndromes as optic pathway tumors in neurofibromatosis type 1, meningiomas in neurofibromatosis type 2, PNET in Li–Fraumeni syndrome, and subependymal giant astrocytoma occurs with tuberous sclerosis [30]. Medulloblastoma was reported to have an incidence of 3.6% in Gorlin syndrome which is an autosomal dominant syndrome with multiple basal cell carcinomas, jaw cysts, and vertebral abnormalities. The incidence of this syndrome in medulloblastoma is 1–2% [52].

Imaging and diagnosis

Some features of congenital or fetal tumors can be detected in the prenatal ultrasound especially in the third trimester. The most common features are polyhydramnios and macrocephaly [30, 53]. Polyhydramnios occurs

due to decreased swallowing secondary to a hypothalamic dysfunction, and this sign is present in about one-third of patients. Macrocephaly can be due to cranial expansion by the tumor or hydrocephalus that is generally caused by the obstruction of the ventricular system or from increased cerebrospinal fluid production from a choroid plexus tumor.

Nowadays, cranial ultrasonography (US) of the newborn represents the first imaging method in brain facilitated by the presence of open fontanelles and less ossified cranial bones, it has the advantages also of being fast, non-invasive and does not produce any side effect, so Cranial US can provide useful findings or be used as the first diagnostic modality when there is a suspicion of a brain mass [54].

During ultrasonography, most intracranial tumors have a heterogeneous pattern with the subversion of normal structures depending on the presence of cystic, necrotic, or hemorrhagic areas. Cerebral tumors are more frequently hyperechoic, and depending on tumor localization, ventricular dilatation may occur. Sometimes, US can show a typical pattern, as in choroid plexus papilloma [55].

MRI brain allows for detailed assessment of the tumor; its relations with the surrounding structures, its morphology and extensions provide essential information needed in planning for surgery. MRI features of the tumors can allow also for differentiation between malignant and benign cases [21] that provide the surgeon with data that can guide the management and discussion with the family as in differentiation between infantile glioblastoma (GBM) and desmoplastic infantile tumors (DIT) where both of them appear as huge supratentorial tumors with cystic and solid components; however, GBM shows heterogeneous enhancement and restricted diffusion in contrast to DIT that shows avid and homogeneous enhancement with no evidence of derestricted diffusion in diffusion sequences [56]. Fat-suppression MRI techniques may be useful in differentiating fat from hemorrhage in teratoma cases [57]. MRI for the whole neuraxis is beneficial for detection of CSF disseminated lesion seen mainly in embryonal lesions and ependymomas, the findings that can guide the management and surgical decisions in these cases [58, 59]. The main disadvantage of MRI is the inadequacy in detecting calcifications that may be characteristic and diagnostic for some lesions as infantile ganglioglioma. Also, MRI requires long time for acquiring images which needs a calm and still patient which is not the case in infants or neonates and their sedation is a must which may delay the management process besides the exposure to more anesthetic risk.

Although computed tomography (CT) brain exposes infants to a large dose of ionizing radiation, it has the advantage of illustrating calcifications easily which can aid in the diagnosis of teratoma cases where multiple calcified portions can be detected which may sometimes reflect the presence of bone and teeth [57]. Calcifications may also be diagnostic in infantile ganglioglioma cases [60, 61].

Surgical excision

The main and first line of treatment of infantile brain tumors is surgical excision as the prognosis is directly related to the extent of resection besides surgery offers specimens for histopathological diagnosis [21, 62, 63]. Surgery in this young age is demanding and challenging owing to the general condition, low weight and limited blood volume of the infant and the frequent huge sizes reached by these neoplasms being have a great time to expand secondary to delayed diagnosis [25, 38].

The extent of resection of brain tumors below two years is variable in different series in the literature where gross total(GTR) or near total resection was achieved in 25% in one series [36], while it ranged between 34 and 43% in others [10, 13, 31, 47] and GTR was accomplished in about 60–70% in others [6, 8, 11, 16, 22]. This heterogenicity was attributed by some investigators to the improvement in diagnostic tools and neuro-anesthesia techniques over time [6], although this may be partially true, there must be a correlation between the extent of resection on one side and the histological types and locations of the resected lesions on the other as the different individual series varies significantly in the number of cases, their histopathology and locations where in series with higher incidence of total or near total resections, one can find higher incidence of benign pathologies with less invasion to the surrounding brain, or intraventricular choroid plexus tumors with good plane of resection and more control of intraoperative bleeding after visualization and coagulation of its pedicle [22].

Conservative management for recurrence or residual lesions is favored as long as the lesion is non-progressive either radiologically or clinically, long-term follow-up with repeated MRI is mandatory in these patients, and reoperation is indicated only on disease progression [36, 64]. But reoperation on the same lesion with the intention to perform a staged resection may be better in these infants especially for tumors that are curable with surgery where high vascular lesions may lead to excessive bleeding and reoperation after the infant being stabilized can increase the extent of resection with better outcome [22].

Reoperation after neoadjuvant chemotherapy is another option of management for infantile brain tumors that was investigated by some authors [65] where reoperation was indicated in tumor regrowth after initial regression, or if there was no further reduction in tumor

volume with repeated cycles of chemotherapy, and in cases of new emergency or urgent radiographic changes as intra-tumoral hemorrhage. The authors found that neoadjuvant chemotherapy had effectively devascularized all tumors and the volumes of most tumors were decreased, and these effects enhanced their ability to achieve a complete resection.

There are variable rates of operative and perioperative mortality in the literature [5, 6, 13, 19, 20, 22, 66] that range from 5.6 to 33% in most of literature, while no mortality was reported by Haddad et al. [7] and higher rate (57%) was found in Tewari et al. study [67]. This heterogenicity may be explained by heterogeneous pathologies, variations in vascularity of the lesions and differences in the experience of neurosurgeons, anesthesia, and intensive care teams. The higher rate of perioperative mortality is certainly related to the infants' general conditions and their sensitivity to hypothermia, blood loss and massive blood transfusion which all must be kept in mind during their management.

Suprasellar Optic pathway and hypothalamic gliomas (OPHG) represent an exception regarding surgical management where a more conservative surgical approach was found to be correlated with better outcome for these lesions [68–70]. The aim of surgery in pediatric OPHG especially in this age is just having a biopsy for diagnosis that is usually followed by chemotherapy and even the biopsy may be not needed in typical radiological OPHG especially in the context of diencephalic syndrome, and debulking can be done for exophytic parts of these lesion, or after failure of chemotherapy to control their progression.

Hydrocephalus is a very common association with infantile brain tumors [9, 71] and shunt requirement for its management ranged from 20% up to 57% [13, 22, 32, 47, 71] in the literature. preoperative insertion of ventriculoperitoneal(VP) shunt may be life saving in emergency situation and can improve the general condition of dehydrated infants due to vomiting before definitive surgery [13]; however, the insertion of VP shunt in very young patients is associated in some cases with peritoneal failure of CSF absorption leading to severe ascites and abdominal distention that may lead to respiratory distress, this may be related to immaturity of the peritoneum or excessive CSF production especially in choroid plexus tumors [72]. This condition is usually managed by insertion of ventriculoatrial (VA) shunt. Upward cerebellar herniation and posterior fossa intratumoral hemorrhage after shunting are another reported complications especially with large lesions and usually have poor outcome [13, 73]. For these complications besides other shunts complications as obstruction, infections and exposure, there is a tendency to perform excision of the lesions directly first leaving hydrocephalus management in the post-craniotomy and follow-up periods [71]. Insertion of external ventriculostomy with gradual withdrawal might decrease shunt requirement as supposed by Ghodsi et al. [6] where only 12.9% of their patients needed permanent VP shunt.

In addition to VP and VA shunts in this age group, subdural-peritoneal shunt is also needed in some cases with choroid plexus tumors where large subdural collections do exist after excision of these tumors [22, 71].

Adjuvant therapy

The use of upfront radiotherapy was used till about 1987 in the primary treatment of infantile and young children with efforts to optimize its factors as time, dose and volume to minimize its late effects on the central nervous system [7, 13, 74], but these trials and efforts lead to poor outcome due to lowering the necessary therapeutic doses and in the same time the radiation complications were not decreased [75]; in the last decades, it was recommended to avoid brain irradiation in this age group due to its harmful effects and risks that are possibly related to vascular lesions or demyelination and these risks persist throughout life [9, 16, 21, 76, 77]. Craniospinal irradiation for the immature and growing brain and spinal cord of infants as well as their growing vertebrae was reported to cause mental retardation, growth retardation, hypothalamus–pituitary axis affection that may lead to severe endocrine affection especially growth hormone and thyroid functions. Intracranial blood vessels in very young children are also sensitive to irradiation, and occlusive neurovascular complications have been reported [19, 47]. Risk of radiation-related secondary neoplasm is greater when exposure occurs early in life, and this risk seems to persist throughout life [78]. Also, newer modalities as stereotactic radiotherapy and proton beam therapy have its potential complications on infants and young children and there are many studies on their long-term effects [79–81].

Chemotherapy appears to be an effective postoperative primary treatment for incompletely resected or malignant pathologies in this age group [25, 82], and different therapeutic approaches were explored [83] as prolonged postoperative chemotherapy and delayed irradiation or without irradiation in another approach, high dose chemotherapy with autologous stem cells transplantation was investigated also. The reached goal of delaying irradiation or its avoidance has proven the beneficial role of chemotherapy in this age group [81] and made it accepted in spite of its neurotoxicity, gliotoxicity and deleterious effects on gray and white matters of the developing brain, hearing and bone marrow [84].

Outcome and prognosis

The prognosis of brain tumors in the first two years of life is generally not good, and this can be attributed to many factors as the malignant pathology of most of these tumors, surgical difficulties faced by the neurosurgeon in dealing with them, risk of anesthesia, difficult postoperative care besides children in this age group are not amenable for radiotherapy. Location of the tumor was correlated with prognosis in many studies where posterior fossa tumors demonstrated lower overall survival rates in comparison with supratentorial lesions [6, 19, 31, 85] others correlated between tumors located in the brainstem, ventricular system, optic chiasm, thalamus, and basal ganglia with worse prognosis in terms of both survival and quality of life [11] as attempted surgical removal of tumors in these locations is associated with high mortality and chemotherapy or radiotherapy for partially resected or non-resected lesions worsen the quality of life. Extent of surgical resection had a significant correlation with prognosis in many studies, and complete resection provides the best possible outcome in terms of survival and disease-free survival rates [38, 86].

The rate of survival of patients with brain tumors under two years is low, and the most common outcome of infantile brain tumors is death within five years of the diagnosis with overall survival rates vary between 20 and 40% [38, 80, 87, 88], and in some series, these rates reached about 56–58% [6, 20, 31, 79, 89].

As the quality of life parameters is difficult to evaluate in pediatric patients, scales measuring the ability to cope with school were used by some investigators for assessment of longer follow-up for infants with brain tumors and results showed that about 50–77% among children who reached school age were able to attend mainstream school [79, 80, 90].

In a study investigating the remote outcome in survivors who reached adulthood [91], it was found that 33% of patients with high grade tumors became long-term survivors in contrast to 20-year survival rate of 82% in patients with low grade tumors. Regarding the clinical and functional outcome of high-grade lesions group of patients, it was reported that most of them were affected by severe late effects of radiotherapy given in their first year of life including second neoplasms, cerebrovascular disease, and coronary valvular disease, and three died at the age of 29, 30, and 41 years. Three of this group of patients were in full-time work and five in part-time work, but none of those who were alive after treatment that included radiotherapy were in full time work. On the opposite hand, among those low grade lesions survivors group 72% were in full-time work and 12% in part-time work.

Conclusions

Brain tumors in the first two years of life are a challenging group of different histopathological entities with underlying specific molecular characterization and genetic predispositions. They have aggressive behavior and general poor prognosis with limited options of management owing to the very young age of this group of patients that omits radiotherapy as one of the main therapeutic lines of management and makes surgical excision, the main curative option in this age group, challenging and a hard mission. Although chemotherapy may be beneficial as an adjuvant therapy and more tolerated in this age group, it has immediate and long-term side effects on the developing brain. Better molecular understanding of these neoplasms might lead to the identification of new therapeutic targets. These lesions are best managed in specialized pediatric oncology centers where a higher level of expertise does exist as well as an individualized multidisciplinary management for each case.

Abbreviations

OPHG: Optic pathway hypothalamic gliomas; PNET: Primitive neuroectodrmal tumors; AT/RT: Atypical teratoid rhabdoid tumors; VP: Ventriculoperitoneal; VA: Ventriculoatrial; CT: Computed tomography; GTR: Gross total resection; CSF: Cerebrospinal fluid; GBM: Glioblastoma; US: Ultrasonography; MRI: Magnetic resonance imaging; miRNA: Micro-ribonucleic acid; DNA: Deoxyribonucleic acid.

Acknowledgements

Not applicable.

Authors' contributions

This is a single author article where the author had reviewed the literature to collect information and data that were used in writing the manuscript.

Funding

No funding.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

Received: 6 August 2021 Accepted: 21 August 2021
Published online: 27 December 2021

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