Ependymoma Tumor Diagnosis: Pathophysiology and Prognosis of Pediatric and Adult Patients

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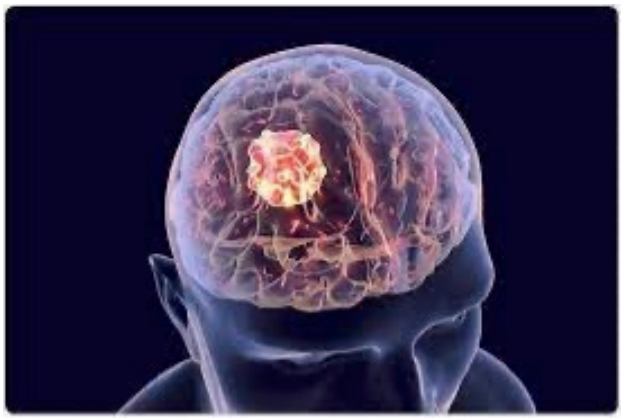
Abstract

Ependymomas are a rare type of tumor that affects the Central Nervous System (CNS) of adolescents and adults. The tumor derives from the Ependymal cells which are responsible for lining the ventricles containing cerebrospinal fluid within the brain and spinal cord. While pediatric patients are more likely to develop the tumor in the brain, adult patients mainly develop the tumor in the spinal cord region. (Gerstner, 2018). Ependymomas range from being slow growing Grade I tumors to malignant and fast growing Grade III tumors which are known as anaplastic. Current medical treatments for this tumor provide more positive outcomes for adult patients versus pediatric patients. This paper will explore the pathophysiology of the disease in both patient types in order to provide insight into possible differences that better explain the clinical outcome

Introduction

One of the negative consequences of cancer is the continuous and unregulated proliferation of cancer cells. Unlike regular cells which grow to appropriately regulated signals, cancer cells grow and divide “uncontrollably”, spreading to normal tissues and organs throughout the body by a process called metastasis. (Cooper, 2000) The unregulated growth of cancer cells is the result of an accumulation of abnormalities within multiple cell regulatory systems and is reflected in a manner that distinguishes cancer cells from their counterparts. These abnormalities can range from various types of mutations in the DNA sequence that can either cause issues with tumor suppressor genes or activating cancer promoting genes. With respect to cancer pathology, the most important issue is the distinction between malignant and benign tumors. (Cooper, 2000) A tumor is any abnormal proliferation of cells. A benign tumor such as a skin wart remains stagnant in a specific location and does not spread to other tissues and parts of the body. A malignant tumor can spread to nearby tissues as well as throughout the body via the circulatory and lymphatic systems through Metastasis. (Cooper, 2000). Brain tumors are a collection of neoplasms that arise either from within the brain itself, or from systemic tumors that have metastasized to the brain. Symptoms of Brain tumors include seizures, headaches, fatigue and cognitive dysfunction. (Butowski, 2015) There are currently over 120 types of cancers and tumors that effect the brain, however some of the more common ones are pilocytic astrocytoma’s, ependymomas, and medulloblastomas in children, and the diffuse astrocytic tumours (including astrocytoma, anaplastic astrocytoma’s, and glioblastomas), oligodendroglia’s, and meningioma’s in adults. (Collins, 2004) . Ependymomas are glial cell tumors that typically arise from the lining cells of the blood vessels of the brain and are less known to be found outside of the central nervous system. These tumors are genetically distinct from each other and affect children more than adults. (Zamora, 2020)



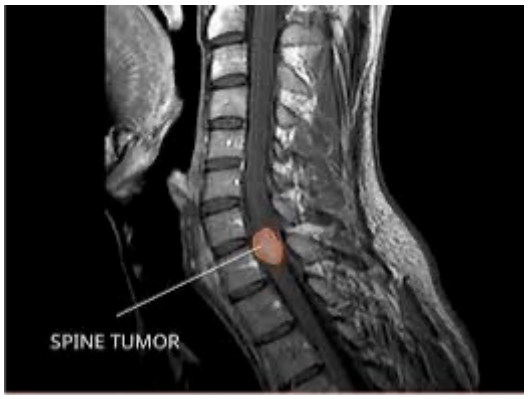
Imaging of a Pediatric Brain Tumor (2020).

Ependymomas Explained

Since ependymomas rarely spread outside the central nervous system, they do not follow the typical classification system. The classification starts with grade I tumors which are slow growing and are often considered benign, including subependymomas and myxopapillary ependymomas. This means they are less likely to be fatal. Subependymomas arise in the ventricular walls and are common in the fourth or lateral ventricles. They are histologically characterized by a hypocellular tissue presenting clusters of cells with a bland nucleus surrounded by glial matrix. Myxopapillary ependymomas arise in the cauda equina, filum terminale or conus medullaris, and present histologically as pseudopapillary structures with mucin-rich microcysts, the cells are cuboidal and radially arranged surrounding a myxoid stroma. These regions are in the tailbone or the base of the spinal cord. These tumors would occur in mostly the adult patient subtype. Grade II ependymomas are present in papillary structures. Cells are arranged regularly and present a clear cytoplasm. Grade III, are anaplastic ependymomas, presenting with abundant mitotic cells with pseudopalisading necrosis. This type is more deadly (Zamora, 2020). Ependymomas develop in all age groups but occur mostly in children and rarely in adults. According to the 2014 report published by the Central Brain Tumor Registry of the United States, ependymomas account for 5.2% of all brain and CNS

tumors in children and adolescents aged 0–19 years. With regards to ethnicity, the incidence rate per 100,000 is 0.40 in Caucasians versus 0.27 in African American (Wu 2016). The survival rate is the highest for those aged 20–44 years and gets lower with increasing age at the time of the diagnosis. The 10-year survival rate is only 28.1% in those aged older than 75 years. In children and adolescents aged 0–19 years, the 10-year survival rate is 66%. (Wu 2016) The prognosis of this tumor type is mainly based on the location of the tumor as well as the age of the patient. A study conducted by Rodriguez analyzed 2408 ependymoma cases- 2132 belonging to the grade 2 category and 276 belonging to the grade 3 category from the Surveillance, Epidemiology and End Results database 1997–2005. Some of the factors that contributed to poor clinical outcomes were younger age, male sex, higher tumor grade, intracranial location, and failure to undergo surgical resection. Even with these findings, the use of the central registry does suggest possible issues with diagnosis. Analysis of ependymoma cases in a single institution found that nearly 20% of cases had been misdiagnosed as another histological type of neoplasm prior to expert review. (Wu, 2016) In order to understand how the prognostic factors for pediatric patients are different from those of adults, (Amirian et al, 2016) the ependymoma cases from the SEER database are analyzed separately for pediatric and adult patients. Anaplastic and infratentorial location of tumors were associated with increased mortality rate in pediatric cases, while a supratentorial location was associated with higher mortality rate in adult patients. Surgical resection proved to be beneficial for both pediatric and adult patients. (Wu, 2016) The unfavorable prognostic impact of a supratentorial location was shown by analysis from a study involving seventy patients aged older than 17 years. However, only older age, and not supratentorial location, was found to be an unfavorable prognostic factor by multivariate analysis from the study. (Wu, 2016) A single institution study of 123 adult ependymoma patients was conducted at the University of Texas MD Anderson Cancer Center. Forty patients had tumors in the brain, 80 in the spinal cord, and 3 at both locations. Although most of the tumors were grade I or II, the study showed that brain location (versus spinal cord) and tumor anaplasia were associated with a worse outcome in adults measured by both overall survival (OS) and progression-free survival (PFS) (Wu 2016). Ependymal tumors have a rare occurrence, comprising 1.7% of all brain tumors, as reported in the CBTRUS statistical report. It has been difficult to find an effective treatment for the disease due to the low percentage of occurrence of these tumors (Zamora, 2020). Studies have shown an improved survival for patients who undergo resection with adjuvant radiation therapy. There is minimal and limited evidence supporting chemotherapy for adult ependymomas (Zamora, 2020). Currently none of the established guidelines use the molecular subgroups to guide treatment of ependymoma. The current consensus recommends that patients with PF-EPN-A positive ependymoma, who are older than 12 months undergo maximal safe micro-neurosurgical removal in addition to local radiotherapy. (Zamora, 2020).

For intracranial ependymomas, surgery is the main treatment. Complete resection without residual disease has presented better clinical outcomes and better overall survival rate than partial resection. (Zamora, 2020) As discussed previously, there is insufficient evidence to support the use of chemotherapy. Patients who are long term survivors from central nervous system tumors present a diverse array of complications, including neurological deficits, cognitive limitations, hearing loss, endocrine and growth abnormalities, and secondary malignancies. Adult patients may present long term complications, most commonly fatigue, numbness and tingling, pain, and disturbed sleep. (Zamora, 2020)Childhood intracranial ependymoma has a poor prognosis, especially in young children when a gross total resection cannot be performed. Even without radiologically proven residuum, around two-thirds of these young children will have a relapse. (Grill, 2003). Adjuvant therapy is necessary for most, if not all, patients. Craniospinal irradiation combined with posterior fossa boost has deleterious effects on cognition. Pediatric oncology teams have tried to use chemotherapy to avoid irradiation and reduce irradiation fields to the tumor bed without altering the prognosis. Cisplatin, at a dose of 120 mg is the only single agent that has reproducibly shown some efficacy in ependymoma. (Grill, 2003) Despite some combinations showing efficacy in the adjuvant setting, childhood intracranial ependymomas can be considered chemo resistant. The overexpression of the multidrug resistance-1 gene and the 06-methylguanine-DNA methyltransferase have been implicated as possible mechanisms for this phenomenon. As the use of chemotherapy with current agents is questionable, phase II studies with new agents and combinations become necessary. (Grill, 2003) Since the main problem of this disease is local relapse, it may not be necessary to irradiate the whole posterior fossa region. However, local control of the disease by irradiation must be improved. In this respect, hyper- fractionation or radio sensitizers may be valuable therapeutic options. The treatment of children with ependymoma is a challenge for all caregivers. There is no doubt that any possible improvement in the management of this rare tumor will only be the result of well-designed cooperative trials (Grill 2003).



A MRI image of an Ependymoma Tumor in the Spinal Cord (N.C.I, 2021).

Conclusion

Ependymomas are a very aggressive type of brain tumor that occur in both pediatric and adult patient types.

While most cases of this tumor type effect pediatric patients in the brain with very little metastasis from other regions of the body, it still has a worse prognosis compared to adult patients. The common treatment for these tumors include surgery as well as chemotherapy, however the tumor has shown to be chemo resistant. Typically when a Tumor is chemo resistant it will end up growing back not too long after the chemotherapy and continue to spread. There has been research conducted that shows chemotherapy may not be the best treatment due to its lasting complications it may cause. Therefore, upon initial surgery, it is recommended that the surgeons remove most of the tumor in order to try and eliminate as much as possible. More research needs to be done to understand ependymomas on a molecular level in order to offer a more effective treatment for pediatric “patients”.

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