Tumour necrosis factor-α and other cytokines in Guillain-Barré syndrome

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Abstract
The efficacy of plasma exchange implicates myelinotoxic humoral factors in the pathogenesis of Guillain-Barré syndrome. Candidate factors include autoantibodies to peripheral nerve myelin, which are not unique to Guillain-Barré syndrome; and cytokines such as tumour necrosis factor-α (TNF-α) which are T cell/macrophage products. Plasma cytokine concentrations were determined in 26 patients with Guillain-Barré syndrome undergoing plasma exchange, 25 with other acute neurological diseases, and 40 healthy controls. Raised TNF-α concentrations (> 25 pg/ml) were found in seven of 26 patients with Guillain-Barré syndrome vs none of 23 disease controls (p = 0.001). The peak grade of clinical deficit correlated with TNF-α concentrations (r = 0.6, p < 0.01). There was no significant difference between interleukin-1β or interferon-γ concentrations in patients and disease controls. The data suggest that TNF-α may be a critical factor in the pathogenesis of Guillain-Barré syndrome.

Patients and methods
Stored plasma samples from 26 patients with Guillain-Barré syndrome undergoing plasma exchange who fulfilled standard diagnostic criteria; 25 patients with other acute neurological diseases including myasthenia gravis, polymyositis, neuropathy associated with malignant disease, stroke, and lumbar canal stenosis; and 40 healthy controls were analysed. Plasma concentrations of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN-γ) were determined by enzyme immunoassay with kits from Medgenix, Immunotech, and Genzyme respectively. Data were not normally distributed and were therefore analysed with standard non-parametric tests. The χ² test was used to compare the frequency of raised cytokine concentrations in patients and controls. Associations between raised cytokine concentrations and severity of disease were sought with Spearman rank correlation analysis.

Results
Three controlled trials have shown that plasma exchange accelerates recovery in Guillain-Barré syndrome.1–3 Thus plasma factors seem to have an important role in mediating myelin damage although both cellular and humoral factors are implicated in the pathogenesis of demyelination in Guillain-Barré syndrome.4 Several studies have sought to characterise autoantibodies to peripheral nerve myelin to account for this humoral element. There is however, no unique specificity detectable in most patients. Pathological studies of experimental allergic neuritis and Guillain-Barré syndrome provide evidence that areas of demyelination are associated with an inflammatory infiltrate of lymphocytes and macrophages.5–6 Both these cell types are known to release cytokines that have local and systemic effects.7 We have investigated the hypothesis that plasma contains such demyelinating T cell/macrophage derived factors.
Discussion

The efficacy of plasma exchange in Guillain-Barré syndrome has stimulated the search for autoantibodies to peripheral nerve myelin in these patients. Antibodies to gangliosides have been found most often but are detectable in only a minority of patients. The detection of these antibodies is not specific for Guillain-Barré syndrome and their presence correlates with axonal damage. These data suggest that such autoantibodies may be a secondary phenomenon after nerve damage. Alternative candidates for the humoral factor include cytokines such as TNF-α, which is derived from T cells and macrophages. Other products of activated T cells such as serum interleukin-2 (IL-2) and IL-2 receptor levels are raised in Guillain-Barré syndrome. Ultrastructural studies support this hypothesis as macrophages are closely apposed to demyelinated axons in necropsy material from patients with Guillain-Barré syndrome. TNF-α is a multifunctional, cytotoxic polypeptide that can induce myelin damage and necrosis of oligodendrocytes in vitro. Our data suggest that TNF-α may be a critical factor in the pathogenesis of Guillain-Barré syndrome as plasma TNF-α concentrations but neither IL-1β nor IFN-γ correlate with disease severity. Raised blood TNF-α concentrations were previously reported in isolated cases of Guillain-Barré syndrome used as disease controls and a recent study correlated raised serum TNF-α concentrations with more severe disease.

Possible mechanisms to explain a pathogenic role for TNF-α include a direct myelinotoxic effect of locally produced TNF-α and an indirect effect via the blood-nerve barrier. A breakdown of the blood-nerve barrier is a key feature of both Guillain-Barré syndrome and experimental allergic neuritis which may be critical in allowing activated T cells access into peripheral nerve. In experimental allergic neuritis demyelination only occurs when both damage to the blood-nerve barrier and activated T cells or their products are present. Preliminary studies identified mRNA for TNF-α in necropsy specimens of peripheral nerve from patients with Guillain-Barré syndrome. Sequential studies in experimental allergic neuritis have shown a temporal association between the detection of immunoreactive TNF-α and peripheral nerve demyelination. Longitudinal studies of TNF-α concentrations are needed to investigate the time course of changes in TNF-α concentrations and their relation to treatment with plasma exchange and γ-globulin. If TNF-α is important in the pathogenesis of Guillain-Barré syndrome it should be possible to show that concentrations of TNF-α, either locally in nerve or in plasma, fall with treatment. Because autoantibodies to TNF-α are detectable in some subjects it is possible that pooled γ-globulin is an effective treatment in Guillain-Barré syndrome because it contains anti-TNF-α activity.

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