Title: Epstein–Barr Virus reactivation as a trigger in autoimmune GFAP Astrocytopathy

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Autoimmune Glial Fibrillary Acidic Protein (GFAP) astrocytopathy is a rare CNS inflammatory disorder, first defined in 2016 and identified by GFAP-IgG in cerebrospinal fluid. Its rarity makes large-scale studies nearly impossible, so each well-designed case series is valuable. Within this context, Handa et al.'s study is noteworthy for its design[1]; they included a well-matched disease control group and conducted thorough CSF analyses (EBV DNA PCR and serology), strengthening the validity of their findings.

Handa et al. detected EBV DNA in the CSF of most patients with GFAP astrocytopathy, consistent with intrathecal EBV reactivation. EBV DNA, targeting the lytic gene *BLLF1*, was present in patients during active disease and absent in most controls, pointing to a specific association. Furthermore, follow-up showed a reduction in CSF EBV DNA levels, albeit measured by semi-quantitative PCR, consistent with transient reactivation rather than latent carriage. Importantly, no patient demonstrated acute EBV IgM antibodies or early antigen IgG, further supporting reactivation rather than primary infection. A limitation is that GFAP antibody titres were not quantified, a missed opportunity to correlate antibody levels with viral load. Nonetheless, the core insight is compelling: GFAP-A relapses were closely linked in time with EBV reactivation, suggesting the virus may trigger an autoimmune cascade.

Of course, detecting EBV DNA in CSF does not by itself prove causation; the virus may be an epiphenomenon. However, the temporal alignment between EBV activity, disease flares, and clinical severity, coupled with a reactivation-type serological profile, makes a causal role more likely. This aligns with a broader pattern of EBV being implicated in other CNS autoimmune diseases, with mounting evidence that it is a necessary trigger for multiple sclerosis. Similarly, some cases of anti-NMDA receptor encephalitis have followed EBV infection. GFAP astrocytopathy can now be viewed in this broader context of infection-triggered autoimmunity. Importantly, EBV is not unique; other infections, such as varicella-zoster virus and dengue fever, have preceded GFAP-A in isolated reports, suggesting a shared post-infectious autoimmune mechanism, possibly via molecular mimicry or bystander activation.

Clinically, these findings highlight both therapeutic opportunities and diagnostic challenges. If EBV reactivation contributes to GFAP-A flares, it raises the possibility of combining antiviral therapy with immunosuppressive treatment. Early antivirals may dampen the trigger, while corticosteroids or B-cell–targeted therapies address the autoimmune inflammation, offering a dual approach to management. Equally important is distinguishing EBV-associated GFAP-A from primary EBV encephalitis. The presence of GFAP-IgG in CSF, together with the absence of acute EBV IgM in serum, favours an autoimmune process requiring immunotherapy rather than antiviral treatment alone. It is even conceivable that some past diagnoses of “EBV encephalitis” represented post-EBV autoimmune astrocytopathy, where timely immunotherapy might have improved outcomes.

By emphasising these points, Handa et al. extend our understanding of GFAP astrocytopathy’s pathogenesis and suggest practical next steps, from vigilant diagnostic testing to exploration of combined antiviral and immunomodulatory strategies. Nonetheless, given its single-centre, retrospective case series design, these findings remain preliminary and require replication before therapeutic trials can be justified.

1. Handa et al. Intrathecal Epstein–Barr virus reactivation in patients with autoimmune glial fibrillary acidic protein astrocytopathy. JNNP 2025….