

# Review

## Epidemiology of Pediatric Brain Tumors

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### Abstract

*Malignant brain tumors are one of the most important causes of death in pediatric age group. Even though there are some hints, evidenced data about the etiology is still scarce. Ionizing radiation, N-nitroso compounds, pesticides, tobacco smoke, electromagnetic frequencies, infectious agents, parental occupational exposures, and medications can be listed as probable risk factors. The advances in technology, mainly in molecular biology and genetics, progressively contribute to the understanding of this unsolved problem. There is consensus about the cancerogenic effect of N-nitroso compounds and preventive role of vitamins.*

**Keywords:** brain, cancer, child, epidemiology, etiology, tumor

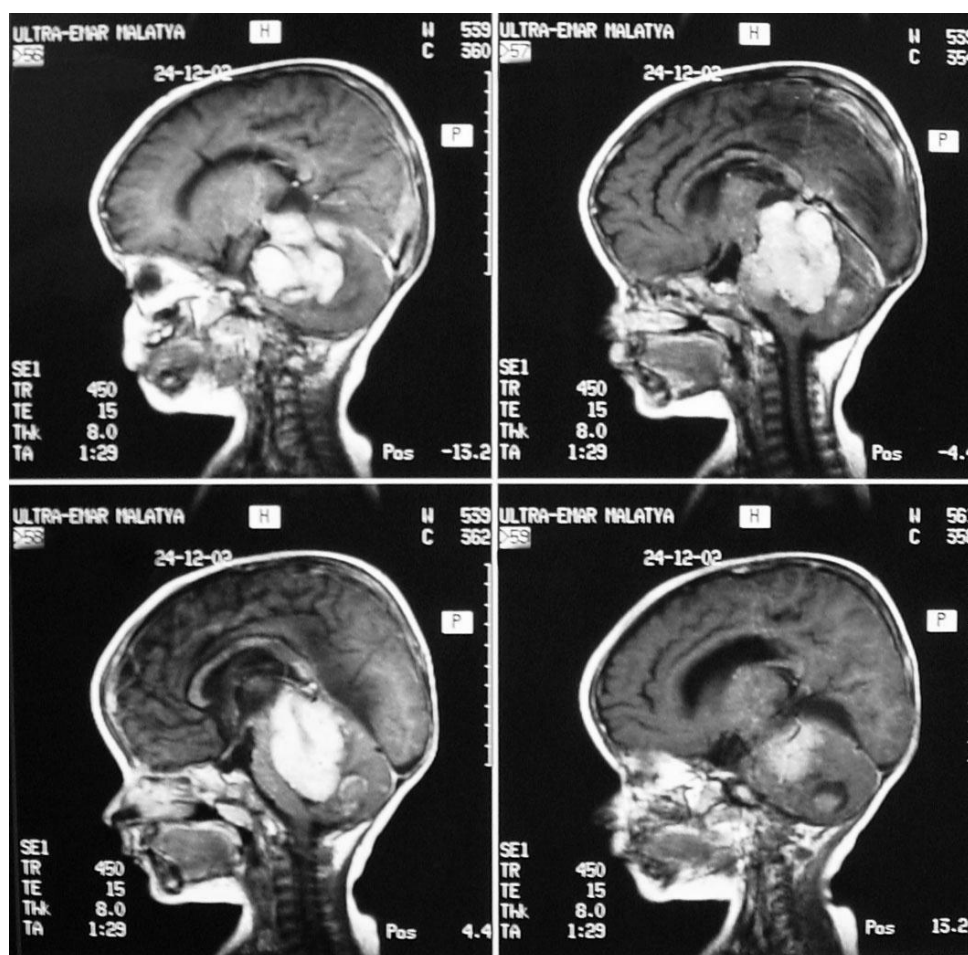
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**Epidemiology of Pediatric Brain Tumors**

The scope of this paper is to focus on the trend of pediatric brain tumor (PBT) incidence within the last thirty years and to make a brief overview on epidemiologic literature. PBTs are the second most commonly seen pediatric neoplasms after hematological malignancies and the first within solid tumors. They are the first etiological cause in pediatric cancer deaths and they cause serious morbidity in this age group (Figure 1-3). Relying on the data of American Cancer Society, 2200 cases under 20 years of age are diagnosed as having “brain tumor” each year ([www.cancer.org](http://www.cancer.org)). PBTs have increased nearly 50% throughout the years 1975 to 2000. Brain tumors are subgrouped according to the cellular morphology and behavioural malignancy. Cerebral tissue is constituted of two main types of cells called “neuron” and “glia” which evolve from primitive neuroectodermal layer. Glial cells are divided into four main groups called astrocytes, oligodendrocytes, ependymal cells, and microglia [1]. The vast majority of primary brain tumors originate from glial cells and are called “glioma” in general terms. Gliomas are subgrouped as astocytomas, oligodendrogliomas, or ependymomas according to their specific cells of origin [2-9].



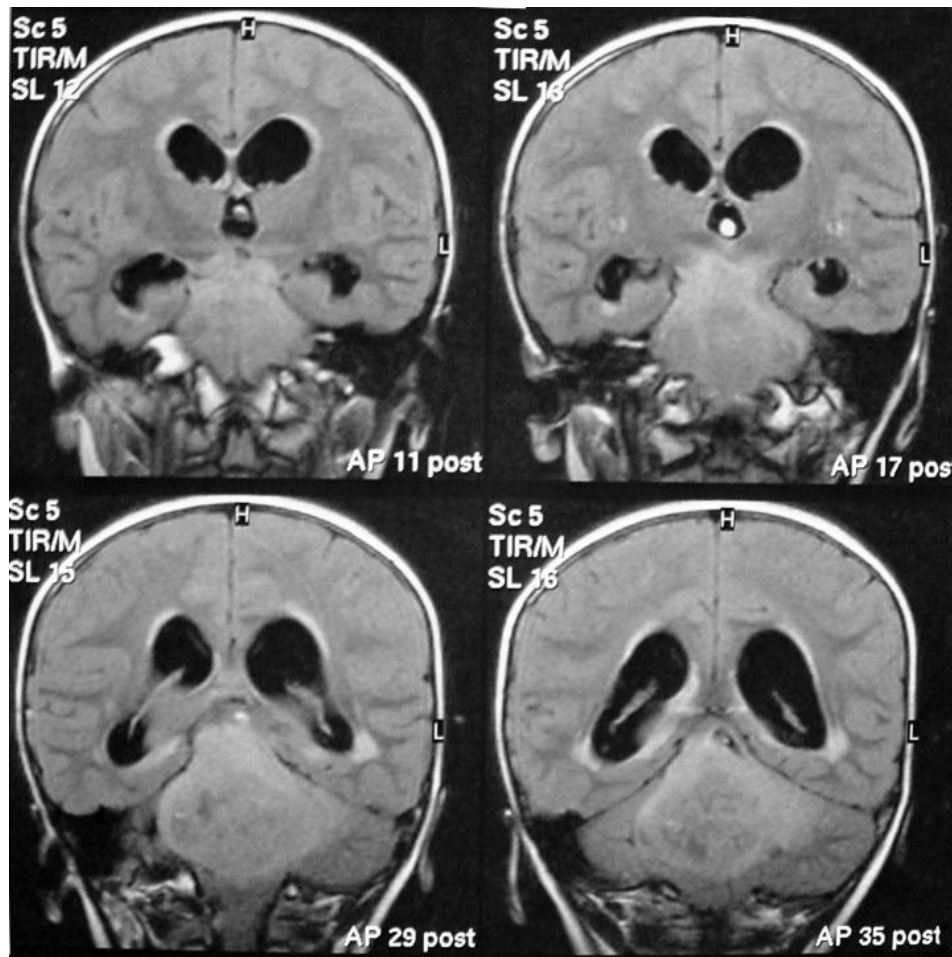
**Figure 1:** Sagittal MRI scan of a pediatric patient revealing a posterior fossa mass (medulloblastoma)

The etiology of the majority of the brain tumors is unknown. Genetic syndromes such as neurofibromatosis, Li-Fraumeni Syndrome, basal cell nevus (Gorlin Syndrome), Turcot Syndrome or ataxia telangiectasia make up only 5% of the etiological reasons. Physical, chemical and infectious causes are also accused for tumorigenesis. Antenatal data on experimental basis is valid for tumor progression. Brain continues its growth within the first three years of life and the blood brain barrier has not fulfilled its development till the end of the first six months after birth. Fetal rats exposed to ethylnitrosurea exhibited fifty times more tendency for brain tumor formation than adult rats [10]. Ionizing radiation, electromagnetic fields, and trauma are the main causes of physical aspect. Ionizing radiation has proven etiological effect on tumor formation. Children who are exposed to radiation due to maternal antenatal diagnostic procedures revealed a higher incidence of central nervous system tumor incidence compared to the normal population. In an Israelian study regarding central nervous system tumor progression in children who received cranial radiotherapy due to tinea capitis showed that the incidence risk is 18.8 times more in nerve sheath tumors, 9.5 times more in

meningiomas, and 2.6 times more in gliomas [11]. A work by Children Cancer Study Group on 6644 pediatric patients irradiated with the diagnosis of acute lymphoblastic leukemia revealed a 7 times more risk of a second malignancy occurrence and 22 times more risk in central nervous system tumor formation compared to the normal population [12].

Exposition to electromagnetic fields is thought to be a risk factor for PBT formation in some epidemiological studies. This was first reported in 1979 in a study performed in Denver focusing on children who lived near high electromagnetic fields. This study stated that those children had higher risks of developing leukemia or brain cancer with resultant fatal results [13]. Later studies showed some data which are open to interpretation while some others exhibited more significant results. There were still some drawbacks such as limited number of cases or the bias on correct evaluation of the magnitude of the electromagnetic field. Some objective criteria such as the distance to the electromagnetic source, the usage of electrical equipments and the conditions related to maternal or paternal occupation were tried to be instituted.

Trauma is not thought to be a major epidemiological factor in the formation of PBTs. The information related to the pediatric age is limited. The data of West Coast Brain Tumor Study Group disclosed that the children who required medical support and clinical follow-up after a head trauma experienced 1.4 times more frequent intracranial meningioma formation compared to the nontraumatic control group. No direct correlation between birth trauma and PBT formation is described [14-17]. There is strong evidence in adult population correlating head trauma and secondary meningioma occurrence.



**Figure 2:** MR coronal images of an intrinsic brain stem glioma causing hydrocephalus in a pediatric patient

PBT formation has been related with some chemical agents. The most significant of these are N-nitroso compounds, tobacco, pesticides, some chemicals related to parental occupation, and some drugs. Carcinogen effect of N-nitroso compounds to nearly forty animal species is known. This agent may be effective by transplacental route in order to induce brain tumor formation. Nitroso compounds in some nutrients including nitrites or some food exposed to nitrogen oxide such as fumed meat / fish / cheese and beer are among the potential risk factors. Two biochemical forms in etiology are important: Nitrosamides and nitrosamines [18].

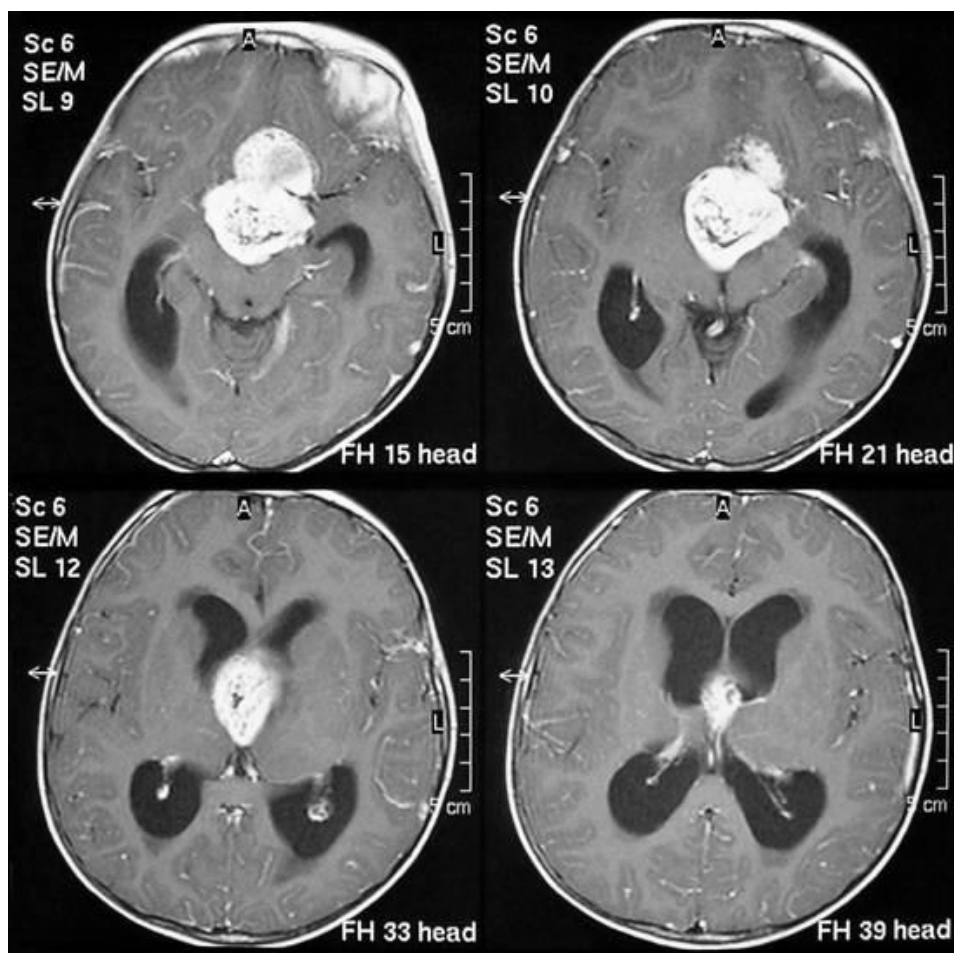
Nitrosamides are strong experimental neurocarcinogens. They have direct alkylating properties and no metabolic activation is required. They are unstable in neutral or alkaline media and quickly interreact under these circumstances. Nitrosamines are more abundant in nutritional sources. They require metabolic activation in liver or gastrointestinal tract in order to get carcinogenic properties. There are some papers in literature dealing with diet and PBT

formation relationship [4,19,20]. Continuous fumed meat consumption (eg. sausages) is believed to be a risk factor. The risk can be decreased by consumption of high quantities of fruits and vegetables or ingestion of multivitamins. There are strong hypotheses regarding the prevention of nitrosing processes by intake of vitamins with antioxidant properties such as vitamin C and E. Nitrosable compounds in food can be converted to amines and amides in acidic media and hypothetically these compounds in gastrum may transpass placenta in order to trigger a malignant transformation. Some risks in PBT formation with consumption of drugs involving precursors of nitroso compounds are also declared. The expected risk of PBT formation with the usage of antihistaminic drugs and diuretics having these properties was 3.4 and two times higher than the normal child population, respectively [4]. A negative correlation was established between the antenatal usage of drugs involving nitroso compounds and astrocytoma formation. In those babies with antenatal consumption of pseudoephedrine which may be converted to nitroephedrine, glioma formation risk other than astrocytoma is found to be 3.1 times more than the population without consumption of this drug [21-24].

It is known that there are more than 3000 chemical agents in tobacco smoke and more than sixty carcinogenic structures are identified including the polycyclic aromatic hydrocarbons and nitrosamines. Numerous toxic effects on fetus are also very well known. Among these, the most accustomed ones are spontaneous abortion and low-weight births. Epidemiological data reveal that there is very low or ignorable correlation between tobacco smoke inhalation and PBT formation. A metaanalysis involving 6566 cases disclosed a 1.05 times higher risk compared to the children of nonsmoking maternal population. No positive correlation could be established in SEARCH study (Surveillance of Environmental Aspects Related to Cancer in Humans) dealing with 3218 cases between PBT formation and prepregnancy cigarette smoking of the family, maternal cigarette smoking, exposure to tobacco smoke during pregnancy and passive smoking of the baby within the first year after birth [26]. Age at diagnosis, histopathology, and tumor location also gave no positive contribution. There is a very limited concordance between antenatal smoke exposure and childhood cancers as a whole. Despite this fact, the most important relationship is still with central nervous system tumors [27]. It is believed that smoking has also a negative effect in spermatogenesis. Exposure of male rats to ethylnitrosourea (ENU) before fertilization disclosed a statistically insignificant increase in frequency of brain tumor formation in new generation [28,29].

Annual consumption of pesticides is about 400 million kilograms and it is known that there are about 24000 different products in the market. It is shown that some of these are

biologically neurotoxic and some are carcinogenic in animals. There are many papers focusing on the positive relationship between the incidence of PBT formation and pesticide consumption [30]. Even though the negative effect is dominant in pediatric population compared to the elders, there is no definite precision. PBT incidence is generally related to the pesticide use in that specific environment [31]. These can be summarized as application of skin strips, exposure to pesticide bombs and agents used for removal of harmful insects. It is believed that exposure to pesticides are more hazardous in prenatal or perinatal period compared to the childhood age [17]. SEARCH study involving 2223 cases from seven different countries disclosed that an experience of five year antenatal exposure to pesticides has twice increased the risk of PBT formation [33].



**Figure 3:** Axial MR image of an optic-chiasmatic-hypothalamic glioma with hydrocephalus in a pediatric patient

Even though there is some accumulating data about the correlation between PBT formation and family occupation in literature, there is still no strict evidence available. Some professional areas such as food preparation in nutritional business, salesmanship, health business,

academic life, agriculture, paint industry, chemistry, electric industry and metal processing are tried to be correlated with PBT incidence. The most convincing data is related to the exposure to polycyclic aromatic hydrocarbons. This result mostly implies to the industries related to petrochemistry and mechanics. Direct maternal influence, contamination of father's clothes with chemicals, smoke, and environmental dust resulting a toxic exposure at home, and the hazardous effects of some chemical agents such as polycyclic aromatic hydrocarbons in spermatogenesis during the preconceptional period are accepted as the most common routes of pathogenesis.

Some interrelation between the drugs and PBT formation has been declared by some authors. A study consisting of approximately 330 thousand children with prenatal use of metronidazole disclosed that no significant cancer incidence were found in the first five years of life. Again with no statistical significance, the incidence of neuroblastomas were 2.6 times higher compared to the control group [34]. Another study from Sweden focusing on intrapartum analgesia showed that the risk of PBT formation in use of narcotic analgesics and penthrane has increased 1,3 and 1,5 times, respectively [35]. In a study of American origin, a risk of 1,4 has been announced for all antiepileptic drugs except phenobarbutane. No additional risk was stated regarding the latter drug [15].

Infectious reasons are also blamed for PBT formation. Influenza and polyoma viruses are thought to be the important causes. About 15% of the cancers seem to be related with bacteria, viruses, and probably with parasites. A study from United Kingdom revealed that the children whose mothers had proven mumps, measles, varicella zoster, and herpes zoster infections during pregnancy experienced 10.6 times more PBT incidence within the first fourteen years of life compared to the control group. Similarly, the children whose mothers are accepted to have influenza or upper respiratory tract infection with no laboratory evidence had 2.2 times more risk of having PBTs [36]. An epidemiological study from Greece disclosed that the pediatric patients whose mothers had serologically unproven influenza during pregnancy had a 3.15 times more incidence of PBT formation [37]. It is shown in animal studies that RNA of influenza virus can transpass the placental route and can be identified in newborn rat brains if encountered in pregnancy [38]. There is no supportive data in ecological studies revealing a correlation between common public infections and brain tumor formation. Other infectious agents which are thought to be responsible for tumorigenesis can be listed as polyoma virus family, simian virus 40 (SV 40) and Jacob-Creutzfeld virus (JCV) [39,40]. It is known that SV 40 is capable of causing brain cancer and

lymphoma in experimental models. In meta-analyses which focus on quantification of viral DNA and gene products, the risk is stated to be 3.9 times more than the controls [40].

It is believed that vitamins with antioxidant properties and folic acid have preventive effects against PBT formation. The protective mechanisms related to vitamins C and E may be related to the prevention of nitrosing processes in vivo. An international cooperative controlled study with six countries from North America, Europe, and Israel showed that prenatal maternal consumption of vitamins (C,E,A,and folate) decrease the PBT incidence [6,7]. Relying on the data of West Coast Brain Tumor Study Group, while nitrite consumption originating from fumed meat increases the PBT incidence, nitrate consumption supplied from vegetables decreases the probability [3]. The preventive role of folic acid in neural tube defects is a known entity. On the contrary, there are some speculations that it has some contribution in PNET formation and neural tube pathogenesis [17,41].

Genetic factors are also effective in PBT formation. Inactivation of tumor suppressor gene p53 has a positive effect in brain carcinogenesis - astrocytoma and glioblastoma formation [42]. One third of the malignant gliomas on pediatric age involve p53 mutations and they are nearly all common below age of three years [43]. Genetic mutations of p53 and overexpression of p53 protein are correlated with short life span in these patients. On the other hand, p53 gene mutations are very rare in PNET.

As a conclusion, PBT incidence has increased about 50% in the last thirty years. This is a result of the technological improvement in diagnostic tools and the increased interest in cancer declarations. There are many hints about the etiology, but evidenced data is stil very scarce. There is consensus about the cancerogenic effect of N-nitroso compounds and preventive role of vitamins.

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