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Letter to the Editor: New Observation

Chronic Herpes Simplex Virus Encephalitis with Unexpected Neuropathological Findings

Kirsten Sjonnesen[1], Walter Hader[2], Qi Xu[3], Julia Jacobs[1], Paolo Federico[4], Kristopher D. Langdon[5] and Juan P. Appendino[1]

[1]Departments of Pediatrics and Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Division of Neurosurgery, Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [3]Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada, [4]Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada and [5]Department of Pathology & Laboratory Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

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We describe herein two young patients who underwent epilepsy surgery following remote infectious encephalitis, and whose subsequent neuropathologic findings demonstrated phosphorylated tau accumulation in the context of chronic HSV encephalitis.

Case 1: A 15-year-old girl underwent surgical resection of the right fronto-parietal-insular region for treatment of drug-resistant epilepsy with progressive epileptic encephalopathy six years after a diagnosis of Herpes Simplex Virus-1 encephalitis (HSVE). The HSVE had initially been confirmed via HSV-1-positive cerebrospinal fluid polymerase chain reaction and she underwent a course of acyclovir intravenously. Post-operatively, an additional course of acyclovir was prophylactically administered. The resected tissue revealed a chronic, granulomatous lymphohistiocytic meningoencephalitis on microscopic examination. Real-time polymerase chain reaction (PCR) detected HSV-1 viral DNA in the formalin-fixed paraffin-embedded sample of parenchyma, whereas immunohistochemical staining did not show evidence of HSV-1 or HSV-2 antigen. Several pyramidal cortical neurons contained basophilic cytoplasmic fibrillary inclusions, and phosphorylated tau immunohistochemistry (AT8 – Thermo Scientific; 1:200) confirmed the focal presence of neurofibrillary tangles, pre-tangles, and fairly dense neuropil threads (Fig. 1).

Case 2: A 21-year-old woman, previously reported by Arnold *et al.*, had undergone surgical resection of the left temporal lobe for treatment of drug-resistant focal epilepsy, five years after experiencing a reported non-specified viral encephalitis in her country of origin. Post-operative prophylactic acyclovir was not administered, and her course was complicated by HSVE reactivation and significant morbidity.[1] The microscopic examination of resected tissue was compatible with chronic encephalitis due to HSVE. Real-time PCR detected HSV-1 DNA; there was no histological or immunohistochemical evidence of HSV-1/-2 inclusions or antigens. Considering the findings described in Case 1, phosphorylated tau staining was performed (*ad hoc; immunohistochemistry protocol as in Case 1*) and demonstrated neuronal cytoplasmic tau and neuropil threads in the cortex and to a lesser extent within the hippocampus, both of which were in close proximity to foci of parenchymal reaction and inflammation.

Discussion

These cases, with contrasting post-operative courses, shared pathologic findings of chronic inflammation and parenchymal HSV-1 DNA detectable by PCR only. Of note, the identification of HSV-1 DNA on PCR does not distinguish between stages of the virus life cycle, and the absence of viral antigen detection by immunohistochemistry likely indicates a non-active stage of HSV-1 infection.[2] Remarkably, foci of abnormal phosphorylated tau accumulation, associated with neuropathologic chronic granulomatous HSVE, were demonstrated within regions of inflammation as well as seemingly uninvolved areas. These foci of accumulation appeared as cytoplasmic phosphorylated tau-immunopositive components, neurofibrillary tangles, pre-tangles, and neuropil threads.

To our knowledge, these represent the youngest cases reported of chronic HSVE associated with tau-related neuropathologic findings. Danics *et al.* recently reported a series of 13 autopsied cases surviving between 9 days and 6 years after HSVE.[3] Eight cases demonstrated neuronal tau-immunoreactivity and neuropil threads, and in three of these, the phosphorylated tau was found in inflammation-associated regions.[3] However, the youngest case found to have tau-related pathology was 41 years old at the time of death.[3]

HSV-1 primary infection and reactivation have been associated with abnormal phosphorylated tau accumulation in *in vivo* murine models and *in vitro* murine, monkey, and human models.[4–6] HSV-1 *in vitro* infection models exposed to acyclovir treatment demonstrate dose-dependent reductions in phosphorylated tau accumulation.[4,5] Further investigation into the possibility that tau

Corresponding author: K. Sjonnesen. Email: kirsten.sjonnesen@ucalgary.ca

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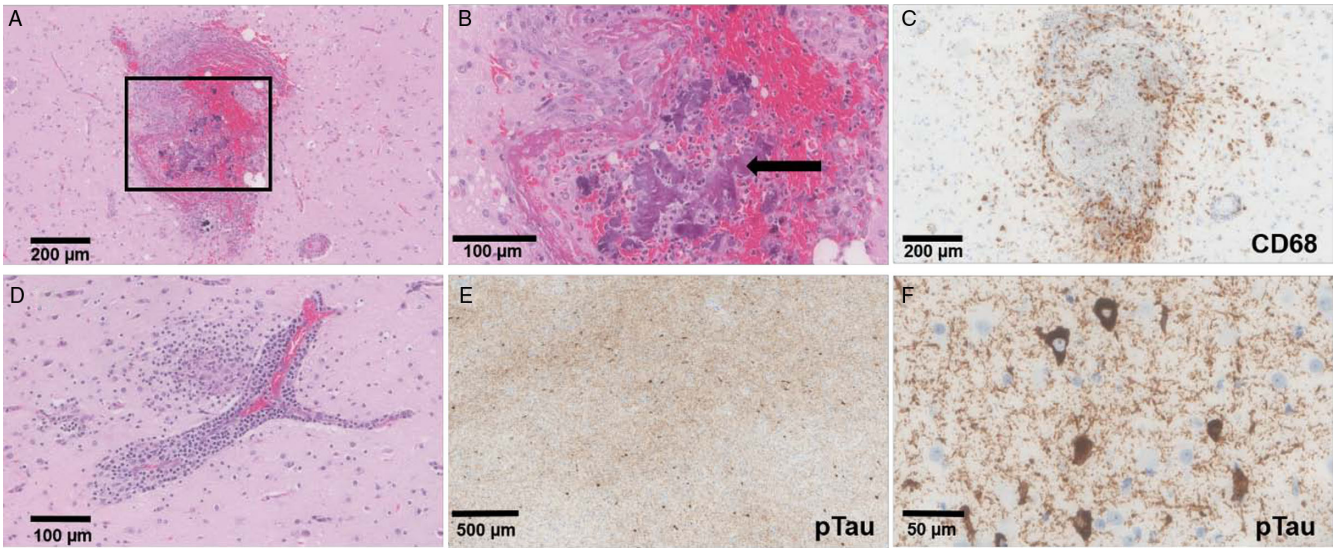

Figure 1: Resected cortical specimen samples from Case 1. Specimen consisted of right posterior frontal cerebral cortex and underlying subcortical white matter. Foci of parenchymal lymphohistiocytic granulomatous inflammation (***a***, ***b*** and ***c*** [CD68 immunohistochemistry]) and perivascular lymphocytic cuffing (***d***), as well as dystrophic parenchymal mineralization (closed arrow in B) are demonstrated. (***e***&***f***) Phosphorylated tau immunohistochemical staining demonstrates intracytoplasmic tau (open arrow in F) and neuropil thread staining (closed triangle in F). Phosphorylated tau staining was completed using AT8, 1:200; phospho-epitope Ser202.

accumulation contributes to long-term neurologic sequelae among HSVE survivors may be warranted. Lastly, for patients with a past or suspected medical history of HSVE, prophylactic use of acyclovir during neurosurgical interventions should be considered.

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