The Relationship between Cytomegalovirus Infection and Guillain–Barré Syndrome

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(See the article by Orlikowski et al, on pages 837–844.)

The association between cytomegalovirus (CMV) and Guillain–Barré syndrome (GBS) was first noted in 1967 [1] and was soon endorsed by other reports and case series. The largest previous case series showed that CMV infection was associated with GBS in 8% of 229 patients from a European and North American trial [2]. In this issue of Clinical Infectious Diseases, Orlikowski et al [2] confirmed this finding in a larger population of people with GBS by using the resources of the French reference centre in Garches, Paris, which has been a major source of useful research into the disease. Of 506 patients with GBS, 63 (12.5%) had serological evidence of primary CMV infection. It is difficult to distinguish between primary and reactivation of infection, an important problem, because ~50% of the nonimmunosuppressed people in developed countries have serological evidence of exposure to CMV. The serological methods used by Orlikowski and colleagues incorporated a test for high immunoglobulin (Ig) G avidity to exclude positive results due to reactivation. Low-avidity IgG antibody is found in primary infection before affinity maturation has occurred. The serological results were supported by the finding of CMV DNA in the plasma by polymerase chain reaction (PCR) in 36 (62%) of 58 subjects who had positive serological test results. The sensitivity of CMV PCR nears 100% for acute infection, but it would be expected to be reduced in the late infectious phase, when GBS occurs because virus is being cleared. Unfortunately no convalescent-phase samples were available for analysis because of the intervening treatment and quantitative PCR was not performed for enough patients to publish the result.

The authors used contemporary French epidemiological data to calculate, for the first time, that the risk of GBS following CMV is in the order of 0.6–2.2 cases per 1000 persons. There were no control subjects in the Orlikowski et al [2] study, but 2 earlier studies had shown that the frequency of recent CMV infection preceding GBS significantly exceeded that of control subjects: in the United Kingdom, 11% of 99 case patients and only 1% of control patients had evidence of recent CMV infection [3]; in the Netherlands, 13% of 154 case patients and only 2% of control subjects [4] had evidence of recent CMV infection.

The study by Orlikowski et al [2] confirms that there are differences between GBS that occurs after CMV infection and GBS that occurs after other infections. The Dutch group assessed a smaller group of 20 patients with serological evidence of recent CMV infection and found that they were significantly younger and had more severe disease, more frequent cranial nerve involvement, and more severe sensory loss when compared with patients with Campylobacter jejuni GBS, among whom sensory loss is less common and motor deficit more common [5]. Orlikowski and colleagues also found that patients with GBS following CMV infection were more likely to be younger and to have persistent disability. In addition, there was an interesting peak in cases among women aged >50 years, surmised to be older people exposed to their grandchildren’s viruses (“feverish granny syndrome”) [6]. Although sensory deficit was more common (72% of 61 CMV-infected patients vs 60% of 442 patients with other cases), this difference was not statistically significant. There was no difference in the frequency of bulbar dysfunction, but the frequency of facial palsy was greater among patients with CMV-associated GBS (49% of 61 CMV-
infected patients) than among the others (24.9% of 442 those with other cases). Seventy percent of the CMV-infected patients were classified neurophysiologically as having acute inflammatory de-myelinating polyradiculoneuropathy (AIDP), and only 7% had axonal disease. These are the percentages which are usually found in European series of patients with GBS, but we have not been told the percentages for the other GBS cases in this series. Follow-up neurophysiological studies are now known to be needed to distinguish reliably between demyelinating and axonal forms of the disease [7] and were not reported in the study by Orlikowski and colleagues. Nevertheless, we have sufficient information to see that CMV GBS is a different disease—or at least a different part of a spectrum of disease—from C. jejuni GBS, something that we knew before but that these new data strongly endorse.

The multivariable analyses of predictors of the need for ventilation in the short-term and the long-term outcome also independently supported the variables included in the Erasmus GBS Outcome and Respiratory Insufficiency Scores (EGOS and EGRIS) [8, 9]. The study was not designed as a validation cohort for these studies but independently identified the same predictors, indicating that CMV GBS behaves in a similar way to an unselected GBS cohort.

The study by Orlikowski et al [2] sheds little light on the pathogenesis of CMV GBS. In C. jejuni GBS, IgG subclass 1 antibodies against ganglioside GM1 are strongly implicated in pathogenesis, probably by means of complement-mediated blockade of nerve conduction or axolemmal destruction [10]. In CMV GBS, earlier studies reported the presence of IgM anti-GM2 antibodies [11, 12, 14] in approximately one-half of patients, compared with 29% patients in Orlikowski and colleagues’ study. However, IgM anti-GM2 antibodies also occur in CMV infections without GBS. Antibodies to ganglioside GM1 do not occur after uncomplicated C. jejuni infection. This reduces but does not eliminate the possibility that antibodies to gangliosides generated by the immune response to the CMV infection are important in pathogenesis. Recent work has highlighted clear differences in the specificity of superficially similar anti-ganglioside antibodies [15]. Additional research into the induction and the subsequent fine specificity of the antibodies would be worthwhile.

Another appropriate line of research is to investigate the T cell–mediated immune response to neural antigens in CMV GBS. In the study by Hadden et al [16], CMV GBS was associated with increased soluble adhesion molecules and interleukin-2 receptor in the blood, compared with other GBS, suggesting more activation of T cells. The histological appearances of the AIDP form of GBS strongly resemble those of experimental autoimmune neuritis, which is a predominantly T cell–driven model. Similarities between CMV and Schwann cell or myelin proteins could initiate an autoimmune response in susceptible individuals. Many different antecedents have been shown to be significantly associated with GBS, now including C. jejuni; Epstein-Barr, varicella zoster, and influenza viruses; Mycoplasma pneumoniae; and possibly Haemophilus influenzae. This wide variety raises the possibility that the preceding infection disturbs the regulatory mechanisms that normally inhibit latent autoimmunity against peripheral nerve antigens rather than providing a specific autoimmune antigenic stimulus.

One uncomfortable thought remains: whether the triggering infection directly invades the peripheral nervous system and contributes to the inflammation. Because GBS occurs after the symptoms of the acute infection have subsided, this possibility has been disregarded. No CMV DNA was identified in the sural nerve biopsy specimen obtained from a patient with CMV GBS [17], but this does not rule out the possibility of ongoing infection in some patients. Because treatment for CMV infection is available, perhaps a trial of antiviral treatment should considered in CMV GBS.

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References