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RISK FACTORS FOR BRAIN TUMORS IN CHILDREN

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An exploratory case-control study was conducted in 15 hospitals in the Baltimore, MD, SMSA of possible etiologic factors associated with brain tumors in children. Eighty-four children with brain tumors were compared to normal children and to children with other malignancies. Parents of these children were interviewed about a variety of possible etiologic factors. The findings included: 1) children with brain tumors as well as children with other cancers had a greater tendency than normal children to have been first births and to have had higher birth weights; 2) more children with brain tumors had a sibling with epilepsy or seizures than did normal children, and several of the mothers of children with brain tumors had themselves had epilepsy or a stroke at a relatively young age; 3) there were no significant differences between the groups with regard to several maternal characteristics, including smoking during pregnancy and prior radiation exposure; 4) more children with brain tumors and children with other cancers were found to have had exposures to insecticides than had normal children; 5) fewer children with brain tumors or with other cancers were reported to have had tonsillectomies than normal children; and 6) more of the children with brain tumors as well as the children with other malignancies were reported to have been exposed to farm animals and to sick pets. This exploratory study is one of the first case-control studies of the epidemiology of brain tumors in children, and the results suggest directions for future epidemiologic studies in this relatively uncharted field.

birth weight; brain neoplasms, etiology and occurrence; insecticides; smoking; tonsillectomy

Cancer is the second leading cause of death in children under the age of 14 years in the United States, and brain tumors are the second most frequent type of cancer, accounting for approximately 20 per cent of all cancers in children (1, 2). Moreover, unlike the improvement in survivorship recently observed for leukemia in children, survival for children with brain tumors has not improved in recent years, with the five-year survivorship remaining about 35 per cent. The improvement in survivorship for leukemia and the lack of such improvement for brain tumors may lead to an increase in the relative importance of brain

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tumors as a cause of mortality in children in the future. In addition, children with brain tumors who do survive more than five years after diagnosis are often left with permanent disabilities, and some die later of recurrences (3).

Despite the magnitude of the problem, the bleak prognosis of this illness in children, and the apparent dearth of etiologic clues, few studies have been conducted to investigate the epidemiologic characteristics and etiologic factors associated with brain tumors in children. There is, however, an urgent need for prevention, which requires the identification of environmental factors that may be causally associated with brain tumors in children so that exposures to these factors might be reduced. Thus far, the only *environmental* factor which has been implicated in the etiology of brain tumors in children is radiation exposure (4–7). A role for *genetic* factors has also been suggested by case reports of familial aggregation of brain tumors (8–13) as well as by reports of the development of brain tumors in patients with genetically determined disorders, such as von Recklinghausen's disease (neurofibromatosis) and tuberous sclerosis (14–20).

In addition, experiments in a variety of animal species have shown that chemical carcinogens, including those found in tobacco smoke, produce brain tumors when administered intracerebrally or transplacentally (21–29). Such evidence lends support to the possibility of perinatal chemical induction of brain tumors of infancy and childhood. Animal experiments have also suggested a possible role for hormonal factors in the etiology of brain tumors in which chemically induced tumors have regressed following castration and then grown again following administration of testosterone (30). Experiments with animals also have succeeded in producing brain tumors in a wide variety of animals using a number of known animal oncogenic viruses (31–35). Further support for a possible infectious etiology of brain tumors has been derived from a retrospective study of patients of all ages, in which significantly more patients with brain tumors (particularly with astrocytomas) than controls were found to have serum antibodies to toxoplasmosis (36). In view of the limited knowledge available regarding the causes and epidemiologic patterns of brain tumors in *children,* a community-wide, hospital-based case-control study was conducted to explore possible associations of selected environmental factors—including chemical and hormonal factors—with the development of brain tumors in children.

Methods

Study populations

All children under the age of 20 years who were diagnosed with primary malignant brain tumors in the Baltimore, MD, Standard Metropolitan Statistical Area (SMSA) during the period 1965–1975 were ascertained from hospital diagnostic listings, death certificates, hospital tumor registries, and pathology, radiotherapy and clinical oncology records. Twenty-one of Baltimore's 23 short-term, non-federal hospitals permitted review of their records, including all seven of the hospitals which handle the majority of pediatric oncology patients in the area. Eighteen of the hospitals had pediatric patients with brain tumors, and 15 of these permitted contact with parents of the patients. Hospital records were obtained and abstracted for all patients with a diagnosis of a primary brain tumor. The distribution of brain tumor cases by cell types was: 35 astrocytomas, 16 medulloblastomas, 11 ependymomas, five pontine gliomas, two glioblastoma multiforme, two optic gliomas, seven other cell types, and six unspecified cell types.

Children with brain tumors were compared to two groups of controls: The first control group, called *normal controls,* consisted of children with no known malig-

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Data collection

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nant disease and was selected for comparison of normal (non-diseased) children and the children with brain tumors. Normal control children were selected from birth certificates on file at the Maryland State Health Department and matched to children with brain tumors on sex, date of birth (± one year) and race. The second control group, called *cancer controls,* consisted of children with malignancies other than brain tumors who were matched to the children with brain tumors on sex, date and age at diagnosis, and race. When an exact match to a normal control or cancer control was not available, criteria were relaxed for the matching factors in the order that factors are listed above (i.e., matching by sex was relaxed first). The cancer control group was used for two purposes: first, to see if factors associated with brain tumors were also associated with other malignancies in children, and second, to try to determine if selective recall bias on the part of parents of seriously ill children played an important role in the study.

Data collection

Parents of children with brain tumors, of normal controls and of cancer controls were interviewed by trained interviewers about the index child's exposure to several possible etiologic agents including: 1) characteristics of the index child, such as birth order, birth weight, previous medical history, exposure to animals, and radiation and chemical exposures; 2) maternal characteristics such as prenatal use of medications, illnesses, smoking, radiation and chemical exposures during pregnancy, and previous medical history; and 3) family characteristics such as medical history of father and siblings, radiation and chemical exposures of the father, education, religion and residential mobility.

Analysis of data

One hundred and twenty-seven children with brain tumors diagnosed during the period 1965–1975 who were residents of metropolitan Baltimore were identified; 100 of these children were traced, and the parents of 84 of them participated in the interview. 179 cancer controls and 364 normal controls were identified and traced. Parents of 76 normal controls and of 112 cancer controls participated in the interview. General characteristics of brain tumor patients and controls who participated in the interview did not differ greatly and are summarized in table 1. Non-participants in the study tended more than participants to be male, black, and to live in census tracts of lower median rental for housing at the time of birth of the index child. The interviewed subjects yielded 73 matched pairs of patients with brain tumors and normal controls and 78 matched pairs of children with brain tumors and cancer controls. (The total number of subjects varied slightly for each analysis presented due to inadequate information for at least one member of a pair.) The relative risk for a given factor was estimated using the odds ratio for matched pairs (37). McNemar's test for significance (38) was also used, since patients and controls had been matched. Odds ratios (and associated p values) for selected risk factors are given in table 2.

Results

Birth characteristics

Several characteristics of the index child at birth were of interest. First, as shown in table 2, there was a tendency for more children with brain tumors than normal children to have been first births, with an odds ratio of 1.7, although the odds ratio was not statistically significant ($p = .18$). Children with brain tumors resembled the cancer controls who also tended to be first births.

No significant differences were observed between children with brain tumors and either normal controls or cancer controls with regard to maternal

TABLE 1

Per cent distributions of cases and controls by selected characteristics in a study of brain tumors in children in 15 Baltimore SMSA hospitals, 1965-1975

Characteristics	Brain tumor patients (N = 84)	Normal controls (N = 73)*	Cancer controls (N = 78)*
Race			
White	77.4	86.3	78.2
Black	22.6	13.7	21.8
Sex			
Male	47.6	39.7	48.7
Female	52.4	60.3	51.3
Year of birth			
Before 1950	3.6	2.7	1.8
1950–1954	8.3	8.2	8.0
1955–1959	27.4	30.1	20.5
1960–1964	34.5	35.6	38.4
1965–1969	21.4	19.2	21.4
1970 or after	4.8	4.1	9.8
Age (years) at diagnosis			
Under 5	28.9		30.8
5–9	33.7		26.9
10–14	20.5		25.6
15–19	16.9		16.7
Year of diagnosis			
1965–1969	45.7		44.9
1970–1975	54.3		55.1

* Number of controls indicated includes only those who were successfully matched to brain tumor patients and interviewed.

or paternal age at the time of birth of the index child. However, children with brain tumors did differ significantly from normal children with regard to birth weight. Table 2 illustrates that significantly more children with brain tumors weighed 3629 gms (8.0 lbs) or more at birth (matched pairs odds ratio = 2.6, p = .046). There were no significant differences in birth weight between children with brain tumors and children with other malignancies, suggesting that increased birth weight may be generally characteristic of children who develop cancer. Mean birth weights were 3084 gms (6.8 lbs) for children with brain tumors, 2903 gms (6.4 lbs) for normal controls, and 3175 gms (7.0 lbs) for cancer controls.

Religion

There was a tendency for fewer of the children with brain tumors to be Jewish than normal controls. Although the odds ratio was very small (0.17), it was not statistically significant at the five per cent level due to the small number of children involved. A deficiency of Jewish children with brain tumors also was observed when the comparison was made with children with other cancers.

Family history of neurologic disorders

A significantly increased frequency of epilepsy was reported in the siblings of children with brain tumors compared to siblings of normal children, as shown in table 2 (matched pairs odds ratio = 8.0, p = 0.046). The frequency of epilepsy was also slightly increased when compared to siblings of cancer controls, although this difference was not statistically significant at the five per cent level. These differences could not be attributed to differences in family size, since the mean

Matched pairs comparis among ch

Risk factor	Contr grou
Birth order of index child (+ = first birth, − = other birth)	norm canc
Birth weight of index child (+ = ⩾3629 gms, − = <3629 gms)	nor can
Epilepsy in any siblings (+ = yes, − = no)	nor can
Religion (+ = Jewish, − = other)	nor can
Young maternal menarche (+ = <12 years, − = ⩾12 years)	no ca
Older maternal menarche (+ = ⩾15 years, − = <15 years)	no ca
Exterminations for insects (+ = any, − = none)	no ca
Continued maternal smoking† during index pregnancy (+ = continued, − = did not continue)	no ca
Index child living on farm (+ = yes, − = no)	n c
Index child's exposure to sick pets (+ = yes, − = no)	n c
Tonsillectomy in index child (+ = yes, − = no)	n c

* Ratio of discordant pairs

† Includes only mothers w

TABLE 2

Matched pairs comparison of brain tumor cases with normal controls and cancer controls, among children in 15 Baltimore SMSA hospitals, 1965-1975

Risk factor	Control group	Matched pairs odds ratio*	p value	Discordant pairs (Case-Control) + −	Discordant pairs (Case-Control) − +	Concordant pairs (Case-Control) + +	Concordant pairs (Case-Control) − −
Birth order of index child							
(+ = first birth,	normal	1.7	0.18	22	13	3	35
− = other birth)	cancer	1.1	0.86	17	15	8	37
Birth weight of index child							
(+ = ≥3629 gms,	normal	2.6	0.046	18	7	8	38
− = <3629 gms)	cancer	0.9	0.75	18	21	8	29
Epilepsy in any siblings							
(+ = yes,	normal	8.0	0.046	8	1	1	63
− = no)	cancer	1.8	0.55	7	4	0	66
Religion							
(+ = Jewish,	normal	0.17	0.13	1	6	0	65
− = other)	cancer	0.25	0.37	1	4	0	73
Young maternal menarche							
(+ = <12 years,	normal	2.2	0.14	15	7	4	44
− = ≥12 years)	cancer	1.1	0.86	17	15	2	39
Older maternal menarche							
(+ = ≥15 years,	normal	2.2	0.27	9	4	1	56
− = <15 years)	cancer	1.4	0.52	13	9	0	51
Exterminations for insects							
(+ = any,	normal	2.3	0.10	16	7	3	43
− = none)	cancer	1.2	0.84	14	12	7	41
Continued maternal smoking† during index pregnancy							
(+ = continued,	normal	5.0	0.22	5	1	14	0
− = did not continue)	cancer	∞	0.13	4	0	14	1
Index child living on farm							
(+ = yes,	normal	4.0	0.04	12	3	0	57
− = no)	cancer	1.0	0.98	9	9	2	57
Index child's exposure to sick pets							
(+ = yes,	normal	4.5	0.07	9	2	0	62
− = no)	cancer	1.3	1.0	4	3	3	68
Tonsillectomy in index child							
(+ = yes,	normal	0.62	0.33	10	16	5	42
− = no)	cancer	1.2	0.84	12	10	3	53

* Ratio of discordant pairs: (+ −)/(− +).

† Includes only mothers who smoked prior to the index pregnancy; non-smokers are excluded.

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86.3	78.2
13.7	21.8
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60.3	51.3
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8.2	8.0
30.1	20.5
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19.2	21.4
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number of siblings was the same in the brain tumor group and the two control groups. In addition, seven of the children with brain tumors and one child in each of the two control groups had a history of epilepsy themselves, and two of the mothers in the brain tumor group and none in either of the control groups reported having had epilepsy themselves.

It was also of interest that three of the mothers of children with brain tumors had had a stroke relatively early in life, while none of the mothers in either of the control groups had had a stroke. There were no major differences between patients and controls with regard to family history of congenital disorders or cancer.

Possible hormonal factors

A possible role for hormonal factors in the etiology of brain tumors in children was examined from several different perspectives in the present study. First, mothers were asked at what ages they reached menarche. Mean age at menarche did not differ significantly between mothers of cases and mothers of children in either control group. However, as shown in table 2, there was a tendency for mothers of children with brain tumors to have been younger (under age 12: matched pairs odds ratio = 2.2, $p = 0.14$) or older (over age 15: odds ratio = 2.2, $p = 0.27$) than mothers of normal children at the time of menarche. There were, however, no differences in this regard between mothers of cases and mothers of children with other cancers. In addition, mothers of children with brain tumors did not differ from mothers in either of two control groups with regard to use of oral contraceptives prior to the birth of the index child or use of other hormones during the pregnancy with the index child.

Chemical exposures

The present study attempted to investigate several types of exposures to chemical carcinogens which might play a role in the development of brain tumors. For some chemical exposures, such as occupational exposure of the parents, it was found that respondents often could not recall or were not aware of chemicals to which either they or the index child might have been exposed. No significant differences were observed between children with brain tumors and children in either of the two control groups with regard to occupational chemical exposures of their parents either prenatally or postnatally before diagnosis.

To determine whether children had been exposed to insecticides, parents were asked about exterminations in the household prior to diagnosis of the index child. Table 2 shows that more children with brain tumors than normal controls were reported to have had such exposures, with the odds ratio of 2.3 approaching statistical significance ($p = .10$). Children with brain tumors did not differ from children with other cancers with regard to such exposures.

Examination of the role of maternal smoking prior to the pregnancy with the index child yielded no differences between mothers of children with brain tumors and mothers in either of the two control groups. However, as indicated in table 2, there was a tendency for more of the mothers of children with brain tumors than mothers in either of the two control groups who smoked *prior* to the index pregnancy to have *continued* to smoke during the pregnancy, although the number of subjects involved was small.

Infectious agents

In view of the animal experiments in which brain tumors were produced using known animal oncogenic viruses, and since toxoplasmosis (which may be transmitted by animals) has been linked to brain tumors in humans, an attempt was made in the present study to determine if children with brain tumors had a

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Significantly more children with brain tumors than normal children were reported to have lived on farms and to have been exposed to farm animals early in childhood (odds ratio = 4.0, $p = 0.04$). However, children with brain tumors did not differ from cancer controls in this regard. In addition, more children with brain tumors than normal children were reported to have been exposed to sick pets in early childhood, with the odds ratio of 4.5 approaching statistical significance ($p = 0.07$). Again, no differences were observed between children with brain tumors and cancer controls in this regard.

Although there were no significant differences with regard to the children's prior history of infectious diseases, there was a tendency for *fewer* children with brain tumors than normal children to have had tonsillectomies prior to diagnosis, but the odds ratio of 0.62 was not statistically significant ($p = 0.33$). Children with brain tumors did not differ from children with other tumors with regard to history of tonsillectomy. Thus, for each of these variables, children with brain tumors and children with other cancers differed from normal children.

Discussion

The etiology of brain tumors in children is largely unknown (39) despite the relative importance of the disease in childhood in terms of its morbidity and mortality. The present study, therefore, was aimed at following up possible etiologic clues derived largely from animal experiments and from the few epidemiologic studies of brain tumors that have been conducted largely in adults. Since the distribution of histologic types of tumors in adults differs from those in children, it is possible that the etiologies of brain tumors occurring at different ages also might well differ. Thus, the present investigation was largely exploratory in nature and was directed to examination of possible etiologic factors only in *children* with brain tumors. Statistical differences have been reported for purposes of highlighting possible directions for future investigations, while recognizing the limitations of the sample size and the exploratory nature of this study. In addition, the failure to observe major differences between cases and cancer controls for most variables would suggest either that many high-risk factors for brain tumors are also risk factors for other cancers, or that selective recall bias of parents may have played a role in the observation of significant differences for some factors.

Birth characteristics

A tendency for more children with brain tumors than normal children to be first births was observed, a finding consistent with the findings of Choi et al. (40). This tendency could be due to parents limiting the size of their families following the birth of a child who developed a brain tumor. However, no significant differences in mean sibship size were observed between families of children with brain tumors and families of normal or cancer controls. The etiologic implications of a finding of lower birth order for children with brain tumors, however, are somewhat obscure, since it is difficult to suggest a causal mechanism or mechanisms that a first birth might activate to produce a tumor. One possibility is that the increased risk associated with low birth order may primarily be an association with young maternal age. Previous studies have demonstrated a tendency for mothers of children with brain tumors to be either younger (40) or older (41) than mothers of normal children. The present study, however, demonstrated no tendencies toward differences in maternal age in either direction.

It is of interest that, in contrast to previous studies (39, 40), the brain tumor patients tended to be of higher birth weight

than normal children. This is particularly noteworthy since the children with brain tumors tended to have lower birth orders than normal children, and first births generally tend to be of *lower* birth weight than subsequent births (42). Though we cannot be certain of the etiologic implications of higher birth weights in children with brain tumors, an intriguing possibility is that the higher birth weights may reflect a general tendency in the children with brain tumors (as well as children with other cancers) toward increased cellular division and growth. The rate of growth of an individual is primarily determined by the rate of cellular divisions, and, therefore, by the number of cells (43). Thus, large babies may have greater numbers of cells and increased rates of cellular division, both of which conditions could make them more vulnerable to carcinogenic agents. If this hypothesis is true, the fact that most cell division and growth in the brain is largely completed by the sixth postnatal month (44) would suggest that such agents would have to act during prenatal life or early in infancy to manifest a carcinogenic effect in childhood.

Family history of neurologic disorders

The results of this study suggest that there is a higher frequency of neurologic disorders, such as epilepsy or stroke, in first-degree relatives of children with brain tumors than in relatives of children without malignancies. Previously, evidence for familial aggregation was derived largely from case reports. Anecdotal reports of familial aggregation, however, have several limitations for drawing etiologic inferences. First, unusual instances of more than one member of a family having cancer tend to attract the attention of physicians and are thus more likely to be reported in the literature. In addition, such anecdotal reports usually do not explore the possibility that such occurrences might well be expected on the basis of chance alone.

The increased frequency of epilepsy observed in siblings of children with brain tumors compared to siblings of normal controls might also be a chance phenomenon or could be due to a selective recall, since parents of seriously ill children may have a greater tendency than parents of normal children to report such disorders in their children. The findings of the present study also could be consistent with several other interpretations. First, there may be a tendency for families of children with brain tumors to have a common underlying developmental defect or to have defects of the central nervous system or of blood vessels in the brain, which may ultimately lead to the development of stroke, epilepsy or brain tumors. Such a tendency could be either genetically or environmentally determined. A second possibility is that, since epilepsy increases the permeability of the blood brain barrier at the focus of the seizure (44), epilepsy may increase the child's risk of developing a brain tumor by making the brain more vulnerable to blood-borne carcinogens. This could also explain the observation that some of the children with brain tumors themselves had epilepsy many years before their brain tumors were diagnosed. It is also possible, however, that the epilepsy could have been a very early symptom of a subclinical, and, therefore, still undiagnosed brain tumor.

The findings of this study thus suggest that there may be a familial tendency to develop central nervous system disorders such as epilepsy and brain tumors. The relative contributions of genetic and familial environmental factors to this aggregation remain to be investigated.

Religion

Association of a given disease with a particular religious affiliation may be suggestive either of environmental or genetic factors. In the present study,

fewer of the children with brain tumors tended to be Jewish, compared to normal children or children with other cancers, although the numbers of cases involved are very small. This finding, however, is in contradiction to studies in *adults* with brain tumors, particularly gliomas, which showed increased mortality rates in Jews (45, 46). This discrepancy points out the need to carry out studies of the etiology of brain tumors in children separately from studies of brain tumors of adults, since the same causal factors may not be operative in different age groups.

Hormonal factors

The results of the present study also suggest a possible role for hormonal factors in the etiology of brain tumors in children. Though mothers of children with brain tumors showed no differences from mothers in either control group with regard to use of oral contraceptives or other exogenous hormones, two lines of evidence suggest an etiologic role for hormones. First, a reversal of the male-female ratio of incidence rates from greater than one under age ten years to less than one at the age of puberty has been documented previously (1, 2). Second, mothers of children with brain tumors reported reaching menarche at either younger or older ages than mothers in either control group. These findings suggest that if hormonal factors are in fact involved in the etiology of brain tumors in children, endogenous rather than exogenous hormones may be implicated.

Chemical carcinogens

Regarding chemical carcinogenic exposures that the children may have had, the findings remain inconclusive. There was a marked tendency for more children with brain tumors to have had exposures to insecticides when compared to normal children, but no such differences were observed when the comparison was made to children with other cancers. The finding that exposure to insecticides is greater in both children with brain tumors and cancer controls than in normal children may be suggestive of selective recall on the part of parents of seriously ill children in an attempt to somehow explain their childrens' illnesses. However, it is also possible that insecticides may contain nonspecific chemical carcinogens which may induce not only brain tumors in children but cancers in general. Further information regarding particular insecticide agents would be of interest in this regard. In addition, data from the present study showed a tendency for mothers of children with brain tumors who smoked prior to the index pregnancy to continue to smoke during the pregnancy, although frequency of maternal smoking during pregnancy did not differ significantly between cases and controls. The tendency of increased exposures to carcinogens in cigarette smoke during pregnancy may be suggestive of a transplacental carcinogenic effect, which would tend to support the findings from animal studies with regard to maternal exposure to the chemical carcinogens in cigarette smoke during pregnancy.

Infectious factors

Regarding a possible infectious disease etiology of brain tumors, several observations were of interest. First, the possible etiologic role of animal viruses in the development of brain tumors or other cancers in children also was suggested in the present study by the reported increased exposure of children with brain tumors and of cancer controls to farm animals and sick pets. These findings are also consistent with those made for leukemia in previous investigations (47, 48). Consistent with previous findings (49), patients with brain tumors were found to have had a tendency toward fewer tonsillectomies than normal controls. Cassimos et al. (49) have postulated "that tonsils sometimes

favor the development of neoplasms by acting as a gateway for carcinogenic substances, viruses, etc., or by helping in some way to enforce the body's response to antigenic stimuli, some of which contribute to the development of cancer."

Conclusion

In summary, several intriguing observations have been made with regard to possible etiologic factors associated with brain tumors in children. We have observed that there is an increased tendency for children with brain tumors to be first births and to have had higher birth weights than normal children. The previously reported reversal in the sex ratio at puberty and differences between patients with brain tumors and normal controls in maternal age at menarche in the present study suggest a role for hormonal factors. An important role for environmental factors is also suggested with regard to both chemical carcinogens—particularly those in insecticides—and oncogenic viruses, from the excess of children with brain tumors exposed to farm animals or sick pets and from the observation of fewer tonsillectomies in the patients with brain tumors. Thus, the results of this exploratory study indicate specific directions and hypotheses which need to be explored further in future epidemiologic investigations of brain tumors in children.

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