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Genetic Variations and Risk Factors on Medulloblastoma

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ABSTRACT

Medulloblastoma, a highly aggressive brain tumor, presents a complex clinical landscape driven by intricate genetic variations and diverse risk factors. This review delves into the tumor's genetic origins, emphasizing molecular subgroups and their prognostic implications. Examining risk factors such as age, gender, genetics, and ethnicity provides a holistic perspective. Unraveling hereditary forms sheds light on familial predispositions. Racial disparities underscore the importance of tailored approaches. Decoding the complexities surrounding medulloblastoma informs refined diagnostics and personalized treatments, offering hope for enhanced patient outcomes.

KEYWORDS: Medulloblastoma, brain tumor, genetic variations, molecular subgroups, risk factors, hereditary forms, racial disparities, diagnostics, personalized treatment, patient outcomes.

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INTRODUCTION

Medulloblastoma, an aggressive brain tumor, originates in the fourth ventricle and commonly presents with symptoms indicative of increased intracranial pressure and cerebellar dysfunction. The clinical picture includes progressively worsening headache, vomiting, ataxia, truncal instability, nystagmus, and cranial nerve palsies. Visual impairment, lethargy, and papilledema may also be observed [1].

To confirm the diagnosis, an initial suspicion is based on the clinical history and physical examination findings. However, definitive confirmation requires an MRI, which reveals the presence of a cerebellar mass. The subsequent step involves pathologic confirmation post-resection of the tumor. Risk stratification is crucial and involves considering histologic variants, molecular subtypes, and overall risk factors such as tumor size, location, the presence of metastasis, and the patient's age at presentation [2].

The primary goal of treatment is to reduce intracranial pressure and eliminate the tumor burden. The preferred approach includes a combination of strategies, such as maximum safe surgical resection, postoperative radiation therapy, and chemotherapy. Radiation therapy plays a central role in the treatment plan, given the tumor's high sensitivity to radiation. It is particularly effective because medulloblastoma tends to spread along the cerebrospinal fluid pathway [1,3].

While the overall survival rate for patients with average-risk disease exceeds 80%, there is a recurrence rate of 30% after initial treatment. Long-term complications associated with both the disease and its treatment are common, impacting overall quality of life. These complications include neurocognitive deficits, endocrine abnormalities, hearing loss, infertility, stroke, and an increased risk of secondary malignancy [4].

Post-treatment monitoring is essential, extending for 5 to 10 years. Serial MRI scans are conducted to detect any recurrence of the disease. Additionally, patients are monitored for common endocrine deficiencies associated with treatment, such as growth hormone deficiency, gonadal alterations, hypothyroidism, and central adrenal insufficiency [5].

Several pitfalls and considerations are highlighted in managing medulloblastoma. Radiation therapy is to be avoided in children younger than 3 years due to the detrimental effects on the developing central nervous system. For patients displaying signs or symptoms of hydrocephalus requiring sedation for MRI, addressing increased intracranial pressure before sedation is crucial. This involves implementing general supportive measures to decrease intracranial pressure, administering steroids, and considering a preoperative extraventricular drain to prevent acute sedation-related hypoventilation [6].

A potential complication known as posterior fossa syndrome may develop after surgical tumor resection. Despite its dramatic nature, it is emphasized that delays in further treatment modalities should be avoided. This underscores the importance of a comprehensive and timely approach to managing medulloblastoma, considering both the aggressive

nature of the tumor and potential complications associated with its treatment [7].

CAUSES AND RISK FACTORS

While the precise etiology of medulloblastoma remains elusive, the tumor is characterized by an average of 11 genetic sequence variants that disrupt cellular signaling crucial to brain development. This genomic complexity forms the basis for understanding the heterogeneity of medulloblastoma [8].

Exploring Risk Factors:

1. Age Dynamics:

Medulloblastoma predominantly affects early childhood, with bimodal peaks observed between ages 3-4 and 8-9. A median age of presentation falls between 5 and 7 years. Remarkably rare in adults, it is typically diagnosed between ages 20-34 [9].

2. Gender Disparities:

The tumor exhibits a notable gender bias, with a higher incidence in males. Ratios range from 1.4:1 to 2:1, contingent on the specific molecular subtype [10].

3. Genetic Predispositions:

Genomic insights have pinpointed several key candidate genes associated with different subgroups of medulloblastoma. These include TP53, SUFU, CTNNB1, MYC, and PTCH2. Medulloblastoma primarily occurs sporadically, with about 30-45% of cases showing loss of genetic material from chromosome arm 17p, housing important tumor suppressors [11].

4. Hereditary Strains:

Familial Medulloblastoma (OMIM #155255): This form is characterized by autosomal dominant inheritance and is caused by germline inactivating variants in the SUFU gene or BRCA2 gene [12].

Gorlin Syndrome (OMIM #224690): This autosomal dominant disorder, associated with multiple tumor types, including medulloblastomas, is caused by germline variants in DNA mismatch repair genes (e.g., PTCH1) [13].

Turcot Syndrome, Subtype 2 (OMIM #276300): An autosomal recessive disorder linked to familial adenomatous polyposis, medulloblastoma occurs in about 40% of patients and is caused by germline variants in the tumor suppressor gene APC [14].

Li-Fraumeni Syndrome (OMIM #151623): An autosomal dominant disorder caused by variants in the TP53 tumor suppressor gene, it is characterized by a predisposition to various malignancies, including medulloblastoma [15].

Familial Adenomatous Polyposis (OMIM #175100): Another autosomal dominant disorder caused by variants in the APC tumor suppressor gene, it significantly elevates the risk of medulloblastoma [16].

Von Hippel–Lindau Syndrome (OMIM #193300): An autosomal dominant syndrome with a heterozygous variant in the VHL gene, it is characterized by the development of various malignant and benign neoplasms, including medulloblastoma [17].

5. Ethnic and Racial Nuances:

In the United States, there's a racial disparity, with White patients having a higher risk (1.69 per million) compared to Black patients (1.03 per million) [19].

Understanding these causative factors and risk elements provides a foundation for more targeted diagnostics and personalized management strategies for medulloblastoma.

CONCLUSION

Medulloblastoma, an aggressive brain tumor, poses a complex challenge with intricate genetic underpinnings and varied risk factors. Despite the unknown exact cause, genetic alterations play a pivotal role, leading to dysregulation in cellular signaling crucial for brain development. The tumor's heterogeneity is reflected in its molecular subgroups, influencing diagnosis and prognostication.

Risk factors, ranging from age dynamics and gender disparities to genetic predispositions, shed light on the multifaceted nature of this malignancy. Understanding hereditary forms, such as Gorlin syndrome and Turcot syndrome, emphasizes the intricate interplay of genetic factors in medulloblastoma development.

Moreover, the racial disparity observed in the United States highlights the importance of considering ethnic nuances in disease prevalence. White patients exhibit a higher risk compared to their Black counterparts, underlining the need for tailored approaches in different demographic groups.

In unraveling these causes and risk factors, a comprehensive understanding emerges, paving the way for targeted diagnostics, risk stratification, and personalized treatment modalities. Advances in genomics and molecular profiling promise to refine our comprehension further, fostering breakthroughs in the management of this challenging brain tumor. As research progresses, the intricate tapestry of medulloblastoma is slowly being unraveled, bringing hope for improved outcomes and quality of life for affected individuals.

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