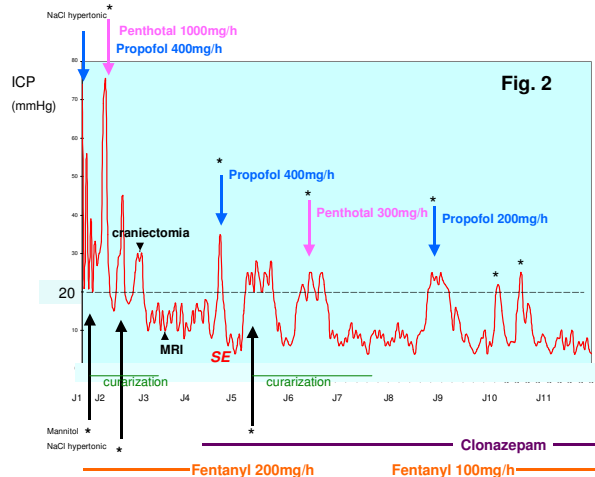
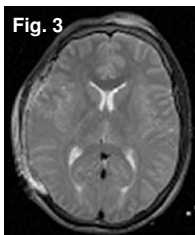


## Introduction & Purpose

Neurological complications of EBV-transmitted infectious mononucleosis (IM) occur in 0.5 % of patients [1]. The precise mechanisms leading to this condition are unclear, both infectious and para-infectious mechanisms have been proposed [2, 3]. We report a patient who improved dramatically after a severe EBV encephalopathy. To determine whether his CNS disorder was due to direct EBV infection or to auto-immune mechanisms, we prospectively studied his immune response against EBV and myelin oligodendrocyte glycoprotein (MOG).

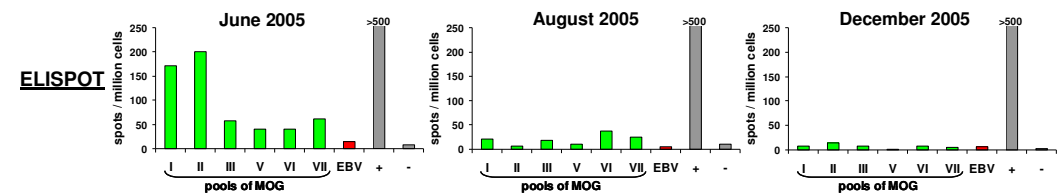
## Case report

In May 2005, a 27 year-old man suffered from an infectious mononucleosis (IM) due to EBV, as documented by positive Monotest and anti-VCA EBV IgM+. Three weeks after IM onset, he presented with partial complex status epilepticus (SE). A head CT showed diffuse cerebral oedema (Fig. 1), a lumbar puncture disclosed an opening pressure at 31 cm H<sub>2</sub>O, 48 WBC/mcl, 1090 mg/L proteins, and normal glucose. HIV testing was negative. PCR in the CSF were negative for S. pneumoniae, N. meningitidis, H. influenzae, L. monocytogenes, HSV and Enterovirus. Considering the temporal relationship between IM and the onset of CNS impairment, the diagnosis of EBV-associated encephalopathy was established. Methylprednisolone (MP) 500 mg/day was given. His condition worsening and the intra-cranial pressure (ICP) rising, a hemicraniectomy was performed three days after neurological onset. Due to persistence of SE, he received alternate treatments of penthotal and propofol to achieve burst suppression (Fig. 2). On day 4, a brain MRI (Fig. 3) showed massive brain oedema but no T2-weighted or DWI lesions so that MP was discontinued. His clinical course improved gradually, he could be extubated on day 13 and resume his studies 6 months later.

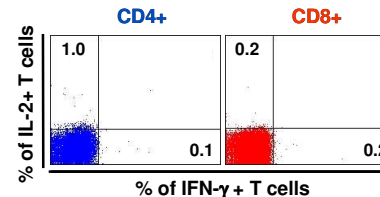


## Laboratory investigations

We examined whether this EBV encephalopathy was due to infectious or auto-immune mechanisms. In June, 15 days after encephalopathy onset, serologies and PCR looking for the presence of EBV in the CSF came back negative. An ELISPOT assay showed no EBV-specific CD8+ T cells (CD4+ T cells not tested) but revealed a potent MOG-specific T cell response (Fig. 4). This MOG-specific response was mediated by CD4+ as well as CD8+ T cells as revealed by an intra-cellular cytokine staining assay (Fig. 5). Two months later, the MOG-specific T cell response had vanished. Six months later, MOG-specific T cell response had disappeared (Fig. 4).



**Figure 4:** Potent T cell response against MOG as determined by ELISPOT assays. Secretion of IFN- $\gamma$  by CD4+ and CD8+ T cells (green) or CD8+ T cells (red) specific for MOG or EBV was examined. For MOG, we used 7 pools of 15-mer peptides overlapping the entire amino acid sequence of the protein. For EBV, we used a selection of immunodominant epitopes. +, positive control (PHA); -, negative control (culture medium).



**Figure 5:** Pool I of MOG induces a CD4+ and a CD8+ T cell response as shown by intra-cellular cytokine staining assay. In addition to IFN- $\gamma$ , MOG I-specific T cells also secrete IL-2 [4]. Stimulation was performed by MOG peptides only, without adding stimulatory cytokines such as IL-2.

## Conclusion

- Despite a very severe EBV encephalopathy with refractory status epilepticus and high intra-cranial pressure, the outcome was excellent. This report emphasizes that an aggressive management is warranted in such patients.
- Our data show that this encephalopathy was not due to direct EBV infection of the brain, but rather to an aberrant immune response, possibly mediated by MOG-specific T cells
- Our results corroborate what has been demonstrated in the Theiler murine encephalomyelitis viral model, suggesting that EBV encephalopathy occur in patients who are unable to mount a vigorous EBV-specific CD8+ T cell response at the time of infectious mononucleosis [5].

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