Journal of Neuroimmunology 279 (2015) 7–10

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Serum cytokine and chemokine profiles in patients with chronic inflammatory demyelinating polyneuropathy

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ARTICLE INFO

Article history:
Received 29 September 2014
Received in revised form 14 December 2014
Accepted 17 December 2014

Keywords:
Chronic inflammatory demyelinating polyneuropathy
Cytokine
HGF
MIP-1α
TNF-α
MIP-1β
IL-1β

ABSTRACT

To identify serum cytokine networks specific to chronic inflammatory demyelinating polyneuropathy (CIDP), serum samples of two subgroups (18 patients with typical CIDP and 12 patients with multifocal acquired demyelinating sensory and motor neuropathy [MADSAM]) were analyzed with multiplex magnetic bead-based cytokine assay. TNF-α, HGF, MIP-1β and IL-1β levels were significantly higher in total CIDP patients than in normal controls. Of these, HGF levels were elevated in typical CIDP patients, but not in MADSAM patients. Patients with high HGF levels showed good responses to steroid treatment. Different cytokine profiles among the CIDP subtypes presumably reflect differences in pathophysiology.

1. Introduction

CIDP is an inflammatory demyelinating disease of the peripheral nervous system. Current hypotheses on the pathogenesis of CIDP are in support of an autoimmune mechanism. Immunohistochemical studies of nerve biopsies have shown T cells infiltrating together with macrophages in the absence of B cells and immunoglobulin deposition (Matsumuro et al., 1994; Rizzuto et al., 1998). Chemokines play a central role in the recruitment of leukocytes to the inflamed tissue. An increase in chemokines, such as CXCL10 (IP-10), attracting mainly Th1 cells, has been reported (Kieseier et al., 2002; Mahad et al., 2002; Press et al., 2003). A study comparing Th1- and Th2-associated cytokines in CIDP patients demonstrated up- and down-regulation of Th1 and Th2 cytokines, respectively (Mei et al., 2005).

On the other hand, plasma exchange is effective in some patients with CIDP, supporting the theory that autoantibodies are related to the pathogenesis. A few reports are available on autoantibodies in CIDP patients. Autoantibodies to myelin proteins and gangliosides have been identified in patients with CIDP (Koski et al., 1985; Tagawa et al., 2000; Yan et al., 2001); however, these autoantibodies were detected only in some patient subgroups. Hence, the significance of autoantibodies remains unclear.

These data show that both humoral and cellular immune factors contribute to the pathogenesis; however, the exact mechanisms remain unclear. This is probably because CIDP is a heterogeneous disease.

Patients with CIDP have several different patterns of clinical course, response to treatment and outcome (McCombe et al., 1987; Barohn et al., 1989; Hughes et al., 1992), and therefore, CIDP is considered to be a heterogeneous disorder. We have previously shown that CIDP has several patterns in the distribution of demyelinating lesions (Kuwabara et al., 2002). By the diagnostic criteria proposed by European Federation of Neurological Societies/Peripheral Nerve Society

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; GBS, Guillain–Barré syndrome; IL, interleukin; FGF-2, fibroblast growth factor-2; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; IP-10, 10 kDa IFN-γ-induced protein; MCP-1, monocyte chemotactic protein-1; MIP, macrophage inflammatory protein; PDGF-BB, platelet-derived growth factor-BB; RANTES, regulated upon activation, normal T cell expressed and secreted chemokine; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; CTACK, Cutaneous T-cell-attracting chemokine; GRO-α, growth-related oncogene-α; HGF, hepatocyte growth factor; LIF, leukemia inhibitory factor; MCP-3, monocyte chemoattractant protein-3; M-CSF, macrophage colony-stimulating factor; MIF, macrophage migration inhibitory factor; MIG, monokine induced by interferon γ; NGF, nerve growth factor; SCF, stem cell factor; SCGF-β, stem cell growth factor-β; SDF-1α, stromal cell-derived factor-1α; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

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http://dx.doi.org/10.1016/j.jneuroim.2014.12.017
0165-5728/

(EFNS/PNS), the disease types of CIDP are classified as 'typical CIDP' and 'atypical CIDP' (Van den Bergh et al., 2010). To date, there have been few reports on CIDP subgroups; however, it is likely that research into the specific differences of the subgroups will contribute to elucidating the pathogenesis of CIDP.

In the present study, we examined the difference of the cytokine patterns between the two subgroups of CIDP, using a multiplex bead-based ELISA on a suspension array system. This study is the first to examine the differences of cytokine patterns among CIDP subgroups.

2. Materials and methods

2.1. Subjects and samples

Pre-treatment sera were obtained from 30 patients (19 men) with CIDP, all of whom fulfilled the EFNS/PNS diagnostic criteria of CIDP. According to the clinical criteria of the EFNS/PNS guidelines, we classified the patients into the following two subgroups: typical CIDP and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) (Van den Bergh et al., 2010); patients with other clinical subtypes of atypical CIDP were excluded from this study because of the small number of patients (0 or 1) during the study period.

Serum samples were obtained at the untreated state. Control sera were obtained from 18 age-matched normal individuals (10 males and eight females), and sera from 19 patients (nine males and 10 females) with Guillain–Barré syndrome (GBS) within 3 weeks of the onset before therapy served as disease controls. All subjects gave informed consent, and all procedures were approved by the Ethics Committee of the Chiba University School of Medicine.

2.2. Cytokine assays

Serum concentrations of 47 cytokines/chemokines were measured using the Bio-Plex human 27-Plex and 21-Plex cytokine panels and a Bio-Plex cytokine reagent kit (Bio-Rad, Hercules, CA) according to the manufacturer's instructions. The 48-cytokine panel comprised interleukin (IL)-1β, IL-1 receptor antagonist (IL-1ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, eotaxin, fibroblast growth factor (FGF)-2, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, 10 kDa IFN-γ-induced protein (IP-10), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β, platelet-derived growth factor (PDGF)-BB, regulated upon activation, normal T cell expressed and secreted chemokine (RANTES), tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), IL-1α, IL-2Rα, IL-3, IL-12(p40), IL-16, IL-18, Cutaneous T-cell-attracting chemokine (CTACK), GRO-α, hepatocyte growth factor (HGF), IFN-α2, leukemia inhibitory factor (LIF), monocyte chemoattractant protein-3 (MCP-3), macrophage colony-stimulating factor (M-CSF), macrophage migration inhibitory factor (MIF), monokine induced by interferon γ (MIG), β-nerve growth factor (NGF), stem cell factor (SCF), stem cell growth factor-β (SCGF-β), stromal cell-derived factor-1α (SDF-1α), TNF-β and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Serum samples were stored at −80 °C until cytokine analysis.

2.3. Statistical analysis

The differences in cytokine levels between the different groups (CIDP, healthy subjects, and GBS patients) were compared by non-parametric paired Wilcoxon tests. In cases where serum values were under the detection range, values were replaced by the lower detection limits.

3. Results

3.1. Elevated cytokines in serum with CIDP

We analyzed serum samples of 30 patients (19 males and 11 females) with CIDP. Eighteen patients (12 males and six females) were diagnosed as typical type and 12 patients (seven males and five females) as MADSAM.

Among the 47 cytokines analyzed, the following were lower than the measurable limits in all the samples: GM-CSF, IFN-α2, IL-1α, IL-3, IL-5, Il-12(p40), IL-15 and LIF. Detailed data of the cytokine profiles are shown in Supplementary data. Five cytokines (HGF, TNF-α, IL-1β, MIP-1α, and MIP-1β) were significantly upregulated in total CIDP, compared with normal controls (Fig. 1). In patients with typical type CIDP, serum levels of HGF and MIP-1β were increased, whereas in MADSAM patients, serum TNF-α, IL-1β and MIP-1α were increased (Fig. 1). In patients with GBS, HGF and IL-1β levels were also high, but TNF-α, MIP-1α and MIP-1β were not increased, compared with normal controls.

3.2. Clinical features of patients with high cytokine levels

HGF levels were significantly higher in the typical type CIDP patients compared with MADSAM patients. Table 1 shows the clinical features of patients with high HGF levels (greater than 2 SD above the mean value of normal controls). All patients showed good response to steroid treatment and had a favorable clinical outcome.

All five patients with high values in IL-1β (above 10 pg/ml) showed high values in TNF-α, MIP-1α and MIP-1β, but they had different phenotype. Four of them presented typical CIDP, and one MADSAM. Among four patients with typical CIDP, they showed various clinical courses (onset and severity).

4. Discussion

In this study, we have provided data indicating that several cytokines are increased in patients with total CIDP and that HGF levels are increased only in patients with typical CIDP. Previous studies on cytokine levels in patients with CIDP have shown an increase of both CXC and CC chemokines (Kieseier et al., 2002; Mahad et al., 2002; Ochi et al., 2003; Press et al., 2003). CXC chemokines predominantly recruit T lymphocytes, whereas CC chemokines recruit both T lymphocytes and monocytes. Similar results were obtained in our study. MIP-1α and MIP-1β, which are CC chemokines, were increased in patients with total CIDP. Both MIP-1α and MIP-1β stimulate CCR5, expressed in Th1 cells, and these chemokines are elevated in sciatic nerves of EAN rats prior to the development of a severe clinical disease (Kieseier et al., 2000). These findings suggest that the two CC chemokines may be related to the recruitment of the inflammatory T cells and monocytes to the peripheral nerve systems.

Increased serum TNF-α concentration has been reported in patients with CIDP (Misawa et al., 2001). Consistent with a previous study, our data showed elevated TNF-α levels in total CIDP. Recent studies showed that TNF-α had toxic effects on myelin, Schwann cells, and endothelial cells (Selmaj and Raine, 1988), increased vascular permeability (Tracey et al., 1988; Sharief et al., 1992), and broke down the blood–brain barrier (Uncini et al., 1999) and blood–nerve barrier (Redford et al., 1995). These results suggested that TNF-α could be involved in the pathogenesis of demyelination and the breakdown of the blood–nerve barrier in CIDP.

We found increased levels of HGF in the serum of patients with total CIDP. In a previous study, HGF levels were also increased in the CSF of patients with CIDP (Sainaghi et al., 2010). High HGF levels were also seen in GBS patients, and those were not disease-specific in CIDP. HGF was first identified as a potent mitogen for mature hepatocytes and was molecularly cloned in 1989 (Nakamura et al., 1984, 1989). HGF exerts neurotrophic effects on various types of neurons including