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Cytomegalovirus infection in early childhood may be protective against glioblastoma multiforme, while later infection is a risk factor

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ABSTRACT

Glioblastoma multiforme is the most common and most aggressive type of primary brain tumor, accounting for 52% of all primary brain tumor cases and 20% of all intracranial tumors. Recently, evidence for a viral cause has been postulated, possibly cytomegalovirus (CMV). In one report, 80% of patients with newly diagnosed glioblastoma multiforme had detectable cytomegalovirus DNA in their peripheral blood, while sero-positive normal donors and other surgical patients did not exhibit detectable virus. However, another study reported that five glioblastoma patients showed no circulating CMV detected either with RT-PCR or blood culture. But CMV could still be a factor in the genesis of glioblastoma multiforme, if age at infection is taken into account, since the incidence of both glioblastoma multiforme and CMV infection are inversely 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 multiforme occurrence would resemble paralytic polio, where low socioeconomic status, poor hygiene and early infection are protective.

Introduction

Glioblastoma multiforme is the most common and most aggressive type of primary brain tumor, accounting for 52% of all primary brain tumor cases and 20% of all intracranial tumors. Glioblastoma multiforme is more common in males and appears to be sporadic, without any genetic predisposition. No conclusive links have been found between glioblastoma multiforme and smoking, diet, cellular phones, or electromagnetic fields. Recently, evidence for a viral cause, cytomegalovirus (CMV), has been postulated [1].

CMV is one of eight human herpesviruses. CMV infects at least half of the population in developed countries, and nearly everyone in developing countries, where poor sanitation and poor hygiene abet its transmission. Although it generally does not cause problems in healthy adults, CMV is a common cause of birth defects, and it can cause a host of serious problems in immuno-compromised people, particularly AIDS patients, who often develop CMV chorioretinitis [2]. Moreover, increased CMV antibody levels are associated with impaired cognition, frailty, functional impairment, and increased mortality among community-dwelling older adults [3].

CMV, glioblastoma, age, and socioeconomic status

Cobbs et al. reported that a high percentage of malignant gliomas are infected by CMV and multiple CMV gene products are expressed in these tumors [4]. Mitchell et al. reported that 80% of patients with newly diagnosed glioblastoma multiforme have detectable cytomegalovirus DNA in their peripheral blood, while sero-positive normal donors and other surgical patients did not exhibit detectable virus [1]. Mitchell et al. suggested an association of CMV with malignant glioma and proposed that subclinical CMV viremia is a previously unrecognized manifestation of glioblastoma multiforme. However, Lehrer et al. reported that five glioblastoma patients showed no circulating CMV detected either with RT-PCR or blood culture [5].

Yet CMV could still be a factor in the genesis of glioblastoma multiforme if age at infection is taken into account; especially since the incidence of both glioblastoma multiforme and CMV infection are inversely related to socioeconomic status.

Data from cancer registries suggest that glioblastoma multiforme incidence is inversely proportional to socioeconomic status. The 2004–2007 age-adjusted incidence rate of glioma per 100,000 persons varied considerably by race (6.5 among whites, 3.3 among blacks) [6]. One study of glioblastoma multiforme demonstrated higher rates among persons residing in high socioeconomic areas, even after statistical adjustment for confounding factors [7]. A Swedish study reported increased odds of glioma among those with a higher family income adjusted for sex, age, and geographic region [8].

CMV sero-positivity is also inversely proportional to socioeconomic status. White et al. reported that prevalence of CMV antibody in subjects between the ages of 6 and 22 years was significantly lower in white than in nonwhite subjects. There was no increase in CMV prevalence with age in white subjects, but the percentage

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of individuals with antibody increased with age among nonwhite subjects [9]. In a study of primary cytomegalovirus infection in pregnancy in two income groups, Stagno et al. found that in the high-income group, 64.5% of the women were sero-negative for CMV infection. In the low-income group, only 23.4% of the women were sero-negative for CMV. Moreover, congenital CMV infections were more frequent in the low-income group.

Hypothesis: similarities of CMV infection and polio

If CMV infection at birth or in early childhood is in fact protective against glioblastoma multiforme, whereas CMV infection in later childhood or adulthood is a risk factor for glioblastoma multiforme, glioblastoma occurrence would resemble paralytic polio.

From ancient times until the late 1800s, polioviruses were endemic wherever crowding and poor sanitation existed. Infants were infected shortly after birth and exposed to all three serotypes of the poliovirus by early childhood. Sporadic cases of paralytic poliomyelitis occurred occasionally in infants (true *infantile paralysis*), although most infections were subclinical. This endemic pattern of activity still occurs in underdeveloped areas of the world, especially the tropics [10].

Improved personal and public hygiene in the late 1800s led to the severe epidemic form of poliomyelitis. Paralytic polio broke out in temperate zones and developed areas of the world. Less crowding and better sanitation reduced infant exposure and produced a growing pool of older children and adults susceptible to infection. When poliovirus infects a previously uninfected population, large epidemics occur with a high rate of paralysis, since newly infected adolescents and adults are prone to develop paralysis and die. Not only did the developed countries experience epidemics of poliomyelitis, but individuals of higher socioeconomic status had a greater risk of paralysis. Similarly, as conditions of sanitation and personal hygiene improve in underdeveloped areas of the world today, the incidence of poliomyelitis is increasing, and epidemics of paralytic polio are occurring [10].

Conclusion

Unlike the viral etiology of polio, the CMV-glioblastoma association is controversial. It is unclear why CMV, a common virus, would cause glioblastoma in only a small subset of those infected, especially since in vitro studies have failed to show that CMV transforms normal cells into cancerous cells.

Yet some preliminary results indicate valganciclovir (Valcyte (Roche)), an antiviral drug, may improve prognosis in glioblastoma patients, despite the questionable CMV association [2]. Valganciclovir is a pro-drug (an ester) of ganciclovir and is used to treat certain types of CMV infection (such as CMV retinitis in AIDS) and is also used clinically to prevent CMV infection in patients receiving solid organ transplants from CMV-positive donors [11].

Certainly, a possible CMV-glioblastoma multiforme association deserves further investigation.

Conflict of interest

I have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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