Detection of human herpesvirus-6 in adult central nervous system tumors: predominance of early and late viral antigens in glial tumors.


The purpose is to determine the incidence of active and latent human herpesvirus-6 (HHV-6) infection in a large cohort of adult primary and recurrent CNS tumors. We screened a tissue microarray (TMA) containing more than 200 adult primary and recurrent CNS tumors with known clinical information for the presence of HHV-6 DNA by in situ hybridization (ISH) and protein by immunohistochemistry (IHC). One hundred six of 224 (47%) CNS tumors were positive for HHV-6 U57 Major Capsid Protein (MCP) gene by ISH compared to 0/25 non tumor control brain (P = 0.001). Fourteen of 30 (47%) tumors were HHV-6 MCP positive by nested PCR compared to 0/25 non-tumor brain controls (P = 0.001), revealing HHV-6 Variant A in 6 of 14 samples. HHV-6A/B early (p41) and late (gp116/64/54) antigens were detected by IHC in 66 of 277 (24%) (P = 0.003) and 84 of 282 (35%) (P = 0.002) tumors, respectively, suggesting active infection. HHV-6 p41 (P = 0.645) and gp116/64/54 (P = 0.198) antigen detection was independent of recurrent disease. Glial tumors were 3 times more positive by IHC compared to non glial tumors for both HHV-6 gp116/64/54 (P = 0.0002) and HHV-6 p41 (P = 0.004). Kaplan Meier survival analysis showed no effect of HHV-6 gp116/64/54 (P = 0.852) or HHV-6 p41 (P = 0.817) antigen detection on survival. HHV-6 early and late antigens are detected in adult primary and recurrent CNS tumors more frequently in glial tumors. We hypothesize that the glial-tropic features of HHV-6 may play an important modifying role in tumor biology that warrants further investigation.

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BACKGROUND:
Human herpesvirus-6 (HHV-6) has been associated with a diverse spectrum of central nervous system (CNS) diseases and reported glial tropism.

OBJECTIVE:
To determine if HHV-6 is present in a series of pediatric brain tumors.

STUDY DESIGN:
Pediatric gliomas from 88 untreated patients represented in a tissue microarray (TMA) were screened for HHV-6 by nested polymerase chain reaction (PCR), in situ hybridization (ISH), and immunohistochemistry (IHC) and compared to non-glial tumors (N=22) and control brain (N=32). Results were correlated with tumor grade and overall survival.

RESULTS:
HHV-6 U57 was detected by nested PCR in 68/120 (57%) tumors and 7/32 (22%) age-matched non-tumor brain (P=0.001). HHV-6 U31 was positive in 73/120 (61%) tumors and 11/32 (34%) controls (P=0.019). Seventy-two percent (43/60) of tumors were HHV-6 Variant A. HHV-6 U57 was confirmed by ISH in 83/150 (54%) tumors and 10/32 (31%) controls (P=0.021), revealing a non-lymphocytic origin of HHV-6. HHV-6A/B gp116/64/54 late antigen was detected by IHC in 50/124 (40%) tumors and 6/32 (18%) controls (P=0.013).

Interestingly, 58% of low grade gliomas (N=67) were IHC positive compared to 19% of high grade gliomas (N=21, P=0.002) and 25% of non-gliomas (N=36, P=0.001). HHV-6A/B gp116/64/54 antigen co-localized with glial fibrillary acidic protein, confirming the astrocytic origin of antigen. Overall, there was no primary association between HHV-6A/B gp116/64/54 antigen detection and survival (P=0.861).

CONCLUSIONS:
We provide the first reported series of HHV-6 detection in pediatric brain tumors. The predominance of HHV-6 in glial tumors warrants further investigation into potential neurooncologic disease mechanisms.