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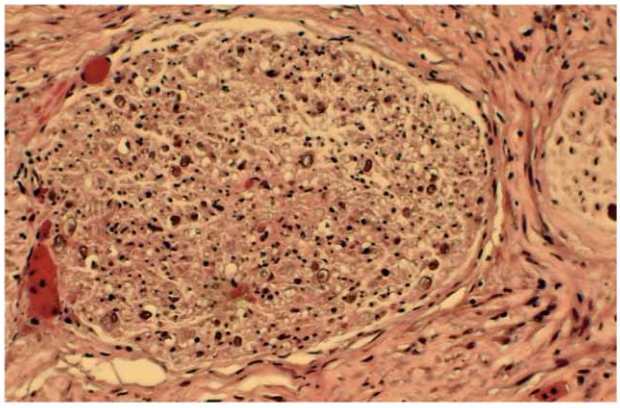

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Virology of Malignant Brain Tumours

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Abstract: Glioblastoma multiforme is the most common and most aggressive type of primary malignant brain tumour, accounting for 52 % of all primary brain tumour cases and 20 % of all intracranial tumours. Evidence for a viral cause of glioblastoma has been postulated, possibly SV40 or more likely cytomegalovirus (CMV). A viral cause is difficult to substantiate, since CMV infection is so common and malignant brain tumours are so rare. One possible basis for a CMV-glioblastoma association may be the "hit-and-run" hypothesis. CMV might be capable, under certain conditions, of acting as a cell mutagen. Age at infection may be one of these conditions, since the incidence of both glioblastoma multiforme and CMV infection are related to socioeconomic status. CMV infection in early childhood, more common in lower socioeconomic groups, may be protective against glioblastoma multiforme, whereas CMV infection in later childhood or adulthood may be a risk factor for glioblastoma. If so, glioblastoma occurrence would resemble paralytic polio, where low socioeconomic status, poor hygiene, and early infection are protective. **EANO Mag 2013; 3 (Pre-Publishing Online).**

Introduction

Glioblastoma multiforme is the most common and most aggressive type of primary malignant brain tumour, accounting for 52 % of all primary brain tumour cases and 20 % of all intracranial tumours [1]. The only effective chemotherapy is temodar [2]. Glioblastoma multiforme is more common in males and appears to be sporadic, without any genetic predisposition. No links have been found between glioblastoma multiforme and smoking or diet. The relation to cell phones is still uncertain [3]. An association between malignant brain tumour and malaria may indicate anopheles mosquito transmission of an etiologic agent, possibly a virus [4].

Cytomegalovirus (CMV) may be a risk factor [5–7], though the CMV-glioblastoma association is controversial [5]. CMV does transform normal cells into cancerous cells [8, 9], and has been implicated as a risk factor in cancers of the cervix [10], prostate [11], and colon [12]. In addition, CMV sequences and viral gene expression exist in most, if not all, malignant gliomas [13].

Risk Factors and Cancer

A risk factor and cancer can interact in 3 ways. The first is the simplest. When a rare form of cancer is associated with a rare exposure, the link between the risk and the cancer stands out clearly. The association can often be discerned accurately by observation alone. A striking example is scrotal cancer. In 1775, a London surgeon, Sir Percivall Pott, discovered that scrotal cancer was much more common in chimney sweeps than in the general population. The link between an unusual malignancy and an uncommon profession was so striking that Pott did not even need statistics to prove the association. Pott discovered one of the first clear links between an environmental carcinogen and a particular type of cancer [14].

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A more vexing situation occurs when a common exposure is associated with a common form of cancer. An example is tobacco smoking and lung cancer. In the mid-1920s, smoking was so common and lung cancer so prevalent that it was initially impossible to definitively identify a statistical link between the 2. No one knew whether the intersection of the 2 phenomena was causal or accidental, until smoking was later identified as a major cause of many cancers through careful clinical studies in the 1950s and 1960s [14].

The most complex intersection between a risk factor and cancer often occurs in the third instance, when a common exposure is associated with a rare form of cancer. This is cancer epidemiology's most difficult problem. Cell phones and brain tumours are one example. A second is the possible relationship of CMV to glioblastoma [14].

Problematic Cytomegalovirus Involvement

Cobbs et al reported that a high percentage of malignant gliomas are infected by CMV and multiple CMV gene products are expressed in these tumours [15]. Mitchell et al found that 80 % of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood, while seropositive normal donors and other surgical patients did not exhibit detectable virus [16]. Mitchell et al suggested an association of CMV with malignant gliomas and proposed that subclinical CMV viremia is a previously unrecognized manifestation of glioblastoma multiforme.

In our own studies, we have collected peripheral blood in anticoagulated tubes from 10 patients with newly diagnosed glioblastoma multiforme referred for radiation therapy [17]. We used standard methods for detecting CMV by reverse transcriptase-polymerase chain reaction (RT-PCR) [18] and peripheral blood culture [19]. None of our 10 patients had circulating CMV detected. Mitchell et al reported that 80 % of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood [16]. The chance of a single glioblastoma patient not having detectable cytomegalovirus would be 20 % or 0.2. Therefore, the chance of none of 10 patients having detectable cytomegalovirus would be 0.2^{10} or $p = 0.000000124$.

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Moreover, CMV seropositivity data and glioblastoma incidence data do not support a CMV-glioblastoma association, since CMV seroprevalence rates are not consistently related to glioblastoma incidence rates [20]. CMV seroprevalence is, however, related to socioeconomic status. CMV infection is significantly lower in whites than in blacks or Hispanics (Mexican Americans), while glioblastoma incidence is higher. CMV seroprevalence rates are significantly higher in women than men, although glioblastoma is more common in men. Therefore, a possible CMV-glioblastoma association cannot be readily substantiated with CMV seropositivity rates.

Possible Basis for CMV Involvement

One possible basis for a CMV-glioblastoma association is the "hit-and-run" hypothesis [21]. CMV might be capable, under certain conditions, of acting as a cell mutagen.

Age at infection may be one of these conditions, since the incidence of both glioblastoma multiforme and CMV infection are related to socioeconomic status, as described above. CMV infection in early childhood, more common in lower socioeconomic groups, may be protective against glioblastoma, whereas CMV infection in later childhood or adulthood may be a risk factor for glioblastoma. If so, glioblastoma occurrence would resemble paralytic polio, where low socioeconomic status, poor hygiene, and early infection are protective [22].

Conflict of Interest

None.

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