

Potential risk factors for brain tumors in children*

An analysis of 200 cases

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Abstract. Two hundred cases of verified brain tumors occurring in patients under 15 years of age were studied in relation to possible etiologic, genetic, and environmental risk factors. They were compared with 100 age-matched patients harboring solid neoplasms outside the nervous system, as well as with 100 normal children. In our study, first-degree relatives of a brain tumor child did not show a higher incidence of either tumors or of epilepsy and strokes as compared with controls. First-born children (46%) with higher birth weights showed a greater tendency to present brain tumors. Dystocia (18.5%), previous miscarriages (18%), and dietary restrictions during pregnancy (3%) were also noted in this study and compared with data in the literature. No evidence of a role of maternal chickenpox and toxoplasmosis could be found. The pharmacological risk also seemed to be minimal. The mother's hormonal profile is deduced from the age at menarche and delivery, as well as from a tendency to miscarriages and complicated pregnancies. With regard to the immunologic aspect, it is worth noting that 15% of the mothers complained of allergies. Live polio vaccine and zoonosis might suggest a possible role of virus-related factors in the oncogenesis of brain tumors in children. Radiation-related risk is possibly present in less than 5% of cases. Parental occupation is not relevant in this series.

Key words: Child – Brain tumors – Risk factors

Epidemiology is a recently greatly developing science that has only since the 1970s dealt with pediatric oncology of the nervous system. This mainly means the work of Choi et al. [9, 10], Farwell et al. [12–15], Gold et al. [16–18], and Preston-Martin et al. [36]. The reasons for this delayed interest are easily identified: primary intracranial tumors are rare in the developmental age (24 each year per million children under 15 years of age [9]; therefore, 100,000 subjects have to be studied in order to encounter two brain tumors). Never-

theless, infancy tumor studies may significantly contribute to the investigation of carcinogenesis even more than corresponding neoplasms in adults because (1) the intervals of exposure to carcinogens are supposed to be shorter and, therefore, easier to define, and (2) neoplastic transformation time may be correlated back to embryogenetic stages. The contribution of these recent epidemiologic studies to the etiologic problem of infantile intracranial tumors is impressive, as is the effort to identify etiologic factors of genetic and environmental risk.

Clinical material and methods

Our work is based on the study of 200 children (group A) bearing a primitive intracranial neoplasm. They were all histologically verified. The relatives and/or the family doctor were interviewed by means of a questionnaire, involving strict, preformulated questions and precoded answers. One hundred children of the same age, but bearing a solid tumor outside the CNS (group B), and 100 children hospitalized for nonneoplastic illnesses in the Pediatric Clinic of the same medical center (group C) were used as control groups.

Results

Genetic risk

CNS tumors are not hereditary but they could theoretically be an element of inherited syndromes with or without known chromosomal alterations (Table 1). Occasionally intracranial tumors are found in two or more family members. These "familial tumors" are usually limited to one or two generations [8, 12, 27]. "Sporadic" familial tumors are rare and do not prevail in any age. We are aware of 49 familial tumors in children, 35% of the total 138 cases collected from the literature (this frequency was double the normal frequency of tumors in infancy).

Three-quarters of the familial tumors affected brothers and twins. The distribution of the histologic types follows the characteristics of this age group, with predominance of astrocytomas and medulloblastomas. Cerebral tumor as a second malignancy [13, 29, 32, 37] was diagnosed in two

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patients (incidence 1%), both treated with radiotherapy for the first neoplasm. Oncotypes of family members are concordant in 3/4 of the cases (Table 2). Analogy of oncotypes is found in twins, siblings, and parents/children with the same frequency. In two instances, three members of a single family harbored the same oncotype. In another case two twins had a GH-secreting adenoma. Familial tumors show features similar to the corresponding sporadic ones, except for the anticipated age at the time of clinical onset. In Table 3 the familial cases of our series are grouped.

Analysis of our series does not confirm findings reported in the literature [10, 12, 27, 33, 44] that first-degree relatives of patients suffering from brain tumor during infancy will develop other infantile tumors, CNS tumors, or leukemias (Table 4). As far as other neurologic (nonneoplastic) diseases are concerned, a higher incidence of epilepsy and juvenile stroke in first-degree relatives of a brain tumor child was not confirmed.

Environmental risk (phenotypic)

The more frequent occurrence of infantile intracranial tumors in the first-born child reported in the literature [9, 17, 32] is the same as in our experience [42]. This becomes even more evident if we consider only the gliomas (51.5% in first-born children), while in the case of craniopharyngiomas the difference is negligible and for ependymomas the second-born child appears to be the most frequently affected (50% of second-born children vs 33.5% of the total and 24.6% of the control cases).

With regard to the age at menarche and delivery of a mother of a child destined to suffer a brain tumor, no definite information exists. The increased risk for mothers under 20 years of age or over 35 is not confirmed either in our study [42] or in others [17, 27, 40]. The occurrence of previous miscarriages and dystocia at the patient's birth was also considered. We extended our study to include the normality/abnormality of the pertinent pregnancy. The resulting data do not differ substantially from those obtained in the control groups. However, it is worth remarking that 37.5% of ependymomas are preceded by miscarriages as compared with 18% of other brain tumors. Furthermore, children destined to develop posterior fossa tumors (astrocytoma and medulloblastoma) show a slightly greater percentage of dystocia than those of the overall series of primary CNS tumors. Initially, this led us to suspect that dystocia had a considerable correlation with infratentorial anatomic structures, but this hypothesis was soon abandoned when we found a similar incidence of dystocia in the control group.

As for the pharmacologic risk in pregnancy, we mention the surprising coincidence of two females bearing a posterior fossa pilocytic astrocytoma whose mothers took bendedictin (Dependox, Merrill Dow), an antiemetic drug, during the pregnancy. The use of barbiturates, phenytoin or contraceptives during or before pregnancy did not determine differences between the examined groups. Tonsillectomy was present in the history with a comparable incidence in all groups.

Table 1. Inherited syndromes associated with infantile CNS tumors

Phakomatoses
Turcot syndrome
Wiskott-Aldrich syndrome
Louis-Barr syndrome
Recklinghausen
Bourneville
Nevoid basal-cell syndrome

Table 2. Histologic concordance in familial infantile CNS tumors

	No.	Percentage
Concordant ^a tumors	37	75.5
Discordant ^b tumors	12	24.5

^a Concordant: both the child and the other member of the family affected bear histologically analogous CNS tumors

^b Discordant: CNS tumors affecting the child and the other member of the family belong to different histological types

Table 3. CNS familial tumors (personal series)

Brothers	Male, 7 years, brain-stem glioma Male, 12 years, pineal teratoma
Cousin	Female, 14 years, III ventricle glioma
Aunt	Female, 48 years, Rolandic astrocytoma
Cousin	Female, 7 years, cerebellar astrocytoma
Aunt	Female, 49 years, ventricular meningioma

Table 4. Incidence of CNS pathology in first-degree relatives (%)

	Group A	Group B	Group C
Tumors	3.5	3.0	1.0
Juvenile stroke	2.5	3.0	3.0
Epilepsy	3.5	4.0	6.0

As for the immunologic aspect, it is worth noting that 15% of the mothers complained of allergies (Table 5).

Virus-related risk factors in the oncogenesis of brain tumors in children may be suggested by vaccinations (no meaningful data emerged from the analysis of our questionnaire) and zoonosis (patients living in rural areas and/or being exposed to sick pets) [17, 27]. No positively relevant data were found in our series (Table 6).

Parental occupation, often reported as a possible risk factor of infantile intracranial tumor [18, 23, 24, 26, 34, 35, 38], does not appear relevant in this series, even though parents working with chemicals and paintings are slightly more prevalent. A diet based on canned food or prolonged exposure to incense by the parents have also been correlated with the incidence of CNS tumors in children [19], but no positive correlation could be made from the answers in the submitted questionnaire.

Table 5. Immunologic aspects (%)

	Asthma ^a	Allergy ^b
Group A	4.5	15.0
Group B	8.0	27.0
Group C	14.0	35.0

^a Child^b Mother**Table 6.** Zoonosis (%)

	Country	Domestic animals
Group A	15	30.5
Group B	22	34.0
Group C	8	22.0

Discussion

Little is known about risk factors in animal and human neurooncogenesis. Most of the epidemiologic studies, which may greatly contribute to this knowledge, have been adult-oriented. The aim of the present work was to suggest to the epidemiologist, planning a prospective study, some possible targets of investigation and to extrapolate as much as possible from the data accumulated in more than 30 years of experience with childhood CNS tumors [42], by means of a cross-match with the available data in the pertinent literature. Research on neurooncogenesis may gain more from studying childhood than adult tumors in that the interval of neoplastic transformation is shorter and may be easier to define, even in light of embryogenesis.

We examined risk factors of pediatric carcinogenesis belonging to two categories: genetic and environmental. This is in accordance with the existing epidemiologic studies on the subject [4, 7, 10, 17, 27, 39]. Genetics has demonstrated the association of CNS tumors with chromosomal abnormalities, phakomatosis, or other inherited pathology [3, 6, 21, 27]. Moreover, many studies have investigated familial CNS tumors or the coexistence of other neoplastic illnesses in a child bearing an intracranial tumor [8, 12, 27].

The histologic concordance in familial CNS tumors, as reported in the literature, is suggestive, although it merits confirmation. In our opinion these studies strongly encourage investigations aiming to identify oncogenes, or other inherited material, which may facilitate neoplastic transformation [33, 43]. Nevertheless, our findings diverge from the literature if we analyze the incidence either of tumors or nonneoplastic diseases of the CNS in first-degree relatives [10, 12, 27, 33, 43]. The reported increased susceptibility of close members of the family of a child with an intracranial neoplasm to tumors in or outside the nervous system, or to stroke or epilepsy may be another aspect to be confirmed regarding genetic- and environment-related neuropathology [17]. Circulatory anomalies may facilitate neoplasias by the action of increasing the vulnerability of nervous tissue to carcinogens.

The problem of a "second malignancy" only recently became apparent clinically. It is reported to have an incidence for all ages between 2% and 11% [13, 29, 32, 37]. Diagnosis in infancy becomes even more difficult because of the relative rarity of malignant solid tumors and the limited number of long-term survivors. In spite of this, the association leukemia-lymphoma appears most frequently in reports on second malignancy [37].

Specific responsibility has been claimed in epidemiologic studies regarding environmental factors [16–18, 39] correlating, to a statistically significant degree, with an increased incidence of infantile tumors. First-born children are reported to be more frequently affected by intracranial tumors [9, 17, 31, 42], especially if the birth weight is greater than the normal range (which is unusual and suggestive, since first-born children usually weigh less at birth). Our series confirms these findings, but the analysis for each oncotype shows that ependymomas are more likely to develop in second-born children. This prevalence of first-born children in this series, as in the literature, is not due to a decision by the parents to limit new births after the first, threatening experience: families with an equal number of members were compared. The etiologic implication of these data is obscure and may be correlated with the younger age of the mother and to dystocia.

Neither in our study nor in the majority of others [17, 27, 40] did the mother's age at the time of delivery influence the development of a CNS tumor in the child. Analogous results were found analyzing the mother's age at menarche as an indicator of hormonal status which may be related to tumor development in the child [2]. Analysis of the incidence of miscarriages, dystocia, and complicated pregnancy [10], as compared with our series, emphasized that the specific histologic type of the neoplasm may have been preceded by these events: ependymomas were preceded by miscarriages in 40% of the cases and medulloblastomas and cerebellar astrocytoma in 25%, suggesting hormonal imbalance to be a possible cofactor of carcinogenesis [2, 44].

An extensive discussion about the pharmacologic risks in pregnancy is out of place here, but unpublished data collected by us and others suggest that retrospective investigations on this subject should be of great value. It is noted that bendectin has never been demonstrated to have teratogenic characteristics. There are indications that children exposed during fetal life to barbiturates may have a higher incidence of intracranial tumors [16, 20]. The use of an antiepileptic agent (phenytoin) alone or in association with barbiturates during pregnancy has also been correlated with the incidence of infantile CNS tumors [30]. These drugs, potentially teratogenic during pregnancy, may have an oncogenic effect acting in different fetal ages: in particular beginning with the 8th week, which is later than the critical period of organogenesis.

Maternal use of contraceptives or hormonal substances, whose oncogenic effect has been proven outside the CNS [41], have been suspected only in one instance [44] to have a relationship with intracranial tumor development in the pediatric age. This is based on the fact that, since steroid

receptors have been demonstrated on the cell surface of CNS tumors, any hormonal imbalance or stimulus may act on oncogenes through these receptors. Viral oncogenesis has been investigated directly, as related to maternal viral diseases during pregnancy [22]. A potential risk for the child to develop a medulloblastoma has been suggested after rubella infection in the mother [5].

Vaccination of pregnant women against poliovirus determined a significant increase in the incidence of medulloblastomas in the child, when a fatal contamination with SV40 virus occurred [14]. Intracerebral inoculation of the latter in newborn hamsters is known to induce ependymomas [25]. Nevertheless, schoolchildren vaccinated with the same contaminated virus did not show an increased rate of neoplastic diseases, an indirect confirmation that oncogenic power is often age-specific.

Gold et al. [17] reported that children suffering intracranial tumors have less frequently been submitted to tonsilectomy surgery.

There are reports that many children harboring an intracranial tumor live, or used to live, in rural areas [9, 11, 17]. This was considered in relationship with close contact with pets or farm animals bearing oncogenic viruses (zoonosis). We could not confirm this relationship.

A possible correlation was also examined between occupation of parents and incidence of infantile CNS tumors. This is a qualitative feature: it is very difficult to quantify [18, 23, 24, 26, 34, 35, 38]. In fact, each activity implies variable exposure time, means of protection, and general and personal hygiene. However, some substances have been suspected as specific CNS carcinogens such as paper and pulp-mill [26], paintings and solvents [1, 36] and unidentified substances in use in farms and aircraft industries [35]. The father's occupation seems to be mentioned more frequently in the literature as having an influence on the chances of a child to develop a CNS tumor. The data are only little more than anecdotal. Nothing definite can be deduced from our cases.

In conclusion, preliminary studies, carefully planned by epidemiologists, may disclose new perspectives on experimental and clinical research in the field of neurooncogenesis of the developing ages.

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