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Original Research Article

Analyze of the Risk Factors to the Development of the Brain Tumors

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ABSTRACT

Several diseases and medical treatments are discussed as risk factors for the development of brain tumors, including infections, allergy, alterations of immune system, cranial trauma, hormonal factors, epilepsy, cancer family history, etc.

Different occupations and exposure to certain substances are continuously considered as risks for brain tumors. Lower incidence of brain tumors makes it difficult to resolve the debate on the role of environmental triggers in their development. A total 1883 patients with brain tumors are registered from 1993 -2013, 977 (49%) of them were interviewed to review the analysis of risk factors, during the period December 2010-December 2013. We have failed to find a potential correlation between infections and brain tumors, only 2 cases was speculated or rather coexistence between JC virus and cerebral tumors. Regarding allergies by comparing the data of 176 patients with glioma, 134 with meningioma and 53 control subjects, we confirmed that subjects with whatever allergies story (eczema, asthma, etc.) have less risk to be affected by glioma (OR = 0.6 , 96%, 0.5-0.8), but no change for meningioma. In our study we did not found a significant correlation between trauma and brain tumor, while family history was useful in detecting tumors with secondary or metastatic nature, this occurred in 84 patients. Hormonal factors increase the risk for glioma in female, and we determine that the data between epilepsy and tumors are problematic according to the correlation between them. We could not find a correlation between the effects the environmental factors such as domestic, electromagnetic field, but is confirmed that residential exposure may be an important factor in inducing tumors especially in the age of childhood.

Our results showed that the risk occupations such as agricultural pesticides or other chemicals have a relatively increased risk for brain tumors; we have failed to confirm the use of mobile as risk factors. The role of medical factors in development of brain tumors is important for some of them, especially hormonal factors, cranial trauma, family history and is without effect specially in allergy, epilepsy, infections. The role of exposure to radiation, chemicals, radiofrequency is unclear, although this is limited by the number of patients included in our study

Keywords: brain tumors, risk factors, nervous system

INTRODUCTION

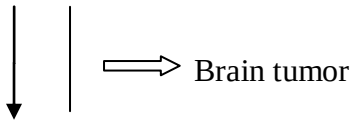
Tumors of the Central Nervous System (CNS) are a heterogeneous group of neoplasms which include all the primary neoplasms or secondary ones developed within the cranial -vertebral cavity. Tumors of the Central Nervous System (CNS) are estimated to be approximately 2% of all the new cancers and the same percentage are reported in European and Non-European population. [1-3]

Tumors are very heterogeneous from the histology view. In the present literature exists a debate on the nature and specificity of the risk factors to the development of the brain tumors. There is a classical hypothesis

of interaction of the extrinsic factors (environmental and medical) and the intrinsic genetic ones.

Classic hypothesis

Genes
(intrinsic)



Environment
(extrinsic)

Sketch nr 1. Classical hypothesis of the development of the tumors of neuro-epitelial tissue (glioma)

Risk factors are divided into *non-modified* factors and *modified* factors.
Non-modified factors we can mention: the age, sex, and relatively the genetics.
Modified risk factors medical history, allergy, environmental agents, smoking…

METHODS

From the 1993 up to 2013 we have registered a total number of tumors of Central Nervous System (CNS) of 1883 cases. Data from 1993 up to 2010 are taken by the register of pathological examinations in both services, Neurosurgery and Pathological – Anatomy. The risk factors were interviewed and analyzed in 977 patients (49%), during the period December 2010 – December 2013.

The statistical analyze was conducted by Dr. Kaloshi G using the software LMP 11 (SAS company). We used OR-exposure odds ratios and IC- 95% confidence interval to determine if the risk factors have an increasing risk to develop brain tumors. The unconditioned logistic regression includes variables as age and sex. Other processing has been needed in order to calculate the potential "confounding".

RESULTS

Risk factors are divided into *non-modified* factors and *modified* factors.

As non-modified factors we can mention: the age, sex, and relatively the genetics.

Age

Age is the main factor in the determination of the incidence and prognosis of the tumors of CNS. The incidence of the tumors seems to present a close relation with patient's age, based on the fact that different tumors have a higher incidence to certain age groups (look at the below table 1)

Table 1 Age group Incidence	
0-4	0.2
05=09	0.8
10=14	1.8
15-19	2.9
20-24	3.4
25-29	3.7
30-34	4.2
35-39	5.8
40-44	7.4
45-49	8.8
50-54	9.2
55-59	10.4
60-64	14.5
65-69	18.9
70-74	16.4
75-79	15.8
80+	12.7

Sex

Sex represents an important risk factor mainly for two types of tumors of CNS, gliomas or neuro-epiteliale tumors and meningiomas where we notice a dominance of males for gliomas and "an exlusive" dominance of females for meningiomas.

Tab 2 Standardized incidence (in x 100.000) according the age group and sex

Sex	Benign	Borderline	Malignant
Males	4	1.1	8.2
Females	7.2	1	6.4

Genetics

Cytogenetic and molecular studies have shown that some homogenous histological groups have common genetic characteristics e. g. GBM (glioblastoma) are carriers of 5-40%of them of EGFR-amplification, of TP53 mutation or PTEN. In astrocytoma, the TP53 is mutated in 30-

40% of tumor cells. Chromosomes 1p and 19q are delectated on 40-90% of the oligodendrogliales tumors. Chromosomes 22 is deleting on 25-50% of ependimoma. VHL is mutuated in 15% of hemangioblastoma. NF2 is delectated or mutuated in 40-50% of meningioma or schwanoma of the ponto-cerebellar angle.

In cooperation with the pathological services in Paris (the group of Prof. J-Y Delattre), in Rome (the group of Prof. Giangaspero F.) and in London (Dr. Latifaj B) we achieved to have our own molecular, imunohistological or genetical data.

Thus:

- deleting of 1p/19q is verified in 19/19 of histological suspected oligodendrogliomas
- TP53 is found mutated in over 150 astrocytomas of the II-III and in over 200 glioblastomas
- EGFR is found amplified in an exclusively manner only in glioblastomas.
- IDH-1, a marker of an early cell differentiation is found in 97% of cases in the gliomas of lower grade and 35 in GBM, while it is absent in 20% in pylocitic astrocitomas and in 80% in GBM *de novo*.

These data confirm that in our series the same progenitor cells if they are subject to certain genetic alternations they can differentiate into tumors with different genetic, phenotype and prognostic characteristics.

Hereditary syndromes

As we explained at the beginning some genetic alterations may be in the composition of hereditary genetic syndromes for the development of different brain tumors.

In our database we were able to reveal the existence of:

- syndromes NF1 in 28 subjects, predisposed for pylocitic astrocitomas, glioma of the optic nerve
- NF2 syndromes in 12 patients, for bilateral vestibular neurinoma (schwannoma)
- Tuberous sclerosis in 8 patients, predisposed for SEGA or epilepsy
- VHL in 3 subjects with cerebellar hemangioblastomas and polycythemia adjacent
- Syndromes Li-Fraumen in 1 patient with mamaes cancer and Ependymoma

Family history

The family history was useful for revealing the tumors of the CNS with a secondary or metastatic nature and this happened in 84 patients.

As modified risk factors for the development of brain tumors are included medical and enviromental risk factors

Even many genetic and environment factors are studied and are still under study we do not have no identified any relevant factor for the development of the brain tumors.

Environmental causes might be:

Environmental

1. Exposure to poison substances
2. Some foods with niter
3. Smoking, alcohol
4. Oil, vinyl chloride
5. Air pollution, formal dehydration
6. Radiation
7. Mobile, radio, electromagnetics

The effect of medical factors to the development of tumros of CNS.

Medical Risk Factors – exposure over 2 years	
Infections	Conflicting results
Allergy	Low risk
Diabetes Mellitus	Without effect
Cranial Trauma	Poor effect
Hormonal Factors	menopause increase the risk (g
Schizophrenia, Depression, meningitis	Without effect
Epilepsy	problematic connection
Cancer family story	high risk

Allergies

An international study with 1178 gliomas, 331 meningiomas and 2493 individuals shows an inverse correlation between the allergic diseases and gliomas but not to meningiomas. [4,5]

In our study comparing the data for 176 patients with gliomas, 134 with meningiomas and 53 checked subjects we were able to confirm that subjects with any allergic history (eczema, asthma, allergic

from pollen or any other agent) they have less risks to be touched by gliomas (OR= 0.696%0.5-0.8) but there is no difference for meningiomas.

Radiation and mutagen sensitivity

Bondy et al [6] shows that the mutagen sensitivity of lymphocytes towards gamma radiation was closely linked with the risk for gliomas. In our study we failed to find informative data about any link between the gamma radiation or previous treatment with x-ray for any pathology and induction or risk of the development of a cerebral gliomas. On the other hand it is reported that the radiation with low dosage per tinea capitis to the children is accompanied with a high risk for benign or malignant brain tumors. [7,8] We have selected 5 families (most of them brothers from the same family) whose members are radiated in their childhood for tinea capitis and they are diagnosed and lately treated/operated for meningiomas. Meanwhile the number of radio-inducted meningiomas is increased with 7 patients treated for tumor cerebral pathology with a relatively benign ongoing.

Infections

Different types of viruses such as, retroviruses, pap viruses and adenoviruses cause tumors of CNS to lab animals. But despite some studies on inducted lymphomas from AIDS, the studies that show a potential role of the viruses in the neoplasms genesis of the brain they are very few.

In such direction we failed to find any information on this potential correlation. May be a role is played by the difficulty of the immune phenotype characterization of any type of recurrent infections.

Only in two cases we hypotheses a relation or a co-existence between JC viruses and cerebral tumors.

Trauma and head injuries

For a long time the head trauma are suspected as predisposing factors or risk for induction of some types of brain tumors. Epidemiological studies are tried to help and determine which types of tumors are related or not with those trauma. Different studies have shown the relation of traumas with gliomas [9] and meningiomas. [10] A great international study with 1178 gliomas, 330 meningiomas and 2236 controll group [11] shows that there is an additional risk for meningiomas to males with a previous trauma and 15-24 years latency, while the risk was very low or inexistent for meningiomas for females or gliomas in both sexes. We did not find any correlation between a trauma and a cerebral tumor, gliomas or meningiomas in our study.

Medicaments, different treatments, vitamins or diet.

None of these factors was accompanied with any minimal risk in the induction of tumors of the nervous system.

Exposure to chemicals

In our study we were able to find a correlation between the residential chemical exposure (prenatal or during childhood) mostly related with the air pollution (benzene, nitrogen dioxide) mostly in Elbasan and suburbs of Fier.

Another way of exposure to different chemical and industrial agents is the exposure in work or during the leisure time (glue, turpentine, manicure, wood, colors, and different sprays).

The job history is studied with the time of exposure (starting of the job and finishing date): less than 2 years, 2-10 and more than 10 years. When the individuals have worked in different job posts for the same deadline, in such a case we will take under consideration the last job position. As this exposure is a rare one in relation to the air, polluted waters exposure the number of the patients in this category was a small one 4 patients thus it was difficult for us to find any reliable correlation.

Use of mobiles and radiofrequencies

The concern on the effects of using a mobile have stimulated the medical communities to undertake different studies in analyzing any existed correlation between the use of mobiles and the additional risks for brain tumors.

There are some contradictory studies. Nevertheless there is something in common to these studies. All of them speak of a long time of exposure to radiofrequencies ready to enable such differences which can be followed with the development of brain tumor.

In our study the average duration of using a mobile varies less than 30 minutes per day up to 3 hours per day while the annual use is 8-9 years.

For this reason we evaluated the cumulative use of mobiles with hours/year (less than 4 hours/year, 4-36 hours/year) and over 36 hours/year). Lastly we failed to find a correlation between the use of mobile and induction of any brain tumor.

CONCLUSION

Several diseases and medical treatments are discussed as risk factors for the development of brain tumors, including infections, allergy, alterations of immune system, cranial trauma, hormonal factors, epilepsy, cancer family history, etc.

Different occupations and exposure to certain substances are continuously charged as risks for brain tumors. Lower incidence of brain tumors makes it difficult to resolve the debate on the role of environmental triggers in their development. We've failed to find a potential correlation between infections and brain tumors, only 2 cases was speculated or rather coexistence between JC virus and cerebral tumors. Regarding allergies by comparing the data of 176 patients with glioma, 134 with meningioma and 53 subjects of control, we confirmed that subjects with whatever allergies story (eczema, asthma, etc.) have less risk to be affected by glioma (OR = 0.6, 96%, 0.5-0.8), but no change for meningioma. We found in our study not a significant correlation between trauma and brain tumor, while family history was useful in detecting tumors with secondary or metastatic nature, this occurred in 84 patients in our study. Hormonal factors increase the risk for glioma in female, and we determine that the data between epilepsy and tumors are problematic. Among the environmental factors we could not find a link between the effects of domestic, electromagnetic field, but managed to confirm that residential exposure may be an important factor in inducing tumors especially in the age of childhood.

Our results showed that as the IARC report [12] the risk occupations such as agricultural pesticides or other chemicals have a relatively increased risk for brain tumors, we have failed to confirm the use of mobile as risk factors. The role of medical factors in development of brain tumors is important for some of them, especially hormonal factors, cranial trauma, family history and is without effect specially in allergy, epilepsy, infections. The role of exposure to radiation, chemicals, radiofrequency is unclear, although this is limited by the number of patients included in our study

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