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Role of varicella zoster virus in glioma risk: Current knowledge and future directions

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Abstract

Introduction

The role of infections in brain tumorogenesis has long been in question. Varicella zoster virus (VZV) is a neurotropic alpha-herpesvirus that causes chicken pox among initial infection. It can then establish latency in the host's dorsal root ganglia and can reactivate later in life causing shingles as well as CNS-related complications. A few studies have been conducted to elucidate the role of VZV infection in glioma susceptibility, but several gaps in knowledge remain. This review presents a brief overview of current epidemiologic knowledge on the relationship between VZV and adult-onset brain tumours and highlights important future directions for continued research on this topic.

Conclusion

The literature is slowly approaching a consensus on the inverse association between VZV infection and immunity and glioma risk. However, several gaps in knowledge remain, and definitive conclusions cannot be drawn about this potentially complex relationship until the possible interactions between VZV immunity and atopy are clarified and the potential effects of the VZV vaccine are assessed.

Introduction

In the United States, the overall annual age-adjusted incidence of primary brain and CNS tumours is 27.4 per 100,000 among adults[1,2,3]. Despite the rarity of these tumours, the associated mortality is substantial. Median survival time varies by brain tumour type; however, the most aggressive type, glioblastoma, has a median survival of only 12-15 months. For the past several decades, a myriad of brain tumour risk factors have been examined, but most findings have been inconsistent. Exposure to high dose radiation, family history, and a few rare genetic syndromes (i.e., Li Fraumeni and neurofibromatosis) constitute the only established etiologic factors, but these account only for a small proportion of cases[1,4].

The role of infections in brain tumorogenesis has long been in question[2,5]. Viral involvement in the aetiologies of various other cancers, such as hepatocellular carcinoma, lymphomas, and cervical cancer, has been established[6,7], and an estimated 18% of cancers worldwide may be attributable to approximately 10 infectious agents[6]. With regard to the role of viruses in brain tumour aetiology, published findings have been mixed. Infections with polyomaviruses (e.g., simian virus 40, BK virus, JC virus) and herpes viruses (e.g., human cytomegalovirus, human herpes virus 6) have all been suspected to be associated with glioma risk[8,9,10,11] .

Polyomaviruses have consistently been isolated from CNS tumour tissues, and human cytomegalovirus proteins and DNA have been detected in tissue samples from malignant gliomas[9]. Human herpes virus 6 virions have also been detected in some paediatric and adult brain tumour tissues (8-37% prevalence range)[8,12,13].

Most of the aforementioned viruses have been shown to be associated with increased glioma risk. However, exposure to varicella zoster virus (VZV), which causes chicken pox and shingles, may be an exception, in that it tends to be associated with lower glioma risk (i.e., an inverse association)[10,14,15].

By contrast to its purported inverse association with glioma, VZV infection/reactivation has also been implicated in positive associations with other cancers. In 1955, Wyburn-Mason first suggested that herpes zoster may precede cancer diagnoses[16]. Since then, studies on the associations between shingles and risk for other cancers have yielded inconsistent results.

A Danish National Registry study including patients hospitalized with shingles between 1977 and 1996 showed a positive association with the risk of all cancer types (relative risk [RR]: 1.2; 95% CI: 1.1 – 1.2). However, this study did not include shingles cases diagnosed in outpatient settings; including only hospitalized shingles patients would select for the most severe cases, which only represent a small subset of all zoster cases[17].

More recently, Ho et al. reported a 9.25 times greater risk of cancer after herpes zoster opthalmicus utilizing information from the Health Insurance Research Database in Taiwan[18]. Another large recent study showed that the hazard ratio for cancer diagnosis after zoster was 2.42 (95% CI: 2.21 – 2.66). The highest hazard ratios were observed in younger patients, and the magnitude varied between different types of cancers. This increased risk was observed in all cancers and in both genders[19]. (Brain cancer was grouped with other eye and central nervous system cancers, and was not examined separately in this study). Nonetheless, other studies have failed to show an

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Critical review

increased risk for cancer following VZV reactivation[20,21]. Findings from studies of the impact of VZV on overall cancer risk are not necessarily generalizable to glioma for several reasons, including the differences between the systemic immune response compared to that of the brain and the effects of the blood-brain barrier on exposure permeability.

VZV is particularly interesting with regard to its potential role in gliomagenesis, as it establishes latency in the nervous system[22], and infection with this virus may indirectly influence the development of atopic disorders[23,24], which, in turn, are suspected to be associated with a decreased glioma risk[25,26,27].

A few studies have been conducted to elucidate the role of VZV infection in glioma susceptibility[10,15,28,29,30], but several gaps in knowledge remain. This review aims to briefly summarize current epidemiologic knowledge on the relationship between VZV and adult-onset brain tumours and to delineate important future directions that will be necessary for evaluating whether an etiologic link may exist.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Infection with VZV (or human herpes virus 3) and the subsequent development of chicken pox was an extremely common childhood ailment in the U.S., particularly prior to the licensing of the live attenuated vaccine in 1995[31]. After primary infection, this neurotropic virus establishes latency in the host's dorsal root ganglia and can reactivate later in life. The lifetime risk for shingles among adults previously infected with VZV was estimated to be about 10-20% prior to the development of the vaccine[32,33]. Reactivation can also result in CNS-related complications, like myelitis, cerebellitis, or even encephalitis[31,34].

One of the first epidemiological studies to report a significant inverse association between VZV and glioma was the San Francisco Bay Area Adult Glioma Study (SFBAGS), in which significantly fewer cases reported a history of chicken pox and/or shingles than controls[35].

Subsequently, a follow-up study by the same investigators supported their previous findings (and reduced the possibility that those findings were due to recall bias) by showing that cases were less likely than controls to be positive for immunoglobulin G (IgG) antibodies against VZV, although not statistically significantly so (OR: 0.6, 95% CI: 0.3 – 1.3)[14]. However, statistical power for the study was limited because blood for serologic analysis was not available on all cases and controls from the parent study .

In 2001, Wrensch et al. again built upon their previous findings by analysing the associations between glioma risk and antibodies against four different herpes viruses, including VZV, in a larger study population (134 cases and 165 controls). They found that glioblastoma (GBM) cases were 60% less likely than controls to be positive for anti-VZV IgG (95% CI: 01.-0.9), controlling for age, ethnicity, and gender[15]. However, the study was underpowered to detect associations for histologic subtypes other than GBM.

In 2005, another analysis from the SFBAGS was conducted, which included 229 glioma cases and 289 controls[10]. Again, cases were less likely to report a history of chicken pox compared to controls, as in the previous studies (adjusted OR: 0.59; 95% CI: 0.40-0.86). Mean log anti-VZV IgG levels were higher for controls than cases and were lowest for GBM cases (antilog mean for controls=1.64±0.09; mean for all cases=1.23±0.09; mean for GBM cases=1.10±0.13). Significant inverse associations with glioma were found for having the highest, compared to lowest, quartile of anti-VZV IgG. The inverse associations between higher levels of anti-VZV antibody and GBM risk were stronger than the associations with other histological subtypes. Differences in antibody levels by sex, race, and age were also explored. The difference in mean anti-VZV IgG levels in cases versus controls was greater among white participants; in fact, non-white cases and controls had very similar levels. A major strength of this study was that the impact of medication use at time of blood draw was discussed.

Among cases, those taking antibiotics at blood draw had higher anti-VZV IgG levels, whereas associations between IgG levels and current medications were not observed among controls. Interestingly, when cases and controls taking antibiotics, dexamethasone, or decadron were excluded, the odds ratios for the highest versus lowest levels of anti-VZV IgG remained in the same direction (OR for any glioma subtype: 0.49; 95% CI: 0.24-0.97), though there was a loss of power for the GBM analysis (OR: 0.40; 95% CI: 0.14-1.10).

In their most recent study, the SFBAGS investigators took a very innovative approach to uncovering the relationship between VZV and gliomagenesis[30].

Ten highly immunogenic and seroprevalent VZV proteins were synthesized and used as antigens to measure seroreactivity among cases and controls. They observed that controls had stronger seroreactivity to VZV antigens than cases, particularly for the VZV ORF2p protein (OR: 0.44; 95% CI: 0.21-0.96, comparing lowest to highest quartiles) and the IE63 protein (OR: 0.26; 95% CI: 0.12-0.58). When

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Critical review

stratified by allergy status, inverse associations between VZV-related seroreactivity and glioma status were present among those with three or more types of allergies, but were not significant among those with two or less allergy types. This finding is particular interesting in light of reported associations between earlier VZV infection and lower atopy risk that are discussed further below. A few interactions between sex and seroreactivity to VZV proteins were also noted.

This series of published findings from the SFBAGS provides strong epidemiologic rationale for continued investigation of the potential role of VZV infection and immunomodulation in glioma development. Nevertheless, it is essential that these findings be corroborated in other populations before definitive conclusions are drawn, as the SFBAGS analyses have relatively small sample sizes, include populations that consist largely of non-Hispanic white individuals, and cannot illuminate the temporal relationships between mounting an antibody response to VZV and the development of the tumour, given that serologic analyses on cases were conducted on blood obtained after tumour diagnosis.

Besides the SFBAGS series, few other epidemiologic studies, to date, have focused directly on examining the potential associations between VZV infection and glioma risk[28,29].

Sjostrom et al. used pre-diagnostic specimens from three Scandinavian cohorts to assess the relationship between antibody levels to four different viruses (VZV, human cytomegalovirus, Epstein-Barr virus, and adenovirus) and glioma risk[28]. The only significant association detected was with VZV antibodies. Specifically, lower levels of anti-VZV IgG were more common in cases than in controls, particularly two years prior to diagnosis (OR: 0.63; 95% CI: 0.37-1.08; p for trend between quartiles=0.03). The major strength of this study is that it provided valuable evidence that the anti-VZV antibody-glioma associations reported in the literature from case-control studies are unlikely to be attributable simply to the effects of post-diagnostic factors (e.g., tumour-associated changes in immunity, chemotherapy, or steroid use).

By contrast, Poltermann et al. were unable to detect associations between VZV (and other herpes viruses) and brain tumours[29]. They found a seroprevalence of anti-VZV IgG of 90.3% (95% CI: 74-98) among a small study population of 35 total glioma patients. They reported that this seroprevalence was similar to the seroprevalence among the general population, but they did not include a control group in their study, nor did they examine antibody levels. The high level of seropositivity in this study is not surprising given that anti-VZV IgG positivity was over 90% in the SFBAGS reports as well[10]. Because chicken pox was a relatively ubiquitous childhood infection prior to vaccine availability, and due to the fact that stronger versus weaker antibody responses have been reported to be relevant to glioma risk, the failure to examine antibody levels in this study requires cautious interpretation of the results.

In addition to data from epidemiologic studies, other lines of evidence also indirectly support the possibility of an inverse association between VZV and gliomagenesis[36].

For example, VZV has been suggested as a potential candidate for oncolytic virotherapy for glioma. Certain viral characteristics, such as its neurotropism and its ability to replicate quickly and lyse malignant glioma cells in vitro, make VZV a particularly intriguing candidate. Furthermore, timing of VZV infection in childhood has been shown to affect future risk of atopic disorders[23,24], which have also been inversely associated with glioma risk[27]. Earlier VZV infection (prior to 8 years of age) has been shown to be protective against asthma, allergic sensitization, and other types of atopy[23]. It remains unclear, however, whether later (e.g., teenage or adulthood) onset of chicken pox may be associated with a more robust immune response to the virus or with increased risk for atopy in adulthood. If so, the inverse associations of glioma risk with VZV immunity and atopic disorders may be linked through a complex network of immunologic pathways that has yet to be understood.

Indeed, some implications of this already exist in the literature— for example, the fact that in the most recent SFBAGS analyses, the inverse associations between glioma and VZV-related seroreactivity were present among those with a higher, but not lower, allergy burden[30]. However, immunological studies are needed to clarify the biological basis behind this interaction.

Currently, the mechanism through which VZV infection and immunity may confer protection against gliomagenesis is unknown. If the protection is not mediated through atopy-related pathways, it may be that VZV antibodies have some cross-reactivity to tumour cells or other oncogenic viruses, and are thus capable of

Table 1: Key future directions for epidemiologic studies of varicella zoster virus (VZV) and brain tumor risk.

· Evaluation of age at primary VZV infection and glioma risk
· Use of additional biomarkers of VZV infection and immunity
· Further examination of interactions between atopy and VZV infection
· Elucidation of differences in immunologic responses between those with wild type VZV infection and those receiving the live attenuated vaccine

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OA Epidemiology
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Critical review

mounting a response against existing tumour cells or extrinsic carcinogens[10].

It has also been hypothesized that individuals who are more likely to develop cancer (or are already in the process of tumorogenesis) may be unable to mount strong immune responses to primary viral infections or reactivation of latent viruses such as VZV. If additional epidemiologic studies can confirm the reported inverse associations between VZV and glioma, mechanistic studies will be strongly warranted, as we cannot determine why this association exists without a better understanding of antibody-mediated immunity to VZV.

Conclusion

The role of VZV and other herpes virus infections in brain tumour aetiology requires further epidemiologic investigation (Table 1). Future studies should focus on assessing how age at primary VZV infection is relevant to anti-VZV antibody response and, in turn, glioma risk. In addition to anti-VZV IgG levels, a more comprehensive panel of biomarkers of VZV infection and immunity, such as viral DNA, measures of viral expression (protein and RNA transcripts), and markers of cell-mediated immunity, should be identified and incorporated into future studies. Furthermore, because most studies of glioma and VZV are case-control studies, more prospective studies are necessary to untangle the temporal relationships between infection and tumorogenesis.

As glioma is a rare disease, this may only be feasible in Northern European countries with centralized medical databases. Finally, as the literature comes to a consensus on the role of VZV infection in glioma risk, interactions between atopy and VZV immunity should also be examined. Stratification of VZV-glioma analyses by IgE levels or childhood history of atopic conditions may provide useful information on how these factors are inter-related.

Another factor that will need to be accounted for in future studies is whether anti-VZV IgG positive participants were immunized against VZV or if they had an actual VZV infection. Antibody composition differs between individuals who experienced a wild-type VZV infection compared to those who were exposed to the live attenuated vaccine. It is, therefore, important to investigate the association between VZV immunity and glioma, distinguishing between infected and vaccinated individuals. If differences are noted between these groups, this knowledge may point toward specific viral antigenic targets that may be of greater relevance to gliomagenesis, perhaps because they resemble an antigen present on tumour cells.

The literature is slowly approaching a consensus on the inverse association between VZV infection and immunity and glioma risk. However, several gaps in knowledge, outlined above, still need to be filled before definitive conclusions can be drawn about this potentially complex relationship.

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OA Epidemiology
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Critical review

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