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Review

Epidemiology of brain tumors in childhood—a review

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Abstract

Malignant brain tumors are the leading cause of cancer death among children and the second most common type of pediatric cancer. Despite several decades of epidemiologic investigation, the etiology of childhood brain tumors (CBT) is still largely unknown. A few genetic syndromes and ionizing radiation are established risk factors. Many environmental exposures and infectious agents have been suspected of playing a role in the development of CBT. This review, based on a search of the medical literature through August 2003, summarizes the epidemiologic evidence to date. The types of exposures discussed include ionizing radiation, *N*-nitroso compounds (NOC), pesticides, tobacco smoke, electromagnetic frequencies (EMF), infectious agents, medications, and parental occupational exposures. We have chosen to focus on perinatal exposures and review some of the recent evidence indicating that such exposures may play a significant role in the causation of CBT. The scientific community is rapidly learning more about the molecular mechanisms by which carcinogenesis occurs and how the brain develops. We believe that advances in genetic and molecular biologic technology, including improved histologic subtyping of tumors, will be of huge importance in the future of epidemiologic research and will lead to a more comprehensive understanding of CBT etiology. We discuss some of the early findings using these technologies.

Keywords: Childhood brain tumors; Transplacental carcinogenesis; Perinatal exposures

Introduction

Approximately 2200 individuals under the age of 20 are diagnosed with a brain tumor each year (American Cancer Society (ACS), 2003). Malignant brain tumors are the leading cause of cancer death among children and the second most common type of pediatric cancer after leukemias (Gurney et al., 1999; National Cancer Institute (NCI), 1991). Astrocytomas account for 52% of childhood brain tumors (CBT), primitive neuroectodermal tumors (PNET) or medulloblastoma/embryonal tumors account for 21%, ependymomas for 9%, and other gliomas 15% (Gurney et al., 1999; National Cancer Institute (NCI), 1991). The etiology of the majority of pediatric brain tumors continues to be largely unknown despite decades of epidemiologic investigation.

Brain tumors are classified under several different schemes according to cell morphology and the degree of malignant behavior. The brain is composed of two main types of cells, neurons and glia, which both arise in early development from the primitive neuroectoderm. Glial cells can be subdivided into four major types: astrocytes, oligodendrocytes, ependymal cells, and microglia (Mischel and Vinters, 2001). The majority of primary brain tumors arises from glial cells and are broadly categorized as gliomas, but are usually broken down into more specific subtypes, such as astrocytoma, oligodendroglioma, and ependymoma (Preston-Martin et al., in press). Although very rare in children, primary tumors

Abbreviations: CBT, childhood brain tumor; CI, confidence interval; CNS, central nervous system; DDE, *p,p′*-dichloro-diphenyl-dichloroethylene; DES, diethylstilbestrol; DNA, deoxyribonucleic acid; EMF, electromagnetic frequencies; ENU, ethylnitrosurea; HCB, hexachlorobenzene; IARC, International Agency for Research on Cancer; JCV, JC virus; MRI, magnetic resonance imaging; NOC, *N*-nitroso compounds; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyl; PNET, primitive neuroectodermal tumor; RNA, ribonucleic acid; RR, relative risk; SV40, Simian Virus 40.

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may also arise from the structures surrounding the brain (the cranial meninges), from the spinal cord and spinal meninges, or from the peripheral nerves (Preston-Martin et al., in press).

A few genetic syndromes play a clear and independent role in brain tumor etiology including neurofibromatosis, Li-Fraumeni syndrome, basal cell nevus (Gorlin's) syndrome, Turcot syndrome (Bunin, 2000; National Cancer Institute (NCI), 1991), and ataxia telangiectasia (Groot-Loonen et al., 1988; Miyagi et al., 1995). A family history of malignant brain tumors also appears to be related to increased risk of CBT (Bondy et al., 1991; Farwell and Flannery, 1984). Together, all these causes are responsible for less than 5% of all brain tumors. Numerous other physical, chemical, and infectious agents that have been suspected to be risk factors have not yet been established as etiologically relevant (Preston-Martin, 1996).

Increase in incidence

From 1973 to 1994, the reported incidence of childhood brain tumors increased by 35% (Smith et al., 1998). It is a matter of considerable debate whether this increase is an etiologic phenomenon or the result of alterations in diagnostic and reporting patterns (Kaiser, 1999). Smith et al. (1998) have performed a detailed statistical analysis of this increase and convincingly demonstrated that it was best described as a jump in incidence around 1985 with lower rates in years before 1985 vs. those 1985 and later. This timing coincides with the rapid proliferation of use of magnetic resonance imaging (MRI) as a tool to evaluate intracranial abnormalities (Smith et al., 1998). Other epidemiologists are not entirely convinced that the increase is adequately explained with only this type of statistical analysis (Kaiser, 1999). A detailed discussion of this debate with regard to all childhood cancers is included in Dr. Preston's article within this issue.

Regardless of the debate over rates of increase, there are many environmental toxins that are suspected of playing a role in CBT development, but the possible etiologic role of most may be no more than suggested by investigations to date. CBT etiology is undoubtedly multifactorial and is likely to vary by tumor type. Recently, there has been substantial interest in the intertwining role of genetics and the environment, and in the way that particular genetic susceptibilities lead to increased vulnerability to environmental factors (Olshan et al., 2000). Lending support to this interest is the fact that different histological subtypes of CBT occur in children of different ages. Astrocytomas peak in incidence twice, at age 5 and again at age 13 (Gurney et al., 1999). PNET and ependymomas are most common in children under the age of 3, then steadily decline as age increases (Gurney et al., 1999; VandenBerg, 2001). This suggests that genetic polymorphisms may play a more substantial role in some tumor types than in others and that individual cell types may be more vulnerable to toxins at different stages of development.

In utero exposures and carcinogenesis

Although only approximately 1% of CBT are present at birth or diagnosed within the first few months of life (Punt, 1995), the majority of CBT occur before the age of five, suggesting that prenatal as well as postnatal insults must be considered as potential etiologic factors (Autrup, 1993). The delay between prenatal exposures to CBT diagnosis several years later may be related to the multistage development of neoplasms. Animal experiments have demonstrated that initiation of tumorigenic growth can take place in utero with postnatal promotion resulting in malignancies (Autrup, 1993). A large multicenter scientific consensus group evaluating transplacental carcinogenesis in general concluded that the evidence is sufficient that preconceptional, in utero, and childhood exposures cause cancers in children and adults (Olshan et al., 2000).

It is generally accepted that a causal association exists between two distinct in utero exposures and the subsequent development of cancers: ionizing radiation and diethylstilbestrol (DES). The relationship between fetal exposure to DES and vaginal adenocarcinoma is widely accepted and is the classic example of transplacental carcinogenesis (Anderson et al., 2000). Several aspects of the specific carcinogenic features of DES will be discussed thoroughly in other articles within this issue. The link between prenatal exposure to ionizing radiation, which acts directly on the deoxyribonucleic acid (DNA) itself (Anderson et al., 2000), and the development of CBT is reviewed below. These associations suggest that transplacental exposure to mutagenic agents in utero can initiate genotoxic or carcinogenic events that will be diagnosed years later as a malignancy.

Transplacental passage of carcinogens

It has been demonstrated that known carcinogenic substances are capable of crossing the placental barrier and entering the fetal bloodstream. In Thailand, researchers showed that aflatoxin, one of the most potent carcinogens known, could be isolated from cord blood of the fetal supply (Denning et al., 1990). Another study showed that DNA adducts related to tobacco smoke carcinogens have been isolated from cord blood DNA at much higher levels in smokers than in nonsmokers, demonstrating that some of the toxic compounds in cigarette smoke are able to cross the placenta (Hansen et al., 1992). Other chemical compounds, not known to be carcinogenic, have been isolated from cord blood as well (Autrup, 1993). These experimental findings are significant because they demonstrate that potentially mutagenic and carcinogenic substances are able to cross the placental barrier and interact with DNA in the developing fetus.

Developmental considerations

General developmental principles

Early stages of development, such as gestation and early childhood, are marked by particular susceptibility to toxic insults. These stages are characterized by extensive amounts of intricately coordinated cell growth and differentiation. Rapid cell growth and proliferation provide the opportunity for mutagenic changes to be swiftly amplified and thus have a more substantial impact, potentially leading to tumor development. The process of differentiation is marked by extensive and highly controlled alterations in gene expression, and also conveys enhanced vulnerability to toxic exposures (VandenBerg, 2001).

The ultimate health effect of any kind of prenatal toxic insult varies substantially with the specific timing of fetal development occurring in utero. This is true for agents producing fatal and teratogenic endpoints as well as neoplastic transformation, and is true for all organs including the central nervous system (CNS) (Napalkov, 1986; Rhind et al., 2003). The importance of timing in determining the end effect has been demonstrated by giving chemical compounds to pregnant animals at specific times during gestation and evaluating the pattern of results (Napalkov, 1986). By extrapolating the animal data from multiple species to the timing of human gestation, we can predict that compounds given from weeks 1 to 6 in humans are most likely to be embryotoxic. Substances given from weeks 2 to 8 may be teratogenic causing structural birth defects, and from week 6 until birth, toxic exposures may lead to neoplastic development (Napalkov, 1986). Which effect occurs depends on exposure dose as well as timing. This potential for tumor induction during the respective period of gestation in animals has been shown in rats, mice, hamsters, and nonhuman primates (Napalkov, 1986).

Unique features in brain development

In animal testing involving multiple species, the nervous system, more than other organ systems, is consistently susceptible to neoplastic transformation following various transplacental exposures (Rice and Ward, 1982). It has been suggested that the constancy of this finding between species of experimental animals indicates that the human nervous system also may be more vulnerable than other organs to transplacental carcinogenic exposures (Rice and Ward, 1982). The human brain is actively developing for a much longer period than the other major organs, which have largely completed organogenesis by week 9 of gestation (Punt, 1995). The brain undergoes rapid growth beginning early in gestation and continuing for 2–3 years following birth (Rice and Barone, 2000). The growth rate of the brain does not peak until approximately 4 months after birth, 1.1 years after conception (Rice and Barone, 2000). Also, some early experiments demonstrated in animals that, compared to other organs, the fetal brain was less able to efficiently excise or repair the alkylated DNA induced by various mutagenic agents (Cooper et al., 1978; Likhachev et al., 1983; Margison and Kleihues, 1975). The combination of this unique deficiency with the prolonged period of rapid cell division and inherent high rate of DNA replication during development makes the brain more likely to replicate mutational errors.

Animal experiments have demonstrated that susceptibility to systemically applied nervous system carcinogens is extremely dependent upon the age at exposure and greatest during prenatal life (Rice and Ward, 1982). More than 60 chemicals have been demonstrated to induce cancers in animals following transplacental exposure, most frequently in the nervous system, kidneys, and lungs (Napalkov, 1986). When many of the same chemicals are given to adult animals, the cells in these tissues, particularly in the nervous system, are much less susceptible to neoplastic transformation (Napalkov, 1986). Some of the classic experiments of transplacental neuro-oncogenesis in animals have been performed using ethylnitrosurea (ENU) (Druckrey et al., 1966). ENU is a highly reactive alkylating agent and is both mutagenic and carcinogenic (Donovan, 1999). It has been demonstrated that rat fetuses are 50 times more susceptible to induction of CNS tumors than adult animals, and that sensitivity varies with the time in gestation when an animal is exposed (Donovan, 1999).

Not only is the developing brain more vulnerable, but it is also much more accessible to potential carcinogens early in life (Rice and Ward, 1982). Although the placenta is sometimes called a "barrier," it has been shown that most xenobiotics pass from maternal to fetal circulation freely (Ring et al., 1999). In adults, the characteristic tight intercellular junctions of the blood–brain barrier render it nearly impermeable to most lipid-soluble substances (Rodier, 1995; Stonestreet et al., 1996). However, in fetuses, the blood–brain barrier is incomplete as it does not fully develop until approximately 6 months of age, making the exposure to neurocarcinogenic compounds at that time potentially more impactful (Adinolfi, 1985; Andersen et al., 2000). Thus, molecules or compounds that are capable of crossing the placenta have the intrinsic potential to gain access to the fetal brain (Adinolfi, 1985).

Each histologic cell type may have a distinct period of time during which it is most vulnerable to malignant transformation. It is logical that if more cells are at risk due to rapid division, a carcinogenic exposure would be more likely to cause a mutation (Anderson et al., 2000). Different regions of the brain undergo different processes of growth and maturation at varying times. Experiments in animals have demonstrated that when a portion of the brain is undergoing active proliferation, it is more vulnerable to anti-mitotic toxins, and when cell proliferation ceases, that region of the brain is more resilient (Rice and Barone, 2000). It is also logical that different cell types would have select vulnerabilities to different toxins. Experimental stud-

ies in animals of in utero exposure to various alkylating agents and oncogenic viruses are able to distinguish which fetal brain cells are the target of neoplastic transformation (Napalkov, 1986; VandenBerg, 2001). The susceptibility of the fetal nervous system cell types was temporally isolated in these experiments, leading to the concept that each given cell type has a "window of vulnerability" during which neoplastic transformation may occur (VandenBerg, 2001). Thus, the timing of a potentially toxic exposure may be as important as the type of exposure in determining what histologic class of brain tumor, if any tumor at all, develops.

As the scientific community learns more about the specific processes and details of neurologic cellular development, it may become possible to approximate the timing of the specific toxic insult that leads to the development of histologically distinct brain tumors. Incidence rates with clear age-related histologic patterns suggest that different agents may be causing different types of cancers. Theoretically, if specific cells are most vulnerable at certain times during development and those cells are also differentially susceptible to various toxins, we may someday be able to know which compound is most likely responsible for a given tumor.

Environmental exposures

The following section will summarize the epidemiologic findings to date regarding the many environmental exposures that have been hypothesized to contribute to the incidence of CBT. Not all individual articles have been listed in the reference section; the references include the more recent citations and selected review articles.

Ionizing radiation

Although many environmental exposures are hypothesized to contribute to the development of brain tumors, only ionizing radiation has a proven etiologic role. A case-control study of over 10 000 Israeli children who had received therapeutic irradiation for *tinea capitis* and were followed into adulthood found an RR of 33.1 [95% confidence interval (CI) = 9.4–116.5] for nerve sheath tumors of the head and neck, 9.5 (3.5–25.7) for meningiomas, and 2.6 (0.8–8.6) for gliomas (Ron et al., 1988). In children, radiation for early childhood cancers has been associated with the later development of CNS tumors (Meadows et al., 1985; Neglia et al., 1991). In 1991, the Children's Cancer Study Group performed a retrospective cohort study evaluating 6644 children who had been treated with radiation for acute lymphoblastic leukemia between 1972 and 1988. They observed a 6.85-fold increase in the expected number of all types of second cancers ($P < 0.05$) and a 21.7-fold increase in CNS neoplasms ($P < 0.05$) (Neglia et al., 1991); 83.7% of the second cancers seen were in patients originally diagnosed with ALL at an age younger than 5 years (Neglia et al., 1991). Of the 24 CNS tumors observed, 14 were high-grade astrocytomas or glioblastoma multiforme and three were PNET (Neglia et al., 1991).

Exposure to radiation during gestation has been related to increased incidence of CBT since 1958. Several more recent studies have also found elevated risks of brain and CNS tumors in children whose mothers underwent diagnostic prenatal radiation (Doll and Wakeford, 1997; Harvey et al., 1985; Rodvall et al., 1990). However, the use of X-ray pelvimetry before delivery is an outdated technique, and for many procedures radiation doses are substantially lower than in the earlier part of the 20th century; thus, this issue is currently less of a compelling concern (Kuijten and Bunin, 1993).

N-nitroso compounds

Another environmental exposure that has received much attention as a potential risk factor for CBT is *N*-nitroso compounds (NOC). NOC have been found to be carcinogenic in 40 animal types, and in the form of *N*-nitrosureas induce brain tumors when exposure occurs transplacentally (Bunin, 2000; Lijinsky, 1992). NOC are divided into two major groupings, *N*-nitrosamines and *N*-nitrosamides. Both are formed by nitrosation under acidic conditions, such as in the stomach (Dietrich et al., in preparation). Nitrosamides are among the most potent of experimental neurocarcinogens (Preston-Martin et al., in press). *N*-nitrosureas (a class of nitrosamides) have been demonstrated to be carcinogenic in animals, and particularly related to the development of CNS tumors (Sampson and Bigner, 1998). Nitrosamides are direct alkylating agents which form DNA adducts, and they do not undergo metabolic activation (Dietrich et al., in preparation). Nitrosamines require metabolism by cytochrome *P*450 before acting as carcinogens.

Dietary NOC, primarily nitrosamines, are found in foods that contain nitrite or have been exposed to nitrogen oxides, such as nitrite-cured and smoked meat and fish, cheese, and beer. There is little data available on the content of nitrosamides in dietary sources (Dietrich et al., in preparation). This is likely because nitrosamide compounds are very unstable in neutral or alkaline conditions and likely do not persist in food. There are, however, nitrosatable compounds in foods that can be converted to both amines and amides under acidic conditions, as in the stomach following ingestion. A mathematical model designed to determine the risk of endogenous NOC formation concluded that the process of nitrosation of foods containing precursors could be an important source of *N*-nitrosamides and *N*-nitrosureas (Shephard et al., 1987).

It is thus theoretically possible that endogenously formed nitrosamide compounds in the maternal stomach could cross the placenta and trigger malignant transformation in the developing fetus (Dietrich et al., in preparation). If this were the case, one would suspect that nitrosamide precursor ingestion would be related to a higher risk of CBT. A

case-control study of all medications that contain NOC precursors, particularly specific antihistamines and diuretics, found a positive association with CBT with odds ratios (OR) of 2.0 ($P = 0.002$) and 3.4 ($P = 0.03$), respectively (Preston-Martin et al., 1982). A later case-control study, which evaluated astrocytoma only, found no alteration of risk (Kuijten et al., 1990). A third study looked at the risk associated with consumption of nitrosatable drugs during pregnancy and subtypes of CBT: astroglial tumors, PNET and 'other glial' tumors. The investigators found an OR of 3.1 (95% CI = 1.1–9.2) for 'other glial' tumors and exposure to nitrosoephedrine (a nitrosation product of pseudoephedrine, frequently found in over-the-counter decongestants), but no other significant associations (McKean-Cowdin et al., 2003).

In epidemiologic studies that include complete dietary surveys, maternal consumption of cured meats is the factor most closely related to increased risk of CBT (Bunin et al., 1993; Kuijten et al., 1990; Preston-Martin et al., 1982). The nitrosation process is inhibited by the presence of vitamin C and vitamin E (Preston-Martin et al., in press). In most of these studies, daily prenatal vitamins or a high vegetable and fruit intake are associated with a reduction in risk. Although it is still unclear what mechanism and even what chemicals may explain this effect, there is ample justification for further investigation in this area.

Pesticides

Pesticides are ubiquitously present in our environment and are suspected of being related to various health problems. In the United States, annual agricultural use of pesticides is about 850 million pounds and there are approximately 24 000 pesticide products currently on the market, though many are used infrequently if at all (Sanderson et al., 1997). Many pesticides are intentionally neurotoxic in activity, and some have demonstrated carcinogenic properties in animals (Gurney et al., 2001; Zahm and Ward, 1998). The combination of these two properties establishes a premise of biologic plausibility that pesticides may be capable of leading to the development of brain tumors in humans (Zahm and Ward, 1998).

Numerous epidemiologic investigations have attempted to evaluate whether pesticide exposure increases the risk of cancer development, with the majority reporting positive associations (Zahm and Ward, 1998). In such studies, the risks of all cancers consistently tend to be higher in studies of exposed children than in exposed adults.

With the number of substances available for use as pesticides, it is reasonable that there would be substantial variability in the type of associations found. It can be very difficult in epidemiologic studies to specifically define the exposure as a particular chemical or class of compounds (Daniels et al., 1997; Zahm and Ward, 1998). Thus, all of the epidemiologic studies evaluating pesticides are vulnerable to a lack of precision with regard to exposure classification, and this is particularly true for occupational exposures (Daniels et al., 1997; Gurney et al., 2001).

Risk of CBT is most frequently elevated with residential use of pesticides, such as no-pest strips, flea and tick medications, and pesticide bombs (Davis et al., 1993; Pogoda and Preston-Martin, 1997). Residential exposures during pregnancy or around delivery tend to be associated with higher risk of CBT in offspring than exposures during childhood (Daniels et al., 1997; Gurney et al., 2001). Paternal occupational exposure during pregnancy, but not during childhood, is also frequently associated with increased risk of CBT (Daniels et al., 1997).

The SEARCH International Brain Tumour Study included a case-control analysis of CBT in children of farm workers with 2223 subjects from seven countries (Efird et al., 2003). The investigators found positive associations of CBT with maternal exposure to pesticides (of undisclosed type) in the 5 years before the index child's birth (OR = 2.0, 95% CI = 1.2–3.2).

In an attempt to limit exposure misclassification, a case-control study conducted in the United States and Canada used an established pesticide job exposure matrix and divided the general category of pesticides into four classes: insecticides, herbicides, and agricultural and nonagricultural fungicides (van Wijngaarden et al., 2003). The investigators found slightly elevated odds ratios ranging from 1.3 to 1.6 for astrocytoma related to paternal exposure to all four classes and for maternal exposure to all but agricultural fungicides. Risk of PNET was increased for paternal exposure to herbicides only.

Studies of human umbilical cords demonstrate that several pesticides are able to cross the placenta and gain access to fetal circulation, specifically polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and *p*,*p*′-dichlorodiphenyl-dichloroethylene (DDE) (Burse et al., 2000). Animal experiments with the carbamate fungicide, mancozeb, demonstrate that it crosses the placental barrier, damages DNA and initiates tumor formation in fetal cells (Shukla and Arora, 2001). Although these compounds are not considered accepted risk factors for the development of CBT, their experimentally demonstrated ability to access the fetus and potentially cause DNA damage suggests that other pesticide compounds may be able to do so as well.

Tobacco

Some of the chemical components of tobacco smoke have been demonstrated to be carcinogenic in animals and in humans, such as polycyclic aromatic hydrocarbons (PAHs) and nitrosamines (Autrup, 1993). Both maternal and paternal smoking during pregnancy and before pregnancy are exposures that have been explored in numerous epidemiologic studies, with the majority finding no or limited association. A recent review article examining the impact of prenatal exposure to tobacco smoke reported that there were no strong associations between exposure and

childhood cancer. However, in the 50 papers included, the most frequent association reported was with tumors of the nervous system (Sasco and Vainio, 1999).

In a meta-analysis of 12 observational studies (including 6566 subjects) that looked at maternal smoking during pregnancy and development of CBT in offspring, the authors reported an RR of 1.05 (95% CI = 0.90–1.21), suggesting no clear association (Huncharek et al., 2002). A large international case-control study performed by the International Agency for Research on Cancer (IARC) evaluating the risks associated with exposure to tobacco smoke looked at 1218 CBT cases and over 2000 controls (Filippini et al., 2002). No association was found among the risk of brain tumors, parental smoking before pregnancy, maternal smoking, regular exposure to environmental smoke during pregnancy, or passive smoking by the child during the first year of life. This lack of association was not altered with age at diagnosis, histology, or site of the tumor.

There is biologic plausibility to a CBT association with paternal smoking specifically before conception, as well as for other toxic exposures. Preconceptional paternal exposures are likely to have a more substantial impact than maternal because paternal germ cells are continually undergoing the process of spermatogenesis and are thus replicating DNA and are more vulnerable to mutagenic changes, while oocytes are already formed by the time of a female's birth (Anderson et al., 2000). Over 20 years ago, it was demonstrated in animal experiments that male rats exposed to ENU before breeding had a statistically significant excess of offspring with brain tumors (Tomatis et al., 1981, 1990). In humans, the sperm of smokers has been found to have a 1.7-fold increase of DNA adducts over the sperm of never smokers ($P = 0.008$) (Horak et al., 2003). In an experimental evaluation of seminal oxidative stress due to smoking, a study of men with and without infertility found a 107% increase in reactive oxidative species in the semen of smokers ($P = 0.001$) (Saleh et al., 2002). These findings suggest that an inciting event for cancer in the offspring of male smokers may be DNA damage or adduct formation in the sperm.

There is also epidemiologic evidence for a CBT association with preconceptional paternal smoking distinct from other types of tobacco exposures. A meta-analysis of 30 studies that evaluated both maternal and paternal smoking and the risk of all childhood cancers found an RR of 1.22 (95% CI = 1.05–1.40) for CBT related to fathers' smoking (Boffetta et al., 2000). The association with CBT was weaker (RR = 1.04, 95% CI = 0.92–1.18) when all the different subcategories of prenatal tobacco exposure were included. A population-based case-control study in Shanghai (where smoking prevalence is very high among men and low in women) compared children whose fathers smoked throughout the 5 years before conception to children whose fathers never smoked (Ji et al., 1997). They found a statistically significant OR of 2.7 (95% CI = 0.8–9.9) for brain tumors in children under the age of five.

This evidence suggests that preconceptional DNA damage may play an etiologic role in the development of CBT. However, it is nearly impossible to completely separate these effects from those of maternal exposure to tobacco smoke either before conception or during gestation.

Electromagnetic frequencies

Exposure to electromagnetic fields is a potential risk factor for CBT that has also been evaluated in multiple epidemiologic studies. This association was first hypothesized in 1979 in Denver when it was reported that children who resided close to high current power lines had an increased risk of dying from leukemia or brain cancer (Wertheimer and Leeper, 1979). Subsequent studies have tended to have inconsistent outcomes and be vulnerable to methodological weaknesses, although several have found a positive association. Exposure to high levels of electromagnetic frequencies (EMF) at close proximity suggests an increased risk, however, the numbers are small (Kheifets et al., 1999). There are several different approaches to the measurement of EMF exposure including proximity to power lines of various strengths, exposure to electrical appliances, and parental occupational exposure. These variations may have a substantial impact on risk assessment (Kheifets, 2001). The largest childhood cancer study, the United Kingdom (UK) Childhood Cancer Study found no association between EMF and childhood cancer, or for CBT specifically, after performing an extensive exposure assessment including several different types of EMF measurement (OR = 0.97, 95% CI = 0.46–2.05) (UK Childhood Cancer Study Investigators, 1999).

Infectious agents

Some cancer investigators believe that approximately 15% of all human malignancies can be attributed to bacterial, viral, or parasitic infections (Anderson et al., 2000). These infections and associated cancers include various types of papilloma viruses in cervical cancer, hepatitis B and C in hepatocellular carcinoma, HTLV- 1 in T-cell leukemia/lymphoma; Epstein–Barr virus in Burkitt lymphoma, *Helicobacter pylori* in gastric cancer, HHV-8 in Kaposi sarcoma, and *Schistosoma haematobium* in bladder cancer (Anderson et al., 2000; Hall and Peckham, 1997). At this point, there are no similar associations for pediatric brain tumors; however, some recent epidemiologic investigations suggest a potential link.

A case-control study in England evaluated various perinatal factors and their impact on CBT. They found that the children of mothers who had a documented viral infection during pregnancy had an 11-fold increased risk of a malignant nervous system tumor with an OR of 10.6 (95% CI = 1.1–503.2) and a P value of 0.017 (Fear et al., 2001). The infections included rubella, mumps, varicella, and herpes zoster. For "probable viral infections" including influenza

and respiratory infections, the OR was 2.2 (0.6–7.2) with a *P* value of 0.211. A case-control study in Greece found an elevated risk of brain tumor or neuroblastoma for children whose mothers had an influenza infection during gestation [OR = 3.15 (95% CI = 1.13–8.77)] (Linos et al., 1998).

A recent ecologic study in England looked at community levels of viral infections and the relationship to nervous system tumors (Dickinson et al., 2002). The authors found an association for children exposed perinatally to high community levels of measles (OR for trend = 2.1, 95% CI = 1.3–3.6) and influenza (OR = 3.3, 95% CI = 1.5–7.4). A later ecologic study by the same investigators in an adjacent larger region in England found only an association between Hodgkin's disease and measles, and no association for nervous system or other tumors (Nyari et al., 2003).

Animal studies have demonstrated that influenza ribonucleic acid (RNA) can cross the placental barrier and has been found in the brains of mice exposed during gestation (Aronsso et al., 2002). In these experiments, the viral RNA persisted for at least 90 days following birth.

The polyoma virus family, including both JC virus (JCV) and Simian Virus 40 (SV40), has been suspected of playing a role in the development of brain cancers as well. Currently, there is extensive scientific investigation into the molecular details of how these viruses may be carcinogenic (Khalili et al., 2003; Vilchez and Butel, 2003). SV40 is known to induce brain cancers and lymphomas in experimental animals, and has been increasingly linked to primary brain cancers in infants and children (Vilchez and Butel, 2003). A recent meta-analysis of studies measuring viral DNA or gene products found that SV40 was associated with brain tumors with an overall odds ratio of 3.9 (Vilchez and Butel, 2003). The types of tumors included astrocytomas, glioblastomas, gliomas, gliosarcomas, medulloblastomas, meningiomas, and oligodendromas.

JCV has been detected in tumors, both malignant and not, in every cell type arising in the CNS. In three studies looking at the presence of JCV in medulloblastomas, investigators found that approximately 77% of the samples contained viral DNA corresponding to JCV (Khalili et al., 2003). The JCV protein, T-antigen, is believed to interfere with cell cycle regulation by a couple of different mechanisms, including inactivation of p53. These findings could indicate that infection with these viruses may be the initiating event in the development of CBT. It is also possible that infection with polyoma viruses may be ubiquitous and only an incidental finding in the tumor cells.

Trauma

Head injury has been postulated to play a role in the development of brain tumors. The increased rate of cell proliferation following significant traumatic injury may contribute to malignant growth (Preston-Martin et al., 1990). The strongest epidemiologic evidence exists in adults for meningiomas (Longstreth et al., 1993; Preston-Martin et al., 1998a, 1998b); this association was first suggested by multiple case reports. The United States West Coast Childhood Brain Tumor Study found a slight increase in risk of CBT (OR = 1.4, 95% CI = 1.0–1.9) for children who received medical attention for a head injury, and no association with birth trauma (Gurney et al., 1996). Trauma appears unlikely to be a major etiologic factor in the development of CBT.

Parental occupation

Workers are exposed to neurotoxic and carcinogenic compounds in many industries. There is concern that some of these compounds may lead to development of CBT in the children of employees. Positive relationships have been reported for parental employment in fields as diverse as food preparation, sales, healthcare, academia, agriculture, painting, the chemical industry, the electric industry, and metal-related jobs (Cordier et al., 1997; Hemminki et al., 1981; Kuijten et al., 1992; Mutanen and Hemminki, 2001; Wilkins and Koutras, 1988). Overall, although there are frequently positive associations between various parental occupations and CBT, those associations are inconsistent and scattered (Kuijten and Bunin, 1993; Mueller and Gurney, 1992). Several factors may contribute to this situation. The levels of exposure to toxins and chemicals may not be consistent for workers within the same industries or over a period of several decades. Different companies may use different manufacturers for their chemical supplies, which may have varying additives that make them more or less biologically accessible. Personal protective equipment usage varies over time and from worker to worker as does ability and individual efficiency with work. In addition, although a fair number of positive epidemiologic relationships have been reported, the possibility of overestimation due to recall bias must be kept in mind (Schuz et al., 2003).

Despite all of the limitations of studies of parental occupation and CBT, reviews of epidemiologic studies examining occupational exposures have found consistent themes of elevated risk of brain cancer with paternal employment in the motor vehicle-related occupations, the chemical and petroleum industries, and with frequent paint exposures (Colt and Blair, 1998; Savitz and Chen, 1990); all of these involve exposure to PAH. Population-based case-control studies have been designed to specifically evaluate PAH exposure in parental occupations and the relationship to CBT. A Texas study found elevated risks for printers and graphic arts workers (OR = 4.5, 95% CI = 1.4–14.7) and chemical and petroleum workers (OR = 3.0, 95% CI = 1.1–8.5) (Johnson et al., 1987). A European study found an elevated risk of PNET with paternal exposure to PAH (OR = 2.0, 95% CI = 1.0–4.0) and high maternal exposure to solvents was associated with an increased risk of both astroglial tumors (OR = 2.3, 95% CI = 0.9–5.8) and PNET (OR = 3.2, 95% CI = 1.0–10.3) (Cordier et al., 1997). Another individual study of note included use of a job matrix designed to quantify occupational exposures to

various chemicals in parents of children with cancers found positive associations for brain cancer and parental exposure to creosote with an OR of 3.7 (95% CI = 0.8–16.6), but only five subjects (Feingold et al., 1992).

Chemical exposures occurring at work could theoretically induce carcinogenesis in offspring through a variety of mechanisms. Maternal exposures during pregnancy are likely to be more relevant than paternal, as some toxins can cross the placenta during gestation and affect the fetus during development (Savitz and Chen, 1990). However, fathers can bring home chemicals and dusts on their persons or clothes, leading to potential maternal exposure or directly exposing the children themselves. Paternal occupational exposure can also lead to preconceptional DNA mutations as discussed above.

Medications

The use of medications during pregnancy and early childhood has also been investigated for a possible epidemiologic relationship with CBT. A large retrospective cohort study in Tennessee evaluated in utero exposure to metronidazole and the effect on rates of childhood cancers in children under 5 years of age (Thapa et al., 1998). The trade name for metronidazole is Flagyl, and it is an antibiotic used to treat bacterial vaginosis and trichomoniasis among other conditions. In this population, it is one of the 10 most commonly prescribed drugs in pregnancy (Piper and Mitchel, 1991; Thapa et al., 1998). Flagyl has traditionally been prescribed regularly in pregnancy because untreated bacterial vaginosis and trichomoniasis have been linked to preterm labor (Carey et al., 2003). Metronidazole is a synthetic compound, and it is believed to have short-lived active nitro-reduced metabolites that cause structural DNA damage, cell functional impairment, and cell death in microbes (Thapa et al., 1998). Metronidazole readily crosses the placenta and accesses the fetal circulation. The investigators found an insignificant increased risk for neuroblastomas in offspring exposed in utero to metronidazole with a relative risk (RR) of 2.60 (95% CI = 0.89–7.59). They found no association with all cancers combined (RR = 0.81, 95% CI = 0.41–1.59) or with CNS tumors (RR = 1.23, 95% CI = 0.29–5.21).

A Swedish case-control study evaluated a variety of perinatal and maternal risk factors for CBT and found elevated risks for all brain tumor types combined for the use of narcotics and penthrane (an anesthetic agent) during delivery [OR = 1.3 (95% CI = 1.0–1.6) and OR = 1.5 (1.1–2.0), respectively] (Linet et al., 1996). Other anesthetic agents were not associated with CBT. They also found increased risk associated with the use of oral contraceptives before conception (OR = 1.6, 95% CI = 1.0–2.8).

A case-control study in the United States evaluated the relationship of anticonvulsant use with the development of CBT (Gurney et al., 1997). Phenobarbital is a barbiturate used often in pediatric patients as an anticonvulsant. It is known to have tumor-promoting properties in animals, raising suspicion that it may play a role in tumor development. The investigators found little or no difference between the use of barbiturates vs. other types of anticonvulsant therapy before tumor diagnosis. They also reported a slight elevation in risk among the children of mothers who used anticonvulsant therapy during pregnancy (OR = 1.4, 95% CI = 0.6–3.2). Other studies have reported a lack of association with medications taken during pregnancy (Kuijten et al., 1990).

Vitamins

It has been suggested in several studies that maternal dietary supplementation with multivitamins may reduce the risk of CBT development. In an international case-control study, risk of all CBT was significantly reduced in children under the age of five whose mothers took multivitamins throughout pregnancy (OR = 0.5, 95% CI = 0.3–0.8) (Preston-Martin et al., 1998). As discussed above, the mechanism of action for the antioxidant vitamins C and E may be in their inhibition of the nitrosation process in the stomach. In support of this hypothesis, the risk associated with maternal consumption of cured meats during pregnancy was substantially attenuated when mothers also took multivitamins (Preston-Martin et al., 1996).

Folic acid is another vitamin of potential interest. Folate is widely known to play a protective role in the development of neural tube defects (NTDs), and it has been speculated that there may be some common mechanism of altered development that could lead to both neural tube defects and PNET in particular (Gurney et al., 2001). A case-control study that looked at risks of PNET associated with specific vitamin intake found a significant reduction in risk with folate supplementation (OR = 0.38, 95% CI = 0.21–0.73) (Bunin et al., 1993). English cancer investigators reported a significant decline of medulloblastoma incidence from 5.5 million per year during the years 1976–1984 to 2.8 in the period 1985–1991 (Thorne et al., 1995). They suggest that the introduction of maternal vitamin supplementation may be partially responsible for this decline. The folate receptor has also been found to be overexpressed in molecular analysis of pediatric CNS malignancies, most commonly ependymomas (Weitman et al., 1994). There is some suggestion that the metabolic pathway of folate may contain polymorphisms that alter the risk of NTDs and the same may be true for CBT as well (Gurney et al., 2001). The specific cellular role that folate may play in the development of CBT has yet to be elucidated, but there is ample opportunity for investigation of the hypothesis that folate is a protective factor.

Genes vs. environment

Brief review of molecular and genetic changes in CBT

Inactivation of the common tumor suppressor protein p53 is believed to contribute to brain carcinogenesis in

human astrocytomas and glioblastomas (Santarius et al., 1997; Shiraishi and Tabuchi, 2003; Zupanska and Kaminska, 2002). Approximately one-third of malignant pediatric gliomas have mutations of p53, and these mutations are much less common in individuals under the age of three (Shiraishi and Tabuchi, 2003). P53 gene mutations and increased expression of the p53 protein are associated with shorter survival in these patients. However, p53 mutations are very rare in PNET.

There are other molecular genetic mutations associated with specific histologic types of pediatric brain tumors. The data that are available are not comprehensive as this avenue of investigation is still relatively new. Malignant gliomas are the most common type of intracranial adult tumor, but are relatively rare in children (Di Sapio et al., 2002). It has been demonstrated that adult glioblastomas can have amplification of the epidermal growth factor receptor (EGFR), mdm2, cyclin-dependent kinase 4 (CDK4), and platelet-derived growth factor receptor (PDGFR) (Di Sapio et al., 1992). One histochemical evaluation of pediatric astrocytic gliomas showed a pattern, similar to adults, of mutually exclusive p53 mutation or (EGFR) amplification (Di Sapio et al., 1992). There was minimal or no amplification of the genes for PDGFR, mdm2, and CDK4. In another histochemical study, 80% of high-grade pediatric gliomas were found to have EGFR activity, but only 7% had gene amplification (Bredel et al., 1999). In a similar study of pediatric high-grade astrocytoma (anaplastic astrocytoma and glioblastoma), investigators found p53 mutations in 53% of the tumors and EGFR amplification in none, a pattern that differs from adult malignancies and some of the other results reported (Cheng et al., 1999).

In adult tumors, ependymomas are associated with a loss of 22q (Santarius et al., 1997) and rarely with p53 mutations, but when present, altered p53 expression is only found in high-grade ependymomas (Shiraishi and Tabuchi, 2003). Neurofibromatosis (NF) is linked to alterations in the tumor suppressor NF 1 and 2 genes on chromosomes 17q and 22q, respectively (Santarius et al., 1997). Mutations in the von Hippel Lindau disease gene located on 3p are found with hemangioblastomas (Santarius et al., 1997). There is currently only a limited amount of information available in this field, but studies of this nature will likely become more common in future years. The molecular characterization of brain tumors has the potential to provide information useful for understanding carcinogenic mechanisms as well as etiologies.

Genetics and the environment

Most epidemiologic investigations of CBT thus far have looked at environmental exposures separately from genetics. However, two case-control studies in Quebec found evidence for gene–environment interactions influencing risk of childhood leukemia following exposure to pesticides and alcohol; this work investigated polymorphisms of genes coding for various metabolic enzymes (Infante-Rivard et al., 1999, 2002). Although these studies did not involve CBT, the varying risk from specific exposures associated with different genetic phenotypes suggests that genetic predisposition may play a substantial role in individual responses to toxic exposures and in the development of pediatric cancers.

The absence of the tumor suppressor gene p53 has been demonstrated to play a role in the development of brain tumors in mice exposed transplacentally to a neurocarcinogen. When p53 heterozygous pregnant mice were administered intraperitoneal injections of ENU, 70% of the p53 null offspring rapidly developed primary brain tumors of glial origin (Oda et al., 1997). Glial brain tumors are not typically found in mice (Peterson et al., 1994). This suggests that loss of p53 may be an early event in neoplastic transformation in the brain, and that the presence of p53 is protective against the effects of potential neurocarcinogens (Oda et al., 1997).

Conclusion

Numerous different environmental exposures have been hypothesized to contribute to the development of CBT and have been explored in epidemiology over the past few decades. The fact that few associations have been consistently replicated in studies by different investigators suggests that there may be multiple distinct etiologies. An alternative explanation for the limited associations is the belief of some cancer investigators that most pediatric tumors reflect the inherent risk associated with the complex process of normal development rather than a response to an external toxic insult (Maris and Denny, 2002). In all likelihood, the truth lies somewhere in between, as the delicate process of development occurring in immature cells and organisms may be more vulnerable to the perturbations of toxic insults than mature, differentiated cells. Genetic polymorphisms in metabolic efficiency, DNA repair capacity, and susceptibilities to toxins in future are likely to help explain why some children develop brain tumors and others do not given similar exposure histories.

Several hypotheses that have been explored by epidemiologic investigators are particularly compelling. The consistent association of cured meat consumption during pregnancy and the development of CBT warrants further investigation. The ability of polyoma viruses to initiate malignant transformation in the brain is an avenue of exploration that may provide significant clues about the mechanisms of carcinogenesis, as well as potential etiologies. The protective role of folate is also intriguing, as is the suggested genetic variation associated with that protection. Childhood cancer epidemiologists should also keep in mind findings from recent studies of brain tumors in adults. One of the most intriguing of such findings is the reduced risk of glioma among those with a history of asthma, eczema, and other allergic conditions. This association has been reported in various populations, (Brenner et al., 2002; Schlehofer et

al., 1992, 1999; Wiemels et al., 2002); however, recent cohort studies in Sweden provided only limited support for this relationship (Schwartzbaum et al., in press). Given the frequency of these allergic diseases in childhood, there is ample opportunity to explore such relationships in a pediatric population as well.

Brain cancer is a relatively rare disease and one with many different histological subtypes. Currently, the field is moving away from a 'cell of origin' approach to one that is based upon molecular features (Burger and Fuller, 1991; Mueller and Gurney, 1992). It now seems likely that true etiologic associations will only be discovered by subtype-specific analysis using molecular characterization of tumors. In all likelihood, these categories will be extremely specific, potentially leading to more information about etiology but also smaller numbers within each category. Because of the rarity of CBT and their apparent etiologic complexity and diversity, future studies must be large and include patients and collaborators from several disciplines and numerous geographic areas. Such studies are beginning to be proposed, such as a large statewide CBT project in California that proposes to incorporate extensive genetic exploration and molecular epidemiology. The hope is that many of these types of projects will be initiated in future years if leads from early studies suggest specific hypotheses that can be investigated relatively efficiently.

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Questions and Answers

Q: *With regard to the apparent increase in childhood brain tumors in the 1980's, there is still some discussion as to whether this is in fact all due to improved diagnostic procedures and reporting. Some clinicians and EPA scientists, in particular, are unconvinced. Is it completely certain that childhood brain tumors are not currently increasing in incidence?*

A: Although the debate regarding the apparent increase in incidence is interesting and may be worthy of further discussion, we believe that the increase is a statistical anomaly. The analysis by Smith et al., that explains the apparent increase as a primarily diagnostic phenomenon and their description of a 'jump' in incidence rates from one side of 1985 to the other are particularly convincing.

Q: *Could you please comment more on the recently reported effect of metronidazole? How large was the increase in risk of neuroblastoma, and with what degree of statistical significance? What is the chemical nature of the drug? Is it expected to have DNA-damaging and/or neurotropic actions?*

A: In 1998, it was reported that women exposed to metronidazole during gestation had an insignificantly increased rate of offspring with neuroblastoma (Thapa et al., 1998). The relative risk reported by the authors was 2.6 with a 95% CI of 0.89 to 7.59. Metronidazole is a synthetic antimicrobial compound that is believed to have short-lived nitro-reduced metabolites that cause direct structural DNA damage as a component of its activity. It is also believed to readily cross the placenta and access the fetal circulation. It is used frequently in pregnancy because the condition it treats, bacterial vaginosis, is commonly linked to preterm labor.

Q: *Lack of a complete blood-brain barrier until six months after birth is important and worth more comment. Which chemicals/toxicants have been studied in this regard in the human, and/or in animal models? How leaky is this barrier at various developmental stages, compared with the adult?*

A: There is less information about quantitative blood-brain barrier permeability in newborn and young mammals compared to adults (Stonestreet et al., 1996 in manuscript). Multiple agents are clinically relevant and known to cause neuronal toxicity if exposure occurs during gestation and not later in life; these include rubella virus, lead, methylmercury, retinoids and thalidomide (Rodier PM. 1995. Developing brain as a target of toxicity. Environmental Health Perspectives. 103 S6:73-6). Cadmium and monosodium glutamate are more examples of substances that enter the developing brain freely in experimental animals, but are prevented access to the mature brain by the blood-brain-barrier (Rodier et al., 1995).

Stonestreet et al., conducted experiments evaluating the blood-brain barrier in sheep during the last two months of gestation and the first month of neonatal life and compared the results to adult animals. They found that influx of radioactive compounds in all regions of the brain decreased significantly with maturation ($p < 0.0001$). In most regions of the brain, the influx was significantly lower ($p < 0.05$) in the brain regions of the adult sheep and in most of the regions of the newborns compared with fetuses at 60% and 90% of gestation. They also reported more regional heterogeneity of influx during gestation and in newborns than in developing animals.

As early as 1926, experiments and scientific speculation about the potential differences in blood-brain barrier permeability between fetuses and adults were being published. Adinolfi's review provides an interesting discussion of the evolution of thinking and experimentation on this topic.

Q: *You cite some remarkable results related to viral infection and malignant nervous system tumors, especially a*

recent British study with an odds ratio of 10.6. Probably having flu has been tested in many studies, any associations? Was medication use considered in the studies of viral infection and flu that you cite?

A: The remarkable odds ratio of 10.6 was reported in a British study that looked at the risk of CBT with regard to viral infections documented by laboratory results, including rubella, mumps, varicella and herpes zoster (Fear et al., 2001). In studies evaluating influenza and other viral infections, the findings are less striking with odds ratios around 2 to 3 (Fear et al., 2001; Linos et al., 1998). Medication did not appear to be considered with regard to acute infection, although it is an excellent question and warrants investigation. This is particularly true since consumption of a decongestant that appears to be a nitrosamide precursor during gestation was positively related to increased incidence of pediatric glial brain tumors (McKean-Cowdin et al., 2003).

Q: *You mention molecular changes briefly. What is the frequency of p53 inactivation in childhood brain tumors, and is this tumor-type specific? Are there other molecular changes that are often seen, or have these not yet been sought?*

A: Inactivation of p53 is believed to contribute to brain carcinogenesis in human astrocytomas and glioblastomas (Zupanska and Kaminska, 2002; Shiraishi and Tabuchi, 2003; Santarius et al., 1997). Approximately one-third of malignant pediatric gliomas have mutations of p53, and these mutations are much less common in individuals under the age of three (Shiraishi and Tabuchi, 2003). P53 mutations are very rare in PNET.

There have been other experiments looking for patterns of molecular changes in pediatric brain tumors, and these have been reviewed in the manuscript in some detail. Because of the small amount of data, some of the early findings have been contradictory. These discrepancies are likely to be resolved and/or clarified with the accumulation of more data.

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