EDITORIAL COMMENTARIES

Modulating the immune response in demyelinating diseases

Guillain-Barré syndrome offers the unusual opportunity of investigating the early stages of a monophasic autoimmune response. Créange *et al* (pp 162–5 of this volume) have shown that the concentration of the immunoregulatory cytokine transforming growth factor (TGF-β1) is decreased in Guillain-Barré syndrome at the time of presentation and increases after treatment with either plasma exchange or intravenous immunoglobulin. These results are in line with a previous report.[1] They also confirm the previously reported increased concentrations of the inflammatory cytokine tumour necrosis factor α.[2] Circulating concentrations of cytokines may not reflect accurately the events in the endoneurium but these findings are consistent with the presence of the message for and expression of these cytokines in peripheral nerves in experimental autoimmune neuritis.[3] The source of the TGF-β1 in Guillain-Barré syndrome is likely to be the endoneurial inflammation, and Créange *et al* recommend measurement of TGF-β1 to identify the inflammatory nature of a neuropathy. More information is needed about the specificity of such an assay as concentrations are likely to be increased non-specifically in inflammatory conditions and after peripheral nerve or CNS injury. It would also be helpful to know whether raised concentrations of this cytokine represent a response to treatment or the evolution of the disease, and whether they predict a favourable outcome. The cells which produce TGF-β1 include megakaryocytes,[4] macrophages, CD8+ T cells, and a subpopulation of CD4+ Th cells. Th1 cells secrete inflammatory cytokines, such as IL-2, interferon-γ, and stimulate cell mediated immunity. Th2 cells produce regulatory cytokines including the interleukins IL-4, IL-5, IL-6, IL-9, and IL-10, which down regulate Th1 cells and enhance B cell responses. In rats treated with oral myelin basic protein to abrogate experimental autoimmune encephalitis, Chen *et al* have proposed a third category of Th cells: these Th3 cells produce TGF-β1, do not have the cytokine profile of Th1 or Th2 cells, but do have the ability to suppress the autoimmune disease.[5] The finding of a decreased TGF-β1 concentration in the blood in the acute phase of Guillain-Barré syndrome does raise challenging questions about the possibility of manipulating the immune response to tip the balance towards immunoregulatory and away from inflammatory cytokines. Immunoregulatory cytokines, including interferon-β, are themselves possible therapeutic agents. When added to lymphocytes in vitro, interferon-β stimulated the production of mRNA message for TGF-β1.[6] Moreover interferon-β suppressed experimental autoimmune encephalitis, although treatment needed to be continued to prevent rebound disease.[7] More information is needed about the time course, role, and effects of cytokines in patients and animal models[8] to direct future clinical trials in human inflammatory neuropathy.

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Risk factors for treatment related clinical fluctuations in Guillain-Barré syndrome

The efficacy of immunomodulatory treatments, either plasma exchange or intravenous immune globulin (IVIg), is now well established in the management of Guillain-Barré syndrome. However, about 5% of patients deteriorate after a period of initial improvement or stabilisation, and two independent reports drew attention to a worryingly high relapse rate after treatment with IVIg.[1 2] A second unrelated issue revolved around the severity of disease that required intervention and in particular whether patients should be treated while still ambulant. Cost and safety considerations preclude widespread adoption of this practice, but it is also possible that early treatment may be associated with a higher relapse rate. These issues have been partly considered by the study of Visser *et al*[3] (pp 242–4 of this volume) who report their data on 16 patients who relapsed after either plasma exchange or IVIg and compared the clinical characteristics with 156 patients who did not relapse. Their findings go some way to reassure us that treatment modality—namely, plasma exchange or IVIg—seems not to have any influence on the risk of relapse. Secondly, the time from onset of weakness to treatment was similar in both groups although, as all patients had to be unable to walk 10 m independently to be randomised, we are still in the dark as to whether ambulant patients tend to relapse more often. A third interesting finding, but not entirely unexpected, is that those patients who have an "acute motor Guillain-Barré syndrome" characterised by a rapid onset of weakness and progression to tetraplegia without any associated sensory loss do not relapse. This may be because this variant of Guillain-Barré syndrome is caused by acute axonal degeneration. As the axons once destroyed cannot regenerate sufficiently quickly to be attacked again by the original immune effector mechanisms (which may have subsided long before), clinical relapse would not be expected to occur. The authors also suggest that fluctuations tended to occur in those patients with a more protracted disease course, as defined by a slightly longer time until the nadir, although the difference did not reach significance. Inevitably, significant results will appear if enough variables are examined and if a Bonferroni correction of 20 (No of variables examined) is applied to these data, then none exceeds the 5% significance level. The authors rightly point out that the numbers are small and so care must be taken not to draw too many conclusions from this study alone. Nevertheless it would be interesting to confirm or refute these findings

by testing the data from the other large treatment study carried out by the Plasma Exchange/Sandoglobulin Guillain-Barré syndrome Trial group[4] to define a subgroup of patients more likely to relapse. The next challenge is to determine the best treatment for relapsing patients and trials are ongoing to answer this question.

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