SHORT REPORT

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

A R Exley, N Smith, J B Winer

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 *v* 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.

(*J Neurol Neurosurg Psychiatry* 1994;57:1118-1120)

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.

Patients and methods

Stored plasma samples from 26 patients with Guillain-Barré syndrome undergoing plasma exchange who fulfilled standard diagnostic criteria⁸; 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 χ^2 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

Plasma samples were obtained at a median of nine days (interquartile range 7-17 days) after the disease onset from the patients with Guillain-Barré syndrome. The severity of disease was graded according to an established scale employed in previous therapeutic trials.¹ At the time of venepuncture four of the patients were able to walk (grade 2 or 3), 14 were bed bound (grade 4), and eight required assisted ventilation (grade 5). Cytokine concentrations in patients were only regarded as raised if they were higher than 95% of all healthy controls.⁹ With these criteria TNF- α concentrations were raised (> 25 pg/ml) in seven of 26 patients with Guillain-Barré syndrome *v* none of 23 disease controls ($\chi^2 49$, $p = 0.001$, fig 1). There was no significant difference between raised (> 2.60 pg/ml) IL- 1β concentrations (two of 26 patients with Guillain-Barré syndrome *v* none of 23 disease controls) and raised (> 200 pg/ml) IFN- γ concentrations (11 of 26 patients with Guillain-Barré syndrome *v* seven of 23 disease controls). The peak grade of clinical deficit correlated with TNF- α concentrations ($r = 0.6$, $p < 0.01$, fig 2). There was no significant difference between patients with and without evidence of a preceding infection.

Clinical Immunology Laboratory,
Department of Immunology, The Medical School, Edgbaston, Birmingham B15 2SZ, UK

A R Exley
N Smith
J B Winer

Correspondence to:
Dr A R Exley

Received 13 December 1993
and in final revised form
28 February 1994.
Accepted 8 March 1994

Figure 1 Plasma cytokine concentrations in patients with Guillain-Barré syndrome and neurological controls. Patients are shown by filled circles, disease controls by open circles.

Figure 2 Plasma TNF- α concentrations in patients with Guillain-Barré syndrome according to peak deficit.

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.¹⁰ The detection of these antibodies is not specific for Guillain-Barré syndrome and their presence correlates with axonal damage.^{11,12} 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.¹³ Other products of activated T cells such as serum interleukin-2 (IL-2) and IL-2 receptor levels are raised in Guillain-Barré syndrome.^{14,15} 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 multi-functional, cytotoxic polypeptide that can induce myelin damage and necrosis of oligodendrocytes in vitro.^{13,16} 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-1 β 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.^{17,18}

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.¹⁹ Preliminary studies identified mRNA for TNF- α in necropsy specimens of peripheral nerve from patients with Guillain-Barré syndrome.²⁰ Sequential studies in experimental allergic neuritis have shown a temporal association between the detection of immunoreactive TNF- α and peripheral nerve demyelination.²¹ 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.²²

This work was supported by a grant from the Arthur Thompson Trust. We thank Dr Boughton for help in obtaining plasma samples. These data were reported in part in abstract form at the Peripheral Nerve Study Group 11th Biennial meeting, Jakobsberg, Boppard, Germany, July 1993.

- Guillain-Barré Syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. *Neurology* 1984;35: 1096-104.
- Osterman PO, Fagius J, Ludemo G, et al. Beneficial effects of plasma exchange in acute inflammatory polyneuropathy. *Lancet* 1984;2:1296-9.
- French Co-operative Group on plasma exchange in Guillain-Barré syndrome. Plasma exchange in Guillain-Barré syndrome: one year follow-up. *Ann Neurol* 1992; 32:94-7.
- Winer JB. Guillain-Barré syndrome revisited. *BMJ* 1992; 304:65-6.
- Lampert PW. Mechanism of demyelination in experimental allergic neuritis: electron microscope studies. *Lab Invest* 1969;20:127-38.

- 6 Prineas JW. Acute idiopathic polyneuritis: an electron microscope study. *Lab Invest* 1972;26:133-47.
- 7 Burke F, Naylor MS, Davies B, Balkwill FR. The cytokine wall chart. *Immunol Today* 1993;14:165-70.
- 8 Asbury AK. Diagnostic considerations in Guillain Barré syndrome. *Ann Neurol* 1981;9S:1-5.
- 9 Michie HR, Manogue KR, Spriggs DR, Revhaug A, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988;318:1481-6.
- 10 Ilyas AA, Willison HJ, Quarles RH. Serum antibodies to gangliosides in Guillain-Barré syndrome. *Ann Neurol* 1988;23:440-7.
- 11 Enders U, Karch H, Toyka KV, Michels M, et al. The spectrum of immune responses to *Campylobacter jejuni* and glycoconjugates in Guillain-Barré syndrome and in other neuroimmunological disorders. *Ann Neurol* 1993;34:136-44.
- 12 Yuki N, Yoshino H, Sato S, et al. Severe acute axonal form of Guillain-Barré syndrome associated with IgG anti-GD1a antibodies. *Muscle Nerve* 1992;15:899-903.
- 13 Beutler B, Cerami A. The biology of cachectin/TNF—a primary mediator of the host response. *Ann Rev Immunol* 1989;7:625-55.
- 14 Hartnung HP, Reiners K, Schmidt B, Stoll G, Toyka KV. Serum interleukin-2 concentrations in Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculopathy; comparison with other neurological diseases of presumed immunopathogenesis. *Ann Neurol* 1991;30:48-53.
- 15 Bansil S, Mithen FA, Cook SD, Sheffert A, Rohowsky-Kochan. Clinical correlation with serum soluble interleukin-2 receptor levels in Guillain-Barré syndrome. *Neurology* 1991;41:1302-5.
- 16 Selmaj K, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. *Ann Neurol* 1988;23:339-46.
- 17 Tsukada N, Miyagi K, Matsuda M, Yanagisawa N, Yone K. Tumor necrosis factor and interleukin-1 in the CSF and sera of patients with multiple sclerosis. *J Neurol Sci* 1991;102:230-4.
- 18 Sharief MK, McLean B, Thompson EJ. Elevated serum levels of tumor necrosis factor- α in Guillain-Barré syndrome. *Ann Neurol* 1993;33:591-6.
- 19 Spies JM, Westland KW, Bonner JG, Pollard JD. Cytokines of activated T cells open the blood nerve barrier. Peripheral Nerve Study Group, 11th biennial meeting [abstracts]. Jakobsberg, Boppard, Germany: July 1993, 95. Aachen: Institute of Neuropathology, 1993.
- 20 Griffin JW, Ho T, Wesselingh SL, Li CY, Asbury AK. Immunopathology of the Guillain-Barré syndrome. Peripheral Nerve Study Group 11th biennial meeting [abstracts]. Jakobsberg, Boppard, Germany: July 1993, 1. Aachen: Institute of Neuropathology, 1993.
- 21 Stoll G, Jung S, Jander S, et al. Tumor necrosis factor- α in immune-mediated demyelination and Wallerian degeneration of the rat peripheral nervous system. *J Neuroimmunol* 1993;45:175-82.
- 22 Fomsgaard A, Svenson M, Bendtzen K. Auto-antibodies to tumour necrosis factor- α in healthy humans and patients with inflammatory diseases and Gram-negative bacterial infections. *Scand J Immunol* 1989;30:219-23.