N-Nitroso Compounds and Childhood Brain Tumors: A Case-Control Study

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ABSTRACT

We questioned mothers of 209 young brain tumor patients and mothers of 209 controls about experiences of possible etiological relevance which they had during pregnancy or which their children had while growing up. Long-suspected brain tumor risk factors such as head trauma and X-rays appeared to be factors for relatively few cases. Increased risk was associated with maternal contact with nitrosamine-containing substances such as burning incense (odds ratio, 3.3; p = 0.006), sidestream cigarette smoke (odds ratio, 1.5; p = 0.03), and face makeup (odds ratio, 1.6; p = 0.02); with maternal use of diuretics (odds ratio, 2.0; p = 0.03) and antihistamines (odds ratio, 3.4; p = 0.002); and with the level of maternal consumption of cured meats (p = 0.008). These drugs contain nitrosatable amines and amides, and the cured meats contain nitrates, chemicals which are precursors of N-nitroso compounds. We propose a hypothesis that brain tumors in these young people are related to in utero exposure to N-nitroso compounds and their precursors, the most potent nervous system carcinogens known in experimental animals.

INTRODUCTION

Brain tumors are an important cause of death and disability in children and young adults. Among persons from 0 to 24 years old, cancer is the second leading cause of death, and the brain is the second most common cancer site. Brain tumors are of particular concern because fewer than one-half of the young victims survive for 5 years (20), and many of those who do remain severely disabled or die later of recurrences (1). Prevention of brain tumors in young people necessitates an understanding of cause.

Since tumors which occur in association with genetic syndromes such as neurofibromatosis account for only a small proportion of all brain tumors (less than 1% in our studies), the search must focus on environmental causes. Exposure to ionizing radiation, which is the best substantiated of the suggested risk factors, has been associated with tumor development in children whose mothers received pelvimetry while they were in utero (17) and in young people who received X-ray treatment for tinea capitis (22). Birth trauma (4), barbiturates (both in utero and childhood exposure implicated) (9), and insecticides (period of exposure not specified) (10) have also been suggested as possible risk factors. In addition, experimentalists have shown that various N-nitroso compounds are potent nervous system carcinogens, particularly when animals are exposed transplacentally (18).

We describe a study of 209 pairs of young (from birth to 24 years old) brain tumor patients and individually matched controls which investigated the possible etiological relevance of a variety of in utero and childhood exposures. The study was designed to provide information not only on exposure to previously studied factors but also on exposure to substances containing N-nitroso compounds or precursors of these compounds.

METHODS

Study Groups. The patients were black young people and white young people with a tumor of the brain or cranial meninges (hereafter called "brain tumor") of any histological type first diagnosed during the years 1972 to 1977. Any young person who was a resident of Los Angeles County and under 25 years old at the time of brain tumor diagnosis was eligible for inclusion if his or her biological mother was available for interview. The Los Angeles County Cancer Surveillance Program identified the patients (12). All diagnoses except one had been microscopically confirmed.

We used a carefully devised algorithm to select an individually matched control for each patient from among his or her friends and neighbors. Each control matched the patient on sex, race, and birth year (within 3 years) and also had a natural mother who was available for interview. Controls selected from among friends and neighbors of patients also matched on socioeconomic status.

Selection of Patients. The Cancer Surveillance Program identified 317 eligible patients whose biological mothers were available for interview. The hospitals and attending physicians granted us permission to contact 294 (93%) of these 317 patients. We were unable to locate the families of 29 patients. We interviewed the mothers of 226 patients (85% of the 265 patients whose families were contacted about the study or 66% of the initial 317 patients).

Selection of Controls. Early in the interview with each case mother, we asked her to think back to the time 1 year before her child’s tumor was diagnosed and remember other children her child’s age with whom he or she spent time or who was known to the family. Thus, in the context of helping the mother remember back to a certain time in her child’s life, we generated a list of potential controls, ranked in order of closeness of association. At the end of the interview, we returned to this list and asked her for permission and help in contacting the mother of the child at the top of the list. If the mother of this child was not available or refused to participate, we contacted the mother of the next child on the list. We interviewed mothers of 153 controls identified in this manner. The friend first on the list became the control for 122 patients; the second friend became the control for 20 patients, the third friend became the control for 8 patients, and the fourth friend became the control for 3 patients. When no friend control was available, we sought a neighbor control by use of a procedure that defines a sequence of houses on specified neighborhood blocks. Our goal was to interview the mother of the first resident in the sequence who matched the patient. If no one was home at the time of our visit, we left a questionnaire at the residence with an explanatory letter and made a follow-up visit after several days. In 41 instances, the first appropriate person became the control. When, in 15 other instances, the first match refused to participate, another matched control in sequence was located and interviewed. For any patient, we visited 60 housing units and made 3 return visits before we conceded failure to secure a matched control. We interviewed mothers of 56 controls identified in this manner. In all, we identified 209 matched controls whose mothers we interviewed. For 17 patients, we were unable to locate a matched control whose mother was willing to participate.
The Interview. A questionnaire sought information from mothers of patients and controls on experiences they had during the index pregnancies and on experiences the children had from birth up to the age of the patient 1 year before tumor diagnosis. Our initial contact with each mother was a telephone call in which we explained the study and asked her to participate. If she agreed, we scheduled a telephone interview at a time convenient for her. A single interviewer conducted all interviews except those with 14 case and 15 control mothers which, of necessity, our Spanish-speaking interviewer conducted. It was not feasible for interviews to be conducted blind, but all questions were asked in a standard manner. The questionnaire included questions on the use of drugs, alcohol, tobacco, and household and personal products. It also included questions about head injury, hospitalization, consumption of certain foods, and exposure to ionizing radiation. We interviewed case and control mothers during 1978 and 1979.

Statistical Analysis. In the analysis of questionnaire data, we used the exact binomial test on individual dichotomous variables. We used the multivariate logistic regression method for matched case-control studies (2, 13) for multivariate analysis and on individual variables with more than 2 possible outcomes. We used the method of Mantel and Halperin (19) to analyze the effect of birth order. Pairs in which either mother failed to answer the relevant question(s) were eliminated. If the patient was an infant at the time of tumor diagnosis (12 patients), we excluded the pair from the analysis of childhood exposure variables. All statistical significance levels quoted (p values) are one-sided unless otherwise stated.

RESULTS

Ninety-two patients were under 10 years old at diagnosis; 117 patients were 10 through 24 years old. Male patients (111 patients) outnumbered female patients (98 patients). Only 17 patients were black compared to 192 who were white. The distribution of patients by histological type of brain tumor was 93 astrocytomas, 31 medulloblastomas, 19 glioblastomas, 12 ependymomas, 17 gliomas of other or unspecified types, 13 meningiomas, 9 neuromas, 3 gangliogliomas, and 11 tumors of other or unspecified types. One patient who died had a posterior cranial fossa brain tumor which was never microscopically confirmed.

Maternal Exposures

Table 1 shows odds ratios for various maternal exposures during the index pregnancy. When compared to control mothers, more case mothers were gainfully employed (odds ratio, 1.4), and more of them had jobs for which they wore protective clothing or equipment (odds ratio, 4.0).

Beer, sidestream cigarette smoke, incense smoke, and face makeup all contain preformed nitrosamines. Case and control mothers were similar in consumption of beer and cigarettes during the pregnancy. More case mothers than control mothers, however, lived in a household with someone else who smoked (odds ratio, 1.5). We also observed an odds ratio of 3.3 for any maternal use of incense and an odds ratio of \( \infty \) \((p = 0.002)\) for frequency of incense use reported as "often" or "occasionally" compared to "rarely" or "never." Frequent ("often" compared to all other categories combined) use of face makeup during the pregnancy (odds ratio, 1.6) was significantly associated with tumor occurrence.

We found strong associations between tumor occurrence and maternal use of certain drugs during the index pregnancy. The odds ratios were 3.4 for antihistamines, 2.0 for diuretics, and \( \infty \) for general anesthesia. Most commonly, mothers used antihistamines to relieve hayfever symptoms and took diuretics to reduce pregnancy-related water retention. General anesthesia was administered to one mother during an appendectomy and to 5 mothers during dental surgery. The antihistamines used were chlorpheniramine-containing drugs (10 patients, 7 controls), Benadryl (3 patients), other drugs not containing chlorpheniramine (4 patients), nasal spray or cough medicine of unspecified brands (3 patients, 1 control), and unspecified medication or shots for asthma or allergies (6 patients, 1 control). We did not ask mothers the brand name of the diuretic they took, but those who volunteered this information all took a thiazide drug, one-half took chlorothiazide drugs and one-half took hydrochlorothiazide drugs. Five of the 6 case mothers who had general anesthesia had sodium pentothal, a barbiturate; the sixth did not specify the drug used. Only 2 case mothers and 3 control mothers took other barbiturates. We did not ask direct questions about either general anesthesia or prenatal vitamins (Table 4); mothers volunteered information about both in response to a question about the use of "other drugs" during the pregnancy.

Table 2 shows odds ratios for each of 3 frequencies of consumption (less than once a month, once a month to once a week, 2 times a week or more) of various foods. Consumption during pregnancy of meats cured with sodium nitrite was associated with development of brain tumors in the offspring. When consumption of all types of cured meats was considered jointly and grouped into 3 levels, the dose-response effect was highly significant \((p = 0.008)\). There was no apparent association between tumor development and maternal consumption during pregnancy of any of the vegetables which usually contain high levels of nitrate (spinach, collards or turnip greens, eggplant, beets, and radishes.)

Similar results were obtained when we analyzed the data separately by type of control (friend or neighbor), by tumor type (glial or other), or by age of the patient at diagnosis (under age 10 or age 10 and over). A multivariate analysis showed that the effect of various maternal exposures (occupation, preformed nitrosamines, cured meats, and drugs) were inde-

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**Table 1**

<table>
<thead>
<tr>
<th>Occupational factors</th>
<th>Discordant pairs (case-control)</th>
<th>One-sided p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worked</td>
<td>33 51 36</td>
<td>1.4 0.07</td>
</tr>
<tr>
<td>Wore protective clothing or equipment</td>
<td>1 12 3</td>
<td>4.0 0.02</td>
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<th>One-sided p value</th>
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<tbody>
<tr>
<td>Drank beer</td>
<td>25 52 31</td>
<td>1.0 0.50</td>
</tr>
<tr>
<td>Smoked cigarettes</td>
<td>38 50 47</td>
<td>1.1 0.42</td>
</tr>
<tr>
<td>Lived with a smoker</td>
<td>55 56 39</td>
<td>1.5 0.03</td>
</tr>
<tr>
<td>Burned incense</td>
<td>3 20 6</td>
<td>3.3 0.005</td>
</tr>
<tr>
<td>Often used face makeup</td>
<td>39 56 35</td>
<td>1.6 0.02</td>
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**Use of drugs**

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<th>Antihistamines</th>
<th>Diuretics</th>
<th>General anesthesia</th>
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<td>4 24 7</td>
<td>8 26 13</td>
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pended to each other; i.e., none could be accounted for by the effect of the other factors.

**Childhood Exposures**

Table 3 shows odds ratios for various exposures during childhood. Four patients and no controls were described as severely bruised about the face and head at birth. Nine patients and only 3 controls had been hospitalized for head injury. Only one of these 9 patients had epilepsy; the onset of his seizure disorder followed the hospitalization for head injury. The odds ratio for having 5 or more full-mouth X-rays starting at least 10 years before diagnosis was 2.5.

The major differences between patients and controls in the use of drugs during childhood related to the fact that 19 patients and no controls took drugs for seizures ($p = 0.0005$). For 9 of these patients, their first seizure occurred during the period from 2 to 4 years before their tumor was diagnosed. An additional 5 children had their first seizure 5 to 8 years before diagnosis. Of the 5 children with long-standing epilepsy (onset 10 or more years before tumor diagnosis), 1 was mentally retarded since infancy, 1 had a brain tumor diagnosed incidentally at autopsy which the pathologist suggested could explain the epilepsy, 2 had seizures which began 1 or 2 years after a serious head injury, and 1 had a severe seizure disorder of unknown etiology. The age distribution of the 19 patients with epilepsy was different from that of all 209 patients. Only 2 of the 19 were under 10 years old at diagnosis, and two-thirds (13 patients) were 15 years old or over compared with only one-third (68 patients) of all patients. The distribution of these 19 patients by histology, however, was similar to the overall distribution by histological type. When we excluded these 19 pairs in which the patients had epilepsy, we found no additional associations between disease and known use of barbiturates (2 patients, 1 control) or known or possible (mother did not recall name of sedative) use of barbiturates (7 patients, 8 controls).

Consumption of cured meats during childhood was also associated with tumor development. The odds ratios for low, moderate, and high consumption during childhood of all cured meats combined were 1.0, 1.3, and 2.3 [$p$ (linear trend) $= 0.01$]. As might be expected, the child's consumption of these foods was highly correlated with the mother's consumption, and childhood consumption of cured meats had little effect after maternal consumption was taken into account.

**Nonsignificant Findings on Variables Discussed in Previous Studies**

**Birth Characteristics.** We found no significant birth order effect among patients when expected numbers were calculated taking sibship size into account (2-sided $p = 0.58$). Mean birth weight of patients (118.8 oz) was not significantly different from that of controls (117.0 oz). Details of the deliveries were similar in many respects for the 2 groups of mothers. In each comparison, the numbers of case and control mothers were similar for preterm delivery (before 9 months), delivery by cesarean section, or prolonged labor (contractions at least every 5 min for 10 hr or more). The 2 groups were also similar in inhalation of gas during labor and use of forceps during delivery. We found no difference in maternal history of abortion prior to the index pregnancy.

**Maternal and Childhood Exposures.** Table 4 shows nonsignificant findings on maternal and childhood exposures discussed in previous epidemiological studies. We failed to find significant associations with maternal exposures during the index pregnancy to pelvic X-rays or permanent hair dyes. More case mothers reported using pesticides often or occasionally, but case and control mothers were similar with respect to whether their homes were treated by an exterminator at any time during the pregnancy. Maternal use of various drugs during the index pregnancy showed no significant associations with tumor occurrence for the use of aspirin, sedatives, amphetamines, or vitamins.

**Table 3**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Patients</th>
<th>Controls</th>
<th>Odds ratio</th>
</tr>
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<tbody>
<tr>
<td>Had 5 or more full-mouth X-rays starting at least 10 years before diagnosis*</td>
<td>12</td>
<td>15</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Restricted to 68 pairs in which the patients were age 15 or older at diagnosis.
A similar number of patients and controls had seen a doctor because of a head injury 1 year or more prior to the date of diagnosis of the patient. Likewise, a similar number of patients and controls had had a tonsillectomy. Patients and controls were similar in their use of drugs other than phenobarbital and in their histories of exposure to therapeutic and diagnostic X-rays. Although we studied a number of other variables, we found few other differences between the childhood experiences of patients and controls. We found no significant differences for contact with pesticides, for treatment of their homes by professional exterminators, for eating of paint flakes, or in personal or family history of nervous system tumors or cancer.

DISCUSSION

Our findings with regard to the association of childhood brain tumors with X-ray exposure are consistent with those of previous investigations. Large cohort studies which have investigated the relationship of in utero X-ray exposure and development of brain tumors in childhood estimated that an odds ratio of 1.4 was associated with such exposure (17). Although our patient series was not large enough for the results to reach significance, the risk of 1.3 found in our study is clearly compatible with that found in the earlier studies. The association that we found among our older patients of an odds ratio of 2.5 associated with exposure to dental X-rays (5 or more full-mouth series starting at least 10 years before diagnosis) is consistent with our findings in a recent study of intracranial meningiomas in adult women (24). All of the patients in our present series with such exposure had their first full-mouth X-rays before age 15 and before 1964 when the average per film exposure for dental X-rays was 1140 mrad (29). A full-mouth series which involves 16 to 20 exposures would have meant, therefore, a total exposure of about 20 rads. This examination results in intersecting lines of radiation within the brain which vary with the angle at which each X-ray is taken. Such points of intersection may be points of high ionization.

Trauma is often regarded by lay persons as related to tumor development and is, therefore, a variable susceptible to bias from differential recall. In an attempt to limit reporting of trauma to injuries of a certain minimum severity and thereby restrict recall bias, we asked mothers to report only head trauma that had been treated medically. We found that patients and controls were similar both in the number of such injuries and in the number for which they had received head X-rays. Incidents of head trauma which required hospitalization were, however, more common among patients (odds ratio, 3.0) but had been experienced by only 9 brain tumor patients. Except for the finding that 4 patients and no controls were described as severely bruised about the head and face at birth, we found little difference between patients and controls on variables which might indicate birth trauma.

Except for the association with sodium pentothal, we found no suggestion, in contrast to a recent study (9), of an association with other in utero or childhood exposure to barbiturates, other than to antiepileptics. We suspect that most of the 19 patients who took phenobarbital to control epilepsy had seizures which were an early brain tumor symptom. Also, we lack details about other anesthetic agents which might have been used in conjunction with pentothal.

The most striking findings in our study do not relate, however, to any of the above previously studied variables. We found brain tumors in young people to be significantly associated with several apparently disparate maternal exposures during the pregnancy including occupational use of protective equipment or clothing, living with a smoker, frequent use of face makeup, burning of incense, use of certain drugs, and frequent consumption of cured meats. Although these risk factors appear unrelated, we included them in the study as a means of measuring sources of exposure to N-nitroso compounds.

Certain N-nitroso compounds (nitrosoureas) are the most potent nervous system carcinogens known to experimentalists, and tumor induction is most complete when exposure occurs transplacentally (18). N-Nitroso compounds are ubiquitous in the environment of a modern industrial society (7). Nitrosamines and other N-nitroso compounds have been found in various occupational settings (7), in sidestream cigarette smoke and incense smoke (3), in prescription and nonprescription drugs (15), and in a wide range of cosmetics, with the highest levels most consistently found in face makeup (5). Cured meat products also contain nitrosamines, and relatively high levels may be released in cooking fumes (26).

Experimentalists have also induced tumors by feeding animals precursors of N-nitroso compounds (nitrite plus amines or amides). When pregnant rats are gavaged with nitrite and ethylurea, their offspring develop brain tumors which can be prevented if ascorbic acid (vitamin C) is gavaged at the same time (14). Cured meat products also contain nitrosamines, and relatively high levels may be released in cooking fumes (26).
shown to interact with nitrite in human gastric juice (16). The rapidity with which such reactions occur and the stability and carcinogenicity of the compounds which result has, for most drugs, not been determined. Hydrochlorothiazide, the diuretic mentioned by one-half of the case mothers, who volunteered the name of the drug, is known, however, to nitrosate readily (8).

Vitamins C and E are effective blocking agents for nitrosation reactions (27). Unlike cured meats, vegetables contain vitamins along with nitrogen compounds. Our finding of an association of brain tumors with cured meats but not with high-nitrate vegetables may indicate that vitamins in vegetables prevent the nitrate from being used to form N-nitroso compounds. Future studies should include direct questions about common foods high in vitamins C and E and about the use of prenatal vitamins. Our hypothesis would predict a protective effect of vitamins which have been shown to block the nitrosation of drugs and to prevent the endogenous synthesis of N-nitroso compounds from sodium nitrite and other precursors (21).

Overall, our findings fit the animal model well. We obtained estimates of exposure to some of many possible sources of nitrosating agents which are ubiquitous in our environment in the workplace and in consumer products, including foods, drugs, and cosmetics. Most of these exposures were associated with increased risk. Our hypothesis is supported by a recent study which found an association between high levels of nitrate in the household water supplies of pregnant women and central nervous system birth defects in their children (25).

Our hypothesis is further supported by the specificity of our findings and by indications that the differences we observed are not attributable to recall bias. Admittedly, recall of diet and events as far back as 30 years ago may be poor; the misclassification engendered by such poor recall would tend, however, to obliterate actual associations. We asked about each N-nitroso variable in a section of the questionnaire which also contained questions about similar variables which we thought were unlikely to be related to brain tumor occurrence and which did not emerge as risk factors. For example, in the dietary section, we asked about 22 separate food items; we included traditional breakfast meats in a section on breakfast foods and lunchmeats in a list with other sandwich fillers. We received no indication that mothers regarded any of the foods as potentially deleterious and no indication that case mothers tended, overall, to choose higher food consumption categories. We asked about face makeup in a section which included questions about the use of hair spray and aerosol deodorant, neither of which was associated with brain tumors. Because we found odds ratios of 1.0 or close to 1.0 for so many of the variables that we studied, we conclude that, for the use of common products, recall of case and control mothers was not related to disease but that living with a smoker (usually the child’s father) was may indicate that paternal exposures are important. The same compounds may be relevant but may act through the father rather than the mother, as suggested by a recent experiment that caused an increased incidence of nervous system tumors in the progeny of male rats exposed to ethylnitrosoureia before mating (28). Our detailed analysis of parental occupational exposures of the 92 pairs in which the patients were under age 10 at diagnosis does suggest that paternal exposures may be related to tumor development (23).

Because of major limitations, this study can do no more than suggest that N-nitroso compounds might be associated with childhood brain tumors. We obtained information on only some of many experiences which probably involve exposure to N-nitroso compounds or precursors. We made no attempt to create indices of total exposure to nitrate and nitrite, amines and amides, or preformed nitrosamines. Indeed, such an attempt might well be futile given the current state of knowledge. An analysis by overall exposure dose was, therefore, not possible. We also lack accurate exposure dose information for any individual source since dose depends on many factors not studied, such as brand used and personal habits of use.

ACKNOWLEDGMENTS

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REFERENCES

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