



Risk Factors for Pediatric Glioma

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Abstract

Brain tumours are a heterogenic group, a subtype of which is arising from glial cells. Pediatric low-grade gliomas are the most common primary CNS tumour group in childhood, representing 25% to over 30% of pediatric CNS tumours. Pediatric high-grade gliomas are relatively rare and have a poor prognosis. Epidemiological studies have reported various potential risk factors, such as demographics, ionizing and nonionizing radiation, allergic conditions, and infections, immunologic, parental, genetic, and developmental risk factors. These risk factors are relatively unclear and understudied; thus, this narrative review aims to summarize all studies connecting risk factors and pediatric gliomas.

Keywords

epidemiology, glioma, high-grade glioma, low-grade glioma, pediatric, risk factors

INTRODUCTION

Primary malignant central nervous system (CNS) tumours are the most common pediatric solid organ tumours and the second most common pediatric malignancies after hematologic malignancies.^[1] More specifically, they represent more than 20% of all pediatric malignancies.^[2] Deaths due to pediatric brain tumours have increased from 17.8% in 1975 to 25.7% in 2006 according to USA data^[3], with brain neoplasms causing one-fourth of all cancer-related deaths in children nowadays^[4]. While pediatric brain tumours are more frequently malignant than adult brain tumours^[5], the 5-year overall survival is better for pediatric brain tumours than for adults^[3].

Gliomas originate from glial cells.^[6] Pediatric gliomas are histologically classified into a grading system by World Health Organisation (WHO) with grades I–IV.^[7] They evolve into low-grade gliomas (LGGs), high-grade gliomas (HGGs), oligodendrogliomas, ependymomas, optic nerve gliomas, brainstem gliomas, and mixed type gliomas.^[7] Genetic alterations, such as in BRAF, FGFR1, and his-

tones, provide significant information for prognosis and clinical course.^[8] LGGs can be treated conservatively, but most experts suggest excision, while HGGs are almost always excised, followed by radiotherapy and chemotherapy.^[6] Recurrence can be managed with surgery, chemoradiotherapy, and radiosurgery.^[6]

Pediatric low-grade gliomas are a group of entities that is highly histologically and molecularly heterogeneous.^[2,7,9] They are the most common primary CNS tumours group in childhood, representing 25% to over 30% of pediatric CNS tumours.^[9,10] The most common LGG single entity is pilocytic astrocytoma (PA; 15% of tumours in patients aged 0 to 19 years)^[10], while other notable minor entities are ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET), and diffuse glioma.^[2,10] Most commonly, LGGs are located in the cerebellum.^[4] About 20% of patients with neurofibromatosis type 1 develop PA during the first decade of life, typically in the optic pathway.^[10] Pediatric LGGs are usually indolent or extremely slow-growing.^[9]

On the contrary, pediatric high-grade gliomas (HGGs) are relatively rare and represent 8%–12% of all primary pe-

diatric CNS tumours.^[11] Glioblastoma multiforme (GBM) is mainly an adult disease, and pediatric GBM is rare.^[12] Malignant gliomas account for 6.5% of all newly diagnosed intracranial tumours in children.^[13] HGGs can occur anywhere within the CNS, but when brainstem lesions are excluded, the most common location is the supratentorial region.^[14] Pediatric HGGs have a poor prognosis.^[15]

Various epidemiological studies have reported potential risk factors for developing pediatric glioma. This narrative review aims to summarize all connections between risk factors and pediatric gliomas.

Demographics

The overall incidence of brain and CNS tumours is higher among females, concerning all age groups in the USA.^[16] On the contrary, males have a higher incidence of malignant CNS tumours and glioma histologies.^[17,18] Gliomas are the most frequent malignant neoplasm between all racial groups, and twice as common in white people compared to any other racial group.^[16] Particularly for the pediatric population, gliomas are most common in white children, with age-adjusted incidence rates of 2.92 per 100,000, while PAs and other LGGs occur more frequently in non-Hispanic children.^[4]

Environmental risk factors for pediatric glioma

Ionizing radiation

Animal models have shown that ionizing radiation induces double-strand breaks, leading to HGGs.^[19] Ionizing radiation in therapeutic or high doses is the most established environmental risk factor for glioma development^[20], particularly in the pediatric population^[21]. Children treated for acute lymphoblastic leukemia (ALL) have a 22-fold increase in CNS tumours^[21], and radiation treatment for a first neoplasm results in a 7.1-fold increased risk for CNS neoplasms^[22]. Also, children who receive prophylactic CNS irradiation have a high risk of developing brain tumours, including gliomas, with a latency estimated at 7 to 9 years and a higher risk for younger ones.^[23]

According to several studies, prenatal X-ray abdominal exposures are only associated with an about 2-fold increased risk for primitive neuroectodermal tumours (PNET), while neonatal diagnostic X-ray exposure is probably not associated with childhood brain cancer.^[24] Interestingly, the evidence thus far does not support a correlation between diagnostic radiation (such as dental radiographs) and glioma in adults.^[25] Studies have found an increased risk for pediatric brain tumours after CT scan exposure, with the risk inversely associated with age at first exposure^[24,26], and this association is dose-responsive^[26,27]. Interestingly, a study in Florida found no connection between the increase in childhood CNS tumours in the 1990s and the installation of a nearby nuclear plant in 1976.^[28]

Nonionizing radiation

Nonionizing radiation includes radiofrequency/microwave (cellular phones, radio) and extremely low-frequency magnetic fields (electrical wiring and power lines). They are characterized as possibly carcinogenic; however, studies have found no significant associations with childhood CNS tumours.^[24] Interestingly, no association was found between early pregnancy exposure to masts and childhood CNS neoplasms^[29], while there are associations between residential proximity to power lines and all brain tumours and glioma risk among adults.^[30] No associations have been reported for paternal occupational exposure to electromagnetic fields and pediatric glioma risk.^[24] Extremely low-frequency exposure during pregnancy from electrically heated waterbeds or blankets was not associated with astrocytomas, PNETs, or other brain tumours.^[31] On the contrary, maternal exposure to extremely low-frequency magnetic fields (during the two years before pregnancy or during pregnancy) was positively associated with CNS tumours and gliomas, especially for sewing machine operators.^[32] Also, exposure at home to high magnetic fields during childhood was non-significantly associated with brain tumours.^[31]

After the 1980s, there has been a significant increase in the use of cellular phones. However, the overall incidence rates of glioma have not been significantly increased.^[33] Radiofrequency exposure in childhood has not been associated with brain tumours.^[31] Cellular phone use in people 7 to 19 years old was not associated with childhood brain tumours (but a non-significantly increased risk was found), as examined by a European multicenter case-control study (CEFALO).^[34] However, various large-scale case-control studies compared cellular phone usage between persons of all ages with and without glioma and found mixed results.^[35]

Allergic conditions, infections, and immunologic risk factors

Allergic conditions, such as asthma, allergies, and eczema, have been investigated for a role in glioma etiology. Adult gliomas are inversely associated with allergic conditions.^[36] Maternally reported asthma decreases the risk for childhood brain tumours, and asthma in children is inversely associated mainly with ependymoma.^[24] Eczema is not inversely associated with childhood brain tumours, unless combined with asthma.^[24] Interestingly, the CEFALO study found no associations between any atopic disease and childhood brain cancer and glioma.^[37] These differences may stem from possible recall bias, as tumour treatment can affect atopic symptoms.^[37] On the contrary, asthma controllers and relievers are associated with an increased risk for CNS neoplasms.^[38] Overall, allergic conditions may be protective for pediatric brain tumour development, but further research is required.^[24]

Various studies tried to correlate infectious exposures with childhood brain cancer.^[24] The number of siblings has been associated with CNS tumours, suggesting an in-

fectious factor in brain cancer's etiology. More specifically, having three or more younger siblings was associated with pediatric astrocytoma, medulloblastoma, ependymoma, meningioma, and neuroblastoma.^[39] Similarly, childhood brain tumour risk was higher after maternal exposure to infection indicators, having siblings, and being at least second-born.^[40] Cases with glioma and embryonal tumours had more sick days with infections during the first six years of life compared with controls.^[41] Children who attended daycare showed slightly lower risks than those who reported social contact only.^[40,42] No associations have been found between pediatric brain tumours and breastfeeding.^[43]

Parental risk factors

Maternal exposure to medications containing amides or amines such as antiepileptics, barbiturates, and antihistamines was examined for connections with offspring's pediatric brain tumours.^[24] Studies found no or little support for an association, overall or for astroglial or other glial subtypes.^[24] However, herbal medicine *Coptidis Rhizoma*, maternal antihypertensives, especially beta-blockers, and prenatal antibiotic use were associated with increased risk for CNS tumours.^[24]

Maternal alcohol consumption is not related to offspring childhood brain tumours.^[24,44] Several studies regarding parental cigarette smoking have found associations with pediatric brain tumours, with mixed results for astrocytomas.^[31] Case-control studies do not agree on whether tap water consumption and nitrite concentration are associated with pediatric brain tumours, while increased nitrite concentration on water may be associated with astroglial tumours.^[31]

There is evidence that prenatal vitamins have a protective effect on offspring's brain cancer risk. Although some studies found no association between childhood brain cancer and maternal vitamin, folate, or iron supplementation, a study reported protective effects of maternal folic acid and multivitamin supplementation.^[24] In contrast, others found a reduced risk for brain tumours related to iron supplementation, grains, and fruit consumption.^[31] The study that reported no associations between maternal iron supplementation and pediatric brain tumour risk included significantly more patients, and further studies are needed for maternal iron supplementation. Pre-pregnancy use of folic acid has been inversely associated with LGGs in children.^[45] Meat consumption is associated with pediatric brain tumours^[31], and studies have associated childhood CNS neoplasms with cured meat intake during pregnancy, especially combined with low vitamin C intake.^[24] Other studies have associated the consumption of french fries and hot-dogs during pregnancy with brain tumours, bacon with PNETs, cured meats with astrocytomas, and non-cured meat with unspecified astrocytomas.^[31] A study reported decreased risk for anaplastic astrocytomas when cruciferous vegetables were consumed during pregnancy, and decreased risk for astroglial tumours but increased risk for anaplastic astrocytomas when fresh fish was consumed.^[46]

Several studies have reported that parental exposure to pesticides is associated with brain neoplasms during childhood.^[24] Paternal exposure to herbicides during the two years prior to childbirth has been associated with astrocytoma for children under or ten years old.^[47] According to a systematic review by Zumel-Marne et al.^[31], exposure to pesticides during pregnancy is associated with offspring brain tumours, especially with HGGs and astrocytomas, but not PNETs. Furthermore, pediatric brain tumours have been associated with parental exposure to diesel exhaust any time before birth^[48], paternal occupational paint exposure before birth^[49], paternal occupational preconceptional exposure to polycyclic aromatic hydrocarbons, (especially for astroglial tumours)^[50], and paternal exposure to lead and animals^[51]. On the other hand, metal working (oil mists) and paternal social class were inversely associated with childhood brain tumours.^[51] Studies have reported that mothers who lived close to major roadways or high traffic may have an increased risk for offspring ependymoma and PNET, while an increased risk for brain tumours was associated only with areas with moderate diesel particulate matter concentrations.^[31]

Anti-inflammatory drugs and diet

Anti-inflammatory drugs and diets, such as curcumin, gamma-linolenic acid, ketogenic or low-calorie diets, and methionine restriction, can potentially be effective for prevention in predisposed individuals or treatment for gliomas in adults.^[52] For instance, ketogenic diet may increase the antitumour effects of classic treatment options for cancer and improve patients' quality of life.^[53] According to a recent study, aspirin use for six months or more in adults was associated with a 38% lower risk for glioma, but their meta-analysis showed only a marginally significant association, and no association for NSAIDs.^[54] Also, various studies suggest that dietary components, such as vitamins, polyunsaturated fatty acids, flavonoids, and phytoestrogens, may protect against gliomas by interacting between environment and genetics.^[52]

Genetic and developmental risk factors for pediatric glioma

Heritable genetic risk factors and hereditary syndromes

About 5%–10% of gliomas occur in familial clusters in all age groups, with first-degree relatives of glioma patients having a 2-fold increased risk of having a brain tumour, mainly when the patient has developed the tumour at a younger age.^[55] Additionally, studies show that siblings of children with CNS neoplasms have increased risks of developing a CNS neoplasm in childhood, particularly if the index child is diagnosed at or before four years old. Children are also at risk for CNS tumours if a parent has this particular tumour type.^[24]

Various inherited monogenic Mendelian cancer syn-

dromes have increased incidence for specific glioma histologies, as mentioned previously. In general, patients with neurofibromatosis type 1, also known as von Recklinghausen disease, develop CNS lesions (4% to 45%), including optic nerve gliomas, astrocytomas, and ependymomas, among others. Neurofibromatosis type 2 (central neurofibromatosis) appears with astrocytomas, among other tumours.^[17] Tuberous sclerosis complex is associated with subependymal giant cell astrocytomas (5% to 15%).^[17] Patients with Turcot syndrome have extremely high rates of brain tumours: 60% develop medulloblastomas, 14% astrocytomas, and 10% ependymomas.^[17]

Other genetic factors

Studies have noted that children of fathers older than 40 years old at the child's birth have an increased risk for developing brain tumours, particularly astrocytomas. Astrocytomas, along with ependymomas, are also associated with maternal age.^[24]

Several studies have reported that childhood CNS cancer risk is associated with higher birth weight and increasing head circumference.^[24] More specifically, a study noted that HGGs were associated with greater than 4000 grams of birth weight, while children born under 2500 grams were protected against LGGs.^[56] A meta-analysis found that over 4,000 grams of birth weight were predictive of astrocytoma and medulloblastoma but not ependymoma.^[57] Additionally, a 2.5-fold increase in CNS cancer risk has been reported for children with congenital anomalies, and for those with nervous system anomalies, about 6-fold greater risk has been found.^[58]

Study strengths and limitations

Our narrative review was thorough, as we critically evaluated previous research on pediatric glioma risk factors. However, all narrative reviews have inherent limitations, such as subjectiveness in including, analyzing studies, and drawing conclusions. Also, most included studies were case-control and limited by their small sample sizes and selection bias, they had different periods of exposure, and exposure assessment was based mainly on interviews, resulting in recall bias. Thus, definitive answers for possible associations are difficult to be drawn.

CONCLUSIONS

Progress has been made in identifying and studying risk factors for pediatric gliomas (**Fig. 1**). Exposure of children to proven environmental risk factors, such as ionizing radiation, has to be minimized as possible for diagnostic tests. Large international datasets, new genetic loci and variants, better exposure assessment, and carefully planned studies for interactions between genes and environment will further help understand pediatric gliomas' risk factors.

	REDUCED RISK	INCREASED RISK
Demographics		Male gender Ethnicity and race Parental age
Developmental factors		Congenital anomalies High birth weight Head circumference
Genetic factors		Cancer syndromes: NF1, NF2, TSC, Turcot
Immunologic factors	Allergic conditions Exposure to infections	
Environmental factors	Maternal folic acid	Ionizing radiation Occupational exposures Pesticides

Figure 1. Summary of risk factors related to pediatric glioma. Stronger risk factors are in bold. Adapted from Johnson et al.^[24]

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Competing Interests

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Резюме

Опухоли головного мозга представляют собой гетерогенную группу, подтип которой возникает из глиальных клеток. Детские глиомы низкой степени злокачественности являются наиболее распространенной группой первичных опухолей ЦНС в детском возрасте, составляя от 25% до более 30% опухолей ЦНС у детей. Детские глиомы высокой степени злокачественности относительно редки и имеют плохой прогноз. Эпидемиологические исследования выявили различные потенциальные факторы риска, такие как демографические факторы, ионизирующее и неионизирующее излучение, аллергические состояния и инфекции, а также иммунологические, родительские, генетические и связанные с развитием факторы риска. Эти факторы риска относительно неясны и недостаточно изучены; таким образом, цель этого описательного обзора состоит в том, чтобы обобщить все исследования, связывающие факторы риска и педиатрические глиомы.

Ключевые слова

эпидемиология, глиома, глиома высокой степени злокачественности, глиома низкой степени злокачественности, педиатрия, факторы риска