1 EPIDEMIOLOGY

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INCIDENCE AND PREVALENCE

Posterior cranial fossa meningiomas (PFMs) represent around 10% of all intracranial meningioma cases.[1-3] Their annual incidence is estimated to be 0.37 per 100,000 person-years, which underscores their relative rarity when compared to supratentorial meningiomas.[4]

AGE DISTRIBUTION AND GENDER PREDILECTION

The age distribution of PFMs reveals a notable peak in the sixth and seventh decades of life, with the average age at diagnosis being 58 years.[4] The incidence steadily rises with age, and females show a significant predilection for PFMs, comprising approximately 65% of the cases.[2]

TUMOR SUBTYPES AND LOCALIZATION

Posterior cranial fossa meningiomas encompass a range of subtypes, each originating from distinct anatomical locations. These subtypes include:

- cerebellar convexity meningiomas – prevalence approximately 20% among posterior fossa cases;
- posterior petrous bone meningiomas – prevalence ranging from 10% to 15%;
- tentorial meningiomas – prevalence between 15% and 20%;
- jugular foramen meningiomas – prevalence around 10%;
- foramen magnum meningiomas – prevalence approximately 5%;
- petroclival meningiomas – prevalence ranging from 10% to 15%.[4-9]

CLINICAL PRESENTATION

The clinical presentation of PFMs encompasses a spectrum of neurological symptoms, often contingent upon the specific anatomical location and affected structures. Common clinical manifestations include ataxia, headache, cranial nerve deficits, and signs of increased intracranial pressure.[10] Among the diverse subtypes of PFMs, cerebellar convexity meningiomas typically manifest with ataxia (62% of cases), while posterior petrous bone meningiomas often lead to cranial nerve deficits (80% of cases). Tentorial meningiomas frequently cause headaches (55% of cases), whereas jugular foramen meningiomas prominently induce cranial nerve palsies (67% of cases). Foramen magnum meningiomas frequently present with

lower cranial nerve involvement (45% of cases), and petroclival meningiomas can result in cranial nerve deficits (75% of cases).[4] These nuanced clinical presentations underscore the complex anatomical relationships in the posterior cranial fossa and the variability in symptoms based on tumor subtypes.[2]

TREATMENT STRATEGIES AND PROGNOSIS

Treatment strategies for PFMs involve a multidisciplinary approach with the primary goal of achieving optimal outcomes while preserving neurological function. Gross total resection (GTR) is typically pursued when feasible, with success rates varying based on tumor subtype.[11, 12] Notably, GTR rates for cerebellar convexity meningiomas are reported to be approximately 80%, while posterior petrous bone meningiomas achieve GTR rates of around 65%. Tentorial meningiomas exhibit GTR rates of approximately 70%, and foramen magnum meningiomas achieve GTR rates of about 50%. Due to their complex anatomical location, petroclival meningiomas achieve GTR rates of approximately 60%.[13] Adjuvant therapies, such as radiation, may be considered to manage residual or recurrent tumors. Individualized treatment plans, taking into account tumor characteristics and patient factors, play a pivotal role in optimizing therapeutic outcomes and overall quality of life. The 5-year overall survival rates for PFMs range from 70% to 90%.[10]

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2 PATHOGENESIS OF POSTERIOR CRANIAL FOSSA MENINGIOMAS

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INTRODUCTION

Meningiomas are primarily benign, slow-growing extra-axial tumors that originate from arachnoid cap cells in the meninges. Although familial or syndromic forms exist, such as neurofibromatosis type 2 (NF2), Gorlin Syndrome, von Hippel-Lindau Syndrome, and multiple endocrine neoplasia (MEN) type 1, in most cases, meningiomas occur sporadically.[1, 2] Exogenous and endogenous risk factors have been identified as contributors to the development of meningiomas, even though the underlying pathogenetic mechanisms remain incompletely understood. In the following paragraphs, we will describe and analyze the pathogenetic role of various risk factors, including ionizing and non-ionizing radiations, occupational risks, lifestyle and socioeconomic conditions, traumatic brain injury, viral infections, immunologic factors, and female sex hormones. These factors are implicated not only in the pathogenesis of posterior fossa meningiomas but also in intracranial meningiomas in general.[2]

IONIZING RADIATION

According to the International Agency for Research on Cancer (IARC), X and Gamma-radiation are recognized as carcinogenic agents with sufficient evidence in humans for causing CNS tumors.[3] Ionizing radiation can lead to the breaking of chemical bonds, the formation of free radicals, and damage to DNA. This, in turn, can result in gene mutations, chromosomal rearrangements, or cellular necrosis, often involving the loss of bases or breaks in one or both DNA strands. Preston *et al.* noted a higher risk for benign tumors but did not find statistical significance for meningiomas.[4] Furthermore, Shintani *et al.* highlighted an association between the risk of developing meningioma and the distance from an atomic blast.[5]

Brain tumors have been reported in pediatric populations exposed to radiation for benign medical conditions, such as skin hemangiomas, tinea capitis (before the introduction of Griseofulvin), hematological malignancies, and primary tumors.[6, 7] The first radiation-induced meningioma was described by Mann *et al.* in 1953 in a child undergoing treatment for optic glioma.[8] In a recent systematic review, Bowers *et al.* found that childhood tumor survivors who received cranial radiotherapy were 8.1 to 52.3 times more likely to develop CNS neoplasms, with 5-year survival rates ranging from 73% to 100% for meningiomas.[7] Some studies have also observed an increased incidence of the risk of meningiomas due to dental X-Rays,[6] although a recent meta-analysis found no association.[9] In recent decades, there has been increased interest in cosmic ionizing radiation, and susceptibility to specific types of tumors and cognitive impairment has been identified in several studies involving flight personnel.[10-12]

NON-IONIZING RADIATION

Since the late 1980s, with the widespread use of mobile phones in everyday life, a potential link between low-level exposure to radiofrequency and health problems, especially brain-related issues, has been hypothesized. Radiofrequency electromagnetic fields (RF-EMF) are considered by the IARC as agents with limited evidence in humans (Group 2B), particularly for glioma and acoustic neuroma, but no clear association has been found between RF-EMF and other brain tumors studied.[7, 13] Most available studies do not show an increased risk of developing meningiomas when considering factors such as duration of exposure, the side of the head used for phone placement, brain location, and the type of phone used.[14] In the INTERPHONE study, an international case-control study conducted in 13 countries, the authors did not report an increased risk of meningioma among mobile phone users.[15] A recent prospective study involving 776,156 UK women recorded a total of 3268 brain tumors, and no statistically significant associations were found for everyday use or at least 10 years of phone use.[16] A recent systematic review and meta-analysis found a lower risk in adults (OR=0.90, 95% CI: 0.83-0.99) for wireless phone use, especially in short-term use (OR=0.85, 95% CI: 0.77-0.94), while in medium/long-term users, no significant changes in the risk of meningioma were found (OR=0.93, 95% CI: 0.75-1.16).[17]

OCCUPATIONAL RISKS AND SOCIOECONOMIC CONDITIONS

The percentage of cancers associated with occupational exposures has been estimated to range from 2% to 8%.[18] Regarding meningiomas, studies have investigated the effects of exposures to metals, their dust, fumes, pesticides, and insecticides and their potential carcinogenic effects, although results have been conflicting.[10, 19] Lead, defined as a probable human carcinogen by the IARC, has been associated with the onset of CNS tumors, as supported by several studies.[20] In a French prospective cohort study involving 181,842 participants, an increased risk of developing meningiomas was found in sugar beet growers (HR=2.54; 95% CI: 1.31-4.90), sunflower farmers (HR=3.56; 95% CI: 1.44-8.82), and pesticide applicators for potatoes (HR=3.09; 95% CI: 1.06-9.03).[21] The associations between meningiomas and metal exposure were also examined in a case-control study across seven countries by Sadetzi *et al.*, which found a positive association with iron exposure, especially among women (OR=1.70, 95% CI: 1.0-2.89).[22, 23]

Analyzing socioeconomic conditions, highly educated women with a university education were found to be more likely to develop meningioma compared to those with primary education.[3] Moreover, a cohort study involving the Swedish population observed an increased risk among unmarried or cohabiting men.[24]

LIFESTYLE

Large European cohort studies conducted in Sweden, Norway, Austria, and the UK have documented a positive association between increased blood pressure and meningioma

(HR=1.29, 95% CI: 1.04-1.58; OR=1.34; 95% CI: 1.20-1.49).[25, 26] The relationship between anthropometric factors, such as BMI and body fat percentage, and brain tumors has been studied by several researchers. Adipose tissue is considered a neuro-immuno-endocrine organ that secretes hormones and other metabolically active substances. An excess of adipose tissue results in an increase in aromatase, which converts androgens into estrogens. Several studies have demonstrated a significant risk of developing meningiomas with an increase in BMI ($P \leq 0.01$; $P=0.028$; $P \leq 0.0001$) and body fat percentage ($P=0.042$).[27] A recent meta-analysis revealed a growing Risk Ratio of 1.18 (95% CI: 1.07-1.31) and 1.48 (95% CI: 1.30-1.69) in overweight and obese individuals, respectively. Additionally, each increment of 5 kg/m^2 was associated with a risk ratio of 1.19 (95% CI:, 1.14-1.25) for meningiomas.[28] However, no statistically significant association was found between meningioma and triglycerides, high-density lipoprotein, and fasting blood glucose.[26] Although tobacco smoke is a well-known carcinogen (belonging to IARC group 1) and is associated with lung cancer and an increased risk of oral cavity, esophagus, colon, bladder, kidney, and breast cancers, there is currently no established association between smoking and meningiomas.[29]

TRAUMATIC BRAIN INJURY

The association between traumatic brain injury (TBI) and the development of meningiomas has long been a subject of interest. First hypothesized by Harvey Cushing, the available data in the literature provide contradictory results.[19] Several case-control studies have documented a statistically significant high risk, with the mean time to diagnosis ranging from 10 to 19 years or more than 20 years after the head injury. A large cohort study conducted in Denmark on 228,055 patients reported a higher tendency for meningioma (OR=1.2; 95% CI: 0.9-1.7) without a significant statistical association.[30, 31] Nygren *et al.* studied the risk of meningiomas after TBI in 311,006 Swedes and did not find an overall increased risk (OR=1.1; 95% CI: 0.8-1.4).[30, 31] This result was later confirmed in the study by Kuan *et al.*, which involved 75,292 patients (OR=1.27; 95% CI: 0.62-2.57).[32]

VIRUS INFECTION AND IMMUNOLOGY

In recent decades, there has been a growing interest in studying the link between tumors and infections. Infections can increase an individual's risk of cancer in various ways, although the underlying mechanisms remain unclear. Oncoviruses, also known as oncogenic viruses, can induce neoplastic mutations, acquire cellular oncogenes, or encode proteins with transforming capacity. In other conditions, viruses can induce a state of chronic inflammation or suppress the immune system.[33] The association between brain tumors and allergies or chronic diseases is still debated, with inconsistent results. A meta-analysis by Wang *et al.* found no significant relationship for asthma and hay fever but reported an inverse association between eczema and meningioma (OR=0.75; 95% CI: 0.65-0.87, $P<0.05$). An international case-control study performed in France, Australia, Canada, Israel, and New Zealand (INTERPHONE study) documented a significant inverse association between any type of allergic diseases and the risk of meningiomas (OR=0.77, 95% CI: 0.63-0.93).[34]

FEMALE SEX HORMONES

Since meningiomas are more common in women, a potential association between female hormones and meningiomas has been explored.[3] The expression of progesterone and estrogen receptors is well-established in meningiomas, with the progesterone receptor expressed in a range of 39% to 95%, while the estrogen receptor is found in lower levels, typically below 10% or undetectable.[35-37] Pregnancy is a phase of the female reproductive cycle that may be a risk factor for meningiomas, which more frequently occur during the third trimester.[38] A European case-control study demonstrated that pregnancy and the number of pregnancies did not represent a risk for women overall, although a positive association was observed with the number of live births in women under 50 years of age.[39] Regarding breastfeeding, Claus *et al.* showed that if performed for at least 6 months, it reduced the risk of meningioma (OR=0.78, 95% CI: 0.63-0.96), while other authors found no association.[37] Several studies have analyzed the association between meningiomas and progestin drugs, such as cyproterone acetate (CPA), nomegestrol, and chlormadinone acetate.[40] Moreover, cases of meningiomas have been described in transgender individuals, where the intake of such medication occurs in high doses and over an extended period.[40] Meningiomas associated with CPA are usually multiple (26.7% *vs.* 6.1%; P=0.0115) and situated in the middle (39%) and anterior skull base (21.9%), with a particular fondness for the sphenо-orbital region.[41] An increased risk of meningiomas was found in premenopausal women who took oral contraceptives (OR=1.8, 95% CI: 1.1-2.9), but no associations were found with hormone replacement therapy during the postmenopausal period (OR=1.1, 95% CI: 0.74-1.67).[41] From a molecular perspective, CPA-related meningiomas are usually low-grade meningiomas with a low percentage of Ki67 expression and are characterized by mutations in *AKT1* or *PIK3CA* in 33.3% of cases.[42]

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