

Etiology of brain and central nervous system cancer (C70–72) in Central and South America

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The etiology of brain and central nervous system (CNS) tumours is multifactorial and probably differs by tumour type and possibly according to the histology or cell type of origin. Although several risk factors have been studied extensively to provide evidence of their association with brain and CNS cancer, epidemiological research has been hindered by the rarity and diversity of these tumours [1]. Several occupations (physician, pathologist, anatomist, firefighter, and farmer) and occupational exposures (the use of plastics, rubber products, formaldehyde, vinyl chloride, arsenic, mercury, and petroleum products) have been inconsistently associated with the risk of brain and CNS tumours [2–4]. Numerous environmental agents are suspected of playing a role in the development of these tumours, but their possible etiologic role has not yet been elucidated. In this section, a brief review of selected risk factors is presented.

Ionizing radiation

Ionizing radiation (X-rays and gamma-rays) has been classified by the International Agency for Research on Cancer (IARC) as an agent with sufficient evidence of carcinogenicity in humans for cancers of the brain and CNS [5]. Therapeutic doses of ionizing irradiation have also been linked to an increased risk of brain and CNS tumours [1, 6–8]. The supporting evidence has mainly arisen from studies of children treated with low doses of ionizing radiation for tinea capitis (a fungal infection of the scalp) or skin haemangioma, and from patients treated with radiation for cancer or benign conditions [2–4]. For instance, children treated with radiation (mean dose of 1.5 Gy) for tinea capitis had 1.98 (95% confidence interval [CI], 0.73–4.69) times the risk of developing a malignant brain tumour 40 years after treatment than non-irradiated groups [9]. Children who received prophylactic CNS irradiation (cumulative dose of ~2500 cGy) for acute lymphoblastic leukaemia have been shown to have an increased risk of brain tumours, which may begin to appear 7–9 years after radiation therapy (as cited in [3]). In a cohort study of 9720 children who received radiation therapy (1800–2400 cGy) for acute lymphoblastic leukaemia in 1972–88, Neglia et al. [10] found that 56% (24/43) of the secondary neoplasms diagnosed during the follow-up (mean, 4.7 years) were of the CNS, representing a 22-fold excess of CNS neoplasms (gliomas and primitive neuroectodermal tumours).

In a recent systematic review of eight cohort studies (7 of therapeutic use and 1 of atomic bomb survivors), Braganza et al. [11] found that previous exposure to ionizing radiation was associated with an increased risk of all types of brain and CNS cancers. The excess relative risk per Gy (ERR/Gy) of all brain and CNS tumours after exposure to ionizing radiation ranged from 0.19 to 5.6. In a subsequent analysis of four of these studies, ionizing radiation had a greater effect for the risk of meningioma (ERR/Gy, 0.64–5.1) than that of glioma (ERR/Gy, 0.079–0.56).

Because of the increased use of diagnostic imaging worldwide, particularly computerized tomography scans of the head, the potential risk of cumulative exposures to ionizing radiation needs to be evaluated further [4]. Children are more sensitive to radiation-induced cancers and the development of studies in this vulnerable population is of particular interest. In Holland, the Dutch Paediatric CT Study, an ongoing national retrospective cohort study, aims to establish the risk of leukaemia and brain tumours in children after radiation exposure from computerized tomography scans [12].

Radiofrequency electromagnetic fields and mobile phones

Radiofrequency waves, which are electromagnetic fields (including those from wireless phones), have been classified as agents with limited evidence of carcinogenicity in humans [13]. Epidemiological studies on the relationship of mobile phones and brain tumours have been particularly difficult to conduct due to the absence of data on the long-term and frequency of use of mobile phones, as well as to decreasing levels of non-ionizing radiation from cell phones over time [7, 8]. Despite evidence indicating that an increased risk of some types of brain tumour is associated with the use of mobile phones [14, 15], associations have not been consistent, and the evidence remains inconclusive. The use of mobile phones was classified by IARC in 2011 as ‘possibly carcinogenic to humans’ [16]. A recent study conducted in the Nordic countries (Denmark, Finland, Norway, and Sweden) revealed that, although mobile phone use increased from 2% in 1980 to 79% in 2002, the incidence of gliomas remained almost constant between 1979 and 2008 in all countries (annual change of 0.4% in men and 0.3% in women) [17].

Occupational exposures

Farming and occupational exposure to pesticides are another factor that has been the object of several studies that ultimately yielded contradictory results and inconclusive evidence [18–20]. One study conducted in Rio de Janeiro, Brazil, showed an increased risk of mortality from CNS cancer in farm workers, which could be associated with exposure to pesticides [21].

In a recent meta-analysis of 21 studies (conducted mainly in Europe and North America), Van Maele-Fabry et al. [22] found that parental occupational exposure to pesticides was associated with a 30–50% increased risk of brain tumours in children and young adults (summary odds ratio [OR], 1.30; 95% CI, 1.11–1.53 in 16 case–control studies; summary rate ratio, 1.53; 95% CI, 1.20–1.95 in 5 cohort studies). They

also evaluated the effect of prenatal exposure windows, maternal or paternal exposure, and exposures by pesticide (all, insecticides, and fungicides) or by occupation (farming, agricultural occupation, and agricultural industry) and found an increased risk of brain tumours (range, 19–57%). These findings are of particular interest to the Central and South American region because agriculture is an important economic activity. Of the Latin American countries, 46% have been recognized as not providing information on pesticide use to the United Nations Food and Agriculture Organization and many of the pesticides that have been prohibited by the Pesticide Action Network continue to be used extensively in the region [23]. Within the countries that report pesticide use, Bolivia, Colombia, and Ecuador used between approximately 31 and 50 thousand tonnes of pesticides (insecticides, herbicides, fungicides, and bactericides) in 2013, which is much higher than that of other Latin American countries [23]. In contrast, Chile, Costa Rica, El Salvador, Guatemala, Peru, Nicaragua, and Uruguay used approximately 12–18 thousand tonnes of pesticides in 2013 [23]. The use of pesticides for agricultural purposes has been shown to have increased in the region [24, 25].

Allergies

Allergic conditions such as asthma, food allergies, and eczema have been found to be associated with a lower risk of certain types of brain tumours (1, 4, 7). A recent meta-analysis of 18 publications covering 20 studies (17 case–control and 3 cohort studies) that included almost 10 000 cases and approximately 120 000 controls revealed that allergic conditions (allergy, atopy, asthma, eczema, and hay fever) reduced the risk of glioma by 22% (summary OR, 0.78; 95% CI, 0.73–0.83) [26]. One limitation of this meta-analysis was that the allergies included were not defined by the detection of immunoglobulin E (IgE) levels in all studies.

Hereditary syndromes and familial aggregation

Rare genetic disorders, particularly hereditary syndromes associated with rare mutations of high penetrance, support the existence of inherited predispositions to CNS tumours. Such predispositions have been described among those with von Hippel-Lindau disease, Li-Fraumeni syndrome, tuberous sclerosis, neurofibromatosis type 1 and 2, and other syndromes related to adenomatous polyps [7, 27]. Neurofibromatosis type 1 or von Recklinghausen disease is the most common and is related to gliomas of the optic nerves and hamartomas, while neurofibromatosis type 2, an autosomal dominant disease, is characterized by the development of schwannomas, meningiomas, and ependymomas [28]. The latter has been studied in Argentina, providing useful information for genetic counselling [29]. Turcot's disease type 1 is associated with the development of astrocytomas [27].

Characteristics found in a large international study showed that most familial gliomas appeared to comprise clusters of two cases suggesting low penetrance with a low risk of developing additional gliomas [30]. Results on familial CNS tumours in five Nordic countries provided evidence of higher risks for spinal and peripheral nerve tumours than

for brain tumours which could partially be explained by syndromic cases in small families. The familial risk is clear in the early onset of brain tumours [31].

Other risk factors

Head injury or trauma, diets high in *N*-nitroso compounds, viral infections, and tobacco smoking have been related to increased risks in some studies, but no definitive association has been established to date [4, 7]. Most of the studies that explored the relationship between head trauma and glioma were case reports; a recent report by Han et al. [32] listed 22 case reports and included a brief review of the scientific literature. The role of retroviruses and herpesviruses, in particular human cytomegalovirus, in the genesis of brain tumours has been studied extensively but the mechanism has not been elucidated. Herpesviruses (and possibly other viruses) have been suggested to infect tumour and/or stroma cells in established tumours and therefore increase tumour malignancy (oncomodulation) [33].

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