

EDITORIAL COMMENTARY

Infections and the Guillain-Barré syndrome

It has long been textbook knowledge that in most patients an infective illness precedes the development of the Guillain-Barré syndrome (GBS). About two thirds of patients report symptoms of an upper respiratory tract or gastrointestinal tract infection predating the disease by 1–4 weeks. Many diverse infectious agents have been incriminated as triggers of this acute polyradiculoneuropathy but only few larger scale and case controlled studies, so important in a disease with a low incidence of 1–2/100 000, have been published.^{1–3} Based on this evidence, infections with the gram negative enteropathogen *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein-Barr virus, and *Mycoplasma pneumoniae* are precipitants of GBS whereas other infections occur no more often in this neuropathy than in controls. The agent most commonly associated with GBS is *Campylobacter jejuni*. In most parts of the western world, the frequency is around 33%, whereas in China and Japan, this figure is around 45–60%.^{3–5} CMV has been identified as the predominant viral cause of an infective illness preceding GBS, present in 10–15% of patients. Association with Epstein-Barr virus infection and infection with *Mycoplasma pneumoniae* seem to be less common, occurring in around 8%–10% and 5%, respectively.^{2–3} These findings are certainly of epidemiological interest but they may also provide us with important insights into the pathogenesis of this immune mediated neuropathy and may explain some aspects of the emerging heterogeneity of this disorder.⁶ A study of the clinical and electrophysiological features of patients with CMV associated GBS that were enrolled in the Dutch GBS trial comparing IVIG with plasma exchange, first indicated that in this subgroup of patients with GBS the disease seems to follow a different clinical pattern with more frequent involvement of cranial nerves and severe sensory loss.⁷ Another feature that would separate CMV related GBS from GBS not preceded by this viral infection is the presence in acute stage serum samples of IgM antibodies to a particular glycoconjugate antigen, the ganglioside GM2, as first described by Irie *et al.*⁸ Two subsequent reports yielded contradictory results.^{9–10} In this issue, pp 376–9, Khalili-Shirazi *et al* contribute to this contentious discussion with a study of 26 patients with GBS of which roughly half had a previous CMV infection and half did not. Also included were patients with recent CMV infection who did not have neurological disease. These authors found, utilising the enzyme linked immunosorbent assay (ELISA) technique and confirmation by thin layer chromatography, IgM antibodies to GM2 in six of 14 patients with GBS with antedating CMV infection but none in patients with GBS unrelated to CMV. Interestingly, humoral immune responses in the IgM class were broader and directed against other gangliosides as well, in keeping with a large body of evidence concerning the range of antibody responses to glycoconjugates in the general GBS population.¹¹ This would rule out an exclusive association of CMV related GBS and antibodies directed to the ganglioside GM2, as was suggested earlier.^{8–9} No significantly raised IgM antibodies to GM2 were detected in serum samples from patients with CMV infection uncomplicated by GBS. Along with previous studies, the present report raises interesting questions about the pathogenetic link between CMV

infection and GBS. There is no evidence that CMV directly infects the nerve in GBS. As Khalili-Shirazi *et al* suggest, CMV as an envelope budding virus may carry host derived glycolipids and render them immunogenic or may enhance production of low affinity natural antibodies and increase their affinity. Antibodies to GM2 cross react with CMV infected cells. Given that GM2 exhibits significant structural homology with GT1a and the major glycolipid GM1 present in human myelin and on the axolemma, cross reactive antibody responses may result in immune mediated nerve damage.¹¹ As nothing is known about the presence and distribution of GM2 in peripheral myelin in humans, the predominance of sensory fibre involvement in CMV related GBS remains elusive. Leaving the association with GM2 antibodies aside, it should also be noted that molecular mimicry based on sequences shared between the virus and the P0 protein of peripheral myelin recognised by T cells has been hypothesised to underlie CMV related GBS.¹² A third possibility, again unrelated to a putative pathogenic role of antibodies to GM2 could be non-cognate bystander activation of peripheral myelin directed T lymphocytes by a cytokine surge after the CMV infection.^{4–13} Taken together, these and previous findings strengthen the link between infective illnesses and the development of GBS. They suggest some form of pathogenetic connection with antibody responses to a particular glycolipid in CMV related GBS although, unlike in *C jejuni* associated GBS, their causal relation seems obscure. Whether the occurrence of GM2 antibodies also in acute CMV infection without neuropathy recently reported by Yuki and Tagawa in their large scale study¹⁰ clouds this issue or implies a requirement for the presence of specific individual host susceptibility factors also remains to be determined.

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