Environmental causes of childhood brain tumours

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Summary

Brain tumours hitherto said to be rare in Africans are now known to be common. They cause considerable concern due to their relatively high morbidity, mortality and enormous cost of care, especially in the developing world. An understanding of the aetiology is particularly important in our region for planning strategies for effective prevention of brain tumours. This review endeavours to outline our current understanding of the aetiology of this disease.

Introduction

A brain tumour is one of the most devastating forms of human cancers. They cause considerable concern due to their relatively high morbidity, mortality and enormous cost of care especially in the developing world where the financial burden is carried by the poor patient and his or her relations.

Brain tumours are the second most common cancer in children, comprising about 20% of all paediatric malignancies, and the most common paediatric solid tumour. The different histological subtypes occur with different relative frequencies among children and adults. The most common tumours of childhood are astrocytic tumours and the primitive neuroectodermal tumors, of which the most common is medulloblastoma.

Brain tumours develop as a consequence of cellular genetic alterations that permit them to evade normal regulatory mechanisms and destruction by the immune system. These alterations may have an inherited or acquired (chemical, physical or biological neurocarcinogens) cause. Overall, only a very small proportion of brain tumours can be attributed to the effect of inherited predisposition. The various implicated and suspected environmental factors includes ionizing radiation, non-ionizing radiation, N-nitroso compounds, viral infections (JC virus, cytomegalovirus, Human immunodeficiency virus, SV-40, varicella-zoster, chicken pox), and head injury.

Ionizing radiation

Ionizing radiation in therapeutic doses is the only unequivocal acquired factor that has been identified for glial and meningeal neoplasms. Irradiation of the cranium, even at low doses, can increase the incidence of meningiomas by a factor of 10 and that of glial tumours by a factor of 3 to 7, with a latency period of 10 years to more than 20 years after exposure. The now discontinued low dose radiation treatment of tinea capitis and skin disorders in children increases the risk of brain tumours well into adulthood, as does radiotherapy for various childhood cancers and leukaemia. Survivors of the atomic bomb in Hiroshima have increased risks of meningioma in proportion to their level of exposure. In utero exposure to diagnostic radiation does not appear to significantly affect the developing foetus. Radiation doses associated with diagnostic X-rays are very small and probably pose minimal, if any, risk; but full mouth dental X-rays have been associated with meningiomas in a small number of studies.

Non-ionizing radiation

Radiofrequency (RF) signals, which fall within the microwave region of the electromagnetic spectrum, are emitted and received by mobile phone handsets. The energy levels of these waves are insufficient to damage or disrupt cellular DNA. The use of cellular telephones, exposure to high-tension wires, the use of hair dyes, head trauma, and dietary exposure to N-nitrosourea compounds or other nutritional factors have all been reported to increase the risk of brain tumours; however, the data are conflicting and unconvincing. When assessing the literature on this topic, interpretation of a small number of early studies from the USA and Sweden must be cautious. They were conducted on relatively small
populations, relating to a time when analogue phones predominated and they had relatively short follow up periods with some methodological shortcomings.

The epidemiological evidence for a causal association between cancer and RF energy is weak and limited. Animal studies have provided no consistent evidence that exposure to RF energy at non-thermal intensities causes or promotes cancer. Extensive in-vitro studies have found no consistent evidence of genotoxic potential and in vitro studies assessing the epigenetic potential of RF energy are quite limited. Recent data in humans do not support the hypothesis that the use of hand-held cellular telephones causes brain tumours, but they are not sufficient to evaluate the risks among long-term, heavy users and for potentially long induction periods.

Extremely low frequency magnetic fields (ELF-MF) of 50–60 Hz are used in domestic and industrial electricity supplies presenting a virtually ubiquitous exposure to the population, although levels of exposure do vary. The neurobiological basis for ELF-MF being involved in malignant transformation is not substantiated. It does not cause direct effect on disrupting cellular DNA or metabolic pathways. Overhead power cables and wiring configurations in houses affect the levels of exposure to ELF-MF in a domestic residence. Current evidence shows that at levels experienced by the general population no risk of brain tumours in children appears to be present.

N-alkyl-nitrosoureas

N-alkyl-nitrosoureas (Figure 1), a category of N-nitroso compound, is the most potent neurocarcinogens yet identified in experimental studies with laboratory animals. Ethyl and methyl nitrosourea are known transplacental carcinogens, particularly for brain tumours in rats. Their ability to cross the blood–brain barrier and their mutagenic potential makes them ideal candidates as initiators in the carcinogenic process.

Figure 1. General structure of N-Nitroso compounds

\[ R_1 \begin{array}{c} N-N=O \\ R_2 \end{array} \]

Humans are exposed to N-nitroso compounds through a variety of avenues, including water, vegetables, meat products, alcohol and tobacco; certain medications, cosmetics, are also sources of exposure. Vegetables and cured meats are major dietary sources. However, results of studies concerning N-nitroso compounds and brain tumours in humans are highly inconsistent.

Nitrosonornicotine has been found in unburned smoking tobacco. Tobacco smoke is a known carcinogen but most of its constituents do not pass the blood–brain barrier. Smoking does not appear to be strongly linked to brain tumours either in adults who smoke themselves or via maternal smoking in pregnancy.

Viral infections

Cytomegalovirus (CMV) infection has been described in association with malignant gliomas. But recent review by Lau et al did not suggest that CMV is significantly associated with brain tumours in humans. At a time it was also thought that live polio vaccines contaminated with SV40 might increase the risk of brain tumours, but the initial observations were not supported by more detailed studies. Examination of brain tumour tissue for evidence of a viral cause has shown the presence of different viral DNA sequences in a proportion of cases. However, the mechanisms of how a virus might initiate malignant transformation remain unknown and more work is needed to elucidate the role of viruses in causing brain tumours.

Although more than 25 million people in sub-Saharan Africa have human immunodeficiency virus infection, little is known regarding their cancer risk. Many cancers have been reported to be increased in patients with AIDS. But only in five of these is there sufficient consistent and strong for conclusion of definite increase in risk. These cancers are Kaposi sarcoma, non-Hodgkin lymphoma, squamous cell carcinoma of the conjunctiva, Hodgkin’s disease and childhood leomyosarcoma. The role of HIV and primary brain lymphoma is well documented.

In utero infections with influenza and chickenpox (varicella) have been cited as a risk factor but the case for this is weak. Significant inverse associations of adult glioma with history of chickenpox and immunoglobulin G antibodies to varicella-zoster virus have been reported. Some recent epidemiological work on a series of children from the north west of England diagnosed with brain tumours has shown geographical distributions, which are suggestive of an infectious aetiology for some of the tumour types. Clustering in time and space and seasonality of diagnosis suggest that infections may be risk factors. Okamoto et al study provides molecular evidence of the association between JC virus and the development of certain ependymomas and choroid plexus papillomas.
Other factors
A lack of association is seen for alcohol consumption, hair dyes, hair sprays and brain tumours. There is also no association between traumatic head injury and primary brain tumours.23.

Protective factors
Some reports indicate that consumption of fruits and vegetables and of vitamins C and E might protect against the occurrence of brain tumours.22,24. Atopic diseases such as asthma, eczema, and allergies have been said to be protective. Independent studies from different countries have suggested that atopic conditions have a "protective" possibility, particularly in the development of gliomas. Patients with gliomas report fewer symptoms of atopy compared to control subjects. This relation might indicate a role for immunologic factors in causation.

Conclusion
Relatively little is still known about the causes of most tumours of the brain. A small percentage of brain malignancies have been identified as having a genetic or familial component with a variety of environmental factors implicated to varying degrees. Ionizing radiation in therapeutic doses is the only unequivocal risk factor that has been identified for glial and meningeal neoplasms. The associations with exposure to various neurocarcinogens N-akyl-nitrosoureas, non-ionizing radiation, head trauma and infective agents are yet to be fully substantiated. Continued research into genetic, dietary, infectious and immune factors may clarify more on the aetiology of brain tumours.

References
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Only poverty reduction will curtail population growth

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The Ministry of Finance, Planning and Economic Development under the Population Secretariat has been reviewing the Uganda National Population Policy. I am pleased to have served as a Consultant in this exercise. The first Uganda Population Policy was developed and enacted in 1995 but since that time, a number of new issues and dispensions such as the Poverty Eradication Action Plan (PEAP) and Millennium Development Goals (MDGs) dictated the need for the review of the policy. The aim is to ensure that the Population Policy is consistent with the objectives and goals of the new dispensions. On Monday July 24, 2006, there was a National Consultative meeting held at Statistics House in Kampala and this meeting called for stakeholders to contribute to the review of the National Population Policy. Having traversed the whole country and assessed the socio-economic status of the local households, I was able to come up with the following findings:

1. There is still rampant poverty among the majority of households in Uganda. In our language of poverty reduction, about 38 out of every 100 people in Uganda live under absolute poverty. Literally, this means that these people are not sure of their source of their next meal!! These households are characterized by many children whom they are unable to adequately look after and to provide even the basic necessities such as food, clothes, health care and school fees. These households are living under total deprivation and impoverishment. Most of the children in these households are prone to diseases since these households can not afford quality health care.

2. The prospect of having mothers bearing a manageable number of children is still difficult to achieve. In many households I visited, children provide labour in agricultural activities including tendering for livestock and others are urged to help their parents run their small businesses. When asked about why parents were not enthusiastic about letting their children to go school, they argued that it was not rewarding as those that have completed schooling were not able to get jobs!! One parent asserted that he has sold his land to pay fees for his son but the son has never secured a job ever-since graduating from Makerere University in 2002. “So what is the purpose of educating children?” he retorted. From further interviews regarding child education, I found out that girls are viewed as source of wealth through payment of bride price. Many families did not find difficulty in terminating the girl’s education if suitors wanted to marry their daughter. This reminds me of a one Mr. Bafokorora hailing from Kabale district that married off her nine (9) year-old daughter and was boasting of the two (2) cows promised to him as bride wealth!! These cultural artefacts are indeed disastrous. There is no other explanation for marrying off a nine year old apart from abject poverty!!.

3. Increasing household income is a daunting task especially in the situation where 68% of the population in Uganda is fully engaged in subsistence farming with rudimentary methods. In all the districts I visited, it is apparent that without the practice of commercial farming, households engaged in agriculture can not significantly