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Th1/Th2 cytokine balance and nitric oxide in cerebrospinal fluid and serum from patients with multiple sclerosis

Abstract

Tumor necrosis factor (TNF-alpha) and IL-10 are key regulators of the T helper (Th)1/Th2 balance, which is critically skewed in many pathological conditions including immune-mediated inflammatory diseases of central nervous system (CNS) such as multiple sclerosis (MS). Nitric oxide (NO) has been reported to have dual effects on CNS pathology, and to play an important role in MS. We

performed a cross-sectional study in 17 randomly selected patients during MS flare-up, and compared levels of TNF-alpha, IL-10 and NO in serum and cerebrospinal fluid (CSF) with the serum values of these mediators in two different control groups, healthy subjects and HIV-infected untreated patients. Serum and CSF values of TNF-alpha, IL-10 and NO were higher in MS patients than in the serum of healthy controls. Two MS patients showed increased levels of NO in CSF, with inversion of the NOSERUM/NOCSF quotient, which is clearly indicative of an intrathecal production of NO. No correlation among the values of both cytokines and NO, and the laboratory parameters analysed in MS patients (IgG index, presence of IgG oligoclonal bands and albumin quotient) was found. The high levels of TNF-alpha and IL-10 (both in serum and CSF) accompanying an MS attack suggest a simultaneous expression of Th1 and Th2 cytokines as opposed to sequential expression of Th1 followed by Th2 as described in the models of experimental autoimmune encephalomyelitis (EAE). Globally, our results support the inherent heterogeneity of the disease.

Full text

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the central nervous system (CNS). The paradigm that multiple sclerosis is causally related to a dysregulation of the balance between proinflammatory Th1-type cytokines and anti-inflammatory Th2-type cytokines mantains a strong foothold in MS research, despite recent critical re-evaluation [1, 2]. This paradigm is mostly based on studies of Th1-mediated experimental autoimmune encephalomyelitis in rodents and monkeys [3]. However, recent data from diverse areas of research challenge this view, with consequences both on the elucidation of MS pathogenesis, and on the urgently needed development of body fluid marker assays to appropriately predict and reflect disease activity.

Cytokines play a critical role in the physiopathology of MS. Currently, Th1-type cytokines are thought to be potent inflammatory inducers, while those of the Th2-type function as regulators to suppress inflammation. Pro-inflammatory Th1 cytokines (*e.g.*, tumor necrosis factor alpha, (TNF-alpha) facilitate migration of inflammatory cells into the CNS and exacerbate myelin-destructive inflammation [3-5]. Th2 cytokines (*e.g.*, IL-10) have anti-inflammatory properties and are known to downregulate Th1 responses [6, 7].

In addition, nitric oxide (NO) has been implicated in the immunopathogenesis of inflammatory diseases of the CNS including MS [8, 9]. NO has a powerful influence on many aspects of the CNS, including synapse plasticity, neuronal development and behaviour responses. It is known that isoforms of nitric oxide synthase (NOS) are not confined to separate cellular lines but rather they can coexist in the same type of cell [9]. NO may be a double-edge sword, mediating neurotoxicity [10] on the one hand and on the other, modulating complex immunological functions which may be protective; recent studies correlate cerebrospinal fluid or serum levels of NO with relapse and other studies suggest that it may be beneficial in the course of inflammation, with a potential role in the elimination of autoreactive T cells, by apoptosis [8].

Since the precise role of Th1 and Th2-type cytokines and NO in MS is still under debate and most findings derive from animal models, the aim of this study was to analyse the expression of TNF-alpha, IL-10, and NO both in CSF and serum of MS patients in acute clinical flare-up, and to investigate the correlation between their levels and other immunological markers of MS.

PATIENTS AND METHODS

A cross-sectional study was carried out in a cohort of 17 randomly selected MS patients with clinical flare-up admitted to the Department of Neurology, General University Hospital "Gregorio Marañón", Madrid. The patients had not received any immunomodulatory drugs for at least for two months prior to the study and were classified into several diagnostic categories based on their clinical manifestations: relapsing-remitting MS (8 patients), chronic progressive MS (1 patient) and probable MS (8 subjects with a first clinical attack suggestive of demyelinating disease, which was later confirmed as MS on the basis of abnormal magnetic resonance imaging (MRI) cranial and/or medullar scan and/or abnormal CSF). Two control groups were included for cytokine and NO levels; 17 healthy subjects for standard baseline measurements, and another control group of 17 HIV^+ patients, antiretroviral therapy naive and considered as positive controls showing high levels of TNF-alpha and NO [11].

All 17 MS patients were studied by cranial and/or medullar magnetic resonance imaging (MRI) to confirm the clinical diagnosis. In all cases the patient's informed consent was obtained.

IgG index, albumin quotient and oligoclonal IgG bands determinations

Patients underwent vene and lumbar puncture between 9:00 and 10:30 h a.m. The CSF and serum samples were frozen at - 20° C until use. IgG and albumin concentrations were determined by kinetic nephelometry (Immage System, Beckman Instruments Inc., Brea, California, USA). Albumin quotient and IgG index were calculated according to the formula of Link & Tibbling [12]. Isoelectric focusing (IEF) and immunofixation with anti-human IgG were performed to detect IgG oligoclonal bands, using the CSF Analysis Kit for Phast System, according to the manufacturer´s instructions (Amersham Pharmacia Biotech, D-79111 Freiburg, Germany). Briefly, IEF electrophoresis-based analysis of CSF and corresponding serum allows the detection of intrathecally synthesized oligoclonal IgG bands in the CSF, not present in the corresponding serum [13]. An increased IgG index and positive oligoclonal bands in CSF are paraclinical criteria indicative of MS.

*TNF-*alpha*, IL-10 and NO production assays*

Cytokine and NO contents in serum were quantified by commercially available, specific enzyme-linked immunoabsorbent assays (ELISAs) in the MS group and in the two control groups in parallel, according to kit instructions. TNF-alpha and IL-10 measurements were carried out as described previously [14] (Innogenetics, Haven, Zwijnaarde, Belgium), and NO production was assessed by the Inc Bioxytech Nitric Oxide Assay (Portland USA), based on the Griess reaction [15]. All concentrations were measured twice. These assays have been extensively validated on human body fluids.

Statistical analysis

Data are presented as mean ± standard deviation. Results were analysed using the non-parametric Mann Whitney U-test; $p < 0.05$ was considered significant.

RESULTS

Demographic characteristics of MS patients at entry to the study are shown in Table 1. Figure 1 shows the individual titration values for TNF-alpha and NO compared between groups, and CSF values compared to serum levels in healthy controls.

The serum values of TNF-alpha from patients with MS were significantly higher than those from the healthy controls and even higher than those in HIV^+ infected patients ($p < 0.001$ and $p < 0.05$, respectively) (Table 2). The serum values of NO were significantly higher in the MS patients compared to healthy controls ($p < 0.005$), but no significantly different from the values found in the HIV-1-infected, untreated patients. Moreover, serum levels of IL-10 were also higher in MS patients than in the two groups of controls, whose levels were undetectable at assay sensitivity.

In our laboratory practice, CSF concentrations of TNF-alpha, IL-10 and NO from patients with diverse and heterogeneous pathological conditions are usually undetectable. However, the values of these parameters in our cohort of MS patients were always above the limit of detection of the techniques. Moreover, the patients with MS had values of TNF-alpha, and NO in CSF which were significantly higher than those in the serum of healthy subjects ($p < 0.001$; and $p < 0.05$, respectively) (Table 2). Interestingly, two of our MS patients showed values of NO in the CSF, higher than in serum: one patient diagnosed with relapsing-remitting MS (IgG Index = 2.54 and presence of OB in CSF) showed a concentration of NO in CSF 100-fold higher to that in serum, and another patient diagnosed with a first bout of MS (IgG Index = 0.77 and positive OB) showed values of NO in CSF 3-fold higher than in serum. Both patients had values of TNF-alpha higher than healthy controls.

However, no correlation between TNF-alpha, IL-10, NO values and the analysed laboratory parameters, IgG index, presence of IgG oligoclonal bands in CSF and albumin quotient, was found.

DISCUSSION

Recent data prompted us to reconsider the role of the Th1 and Th2-type cytokines in MS and the importance of elucidating the effector mechanisms of the disease and their dependence on the Th1 and Th2 signals. Although traditionally a cytopathic role for TNF-alpha is accepted, several recent findings suggest that TNF-alpha is implicated in the regulation of the autoreactive T cells and in the induction of the immune tolerance. A neuroprotective role for TNF-alpha has even been assumed, on one hand inducing the superoxide dismutase, an enzyme that protects neurons from the potentially damaging effects of reactive oxygen species and on the other hand stabilising calcium homeostasis

[4]. When considering the pathogenic role of TNF-alpha in MS, the key question is whether it participates directly in the process leading to cellular death, or whether it promotes proliferation and hence repair and recovery (pro-inflammation *versus* pro-remyelination).

We have found higher values of TNF-alpha in serum from patients with MS in acute clinical flare-up than in controls, in agreement with previously reported data [4, 16, 17]. More interestingly, TNF-alpha was increased in CSF of MS patients even above serum levels of controls. Whether TNF-alpha is inducing pro-inflammation or pro-remyelination (or both), requires further investigation.

Serum concentrations of NO in our patients with MS were higher than in healthy controls, which is in agreement with some published data [18], although other authors have shown contradictory results [19]. These discrepancies may be due to the different measurement methods or the type of patients studied. We have also found high values of NO in the CSF, in 15 of the 17 studied MS patients. Two of them showed increased values of NO in CSF with inversion of the NO_{SERUM}/NO_{CSF} quotient, which is clearly indicative of an intrathecal production of NO. In our study, only one of these two patients had an abnormally high albumin quotient, suggesting an alteration of the blood-brain barrier. Although our data do not demonstrate a correlation between TNF-alpha and NO, they suggest that both mediators play an important role in the pathogenesis of MS. Moreover, our results seem to indicate that the underlying pathogenesis is heterogeneous since we no found correlation within MS groups between pro-inflammatory cytokines and the indexes of IgG, oligoclonal bands and albumin quotients.

The relationship between Th1 and Th2 cytokines in MS is based fundamentally on studies in animal models of EAE. Mice with EAE show a sequential expression, with Th1 cytokines first and Th2 later, that correlate respectively with the acute phase and the recovery. For this reason, MS is considered a Th1-mediated autoimmune disease; however, we found high levels of IL-10 (both in serum and in CSF) in acute flare-up, in accordance to what happens in the model of EAE in outbred marmoset monkey *(Callithrix jacchus)*, in which a simultaneous expression of Th1 and Th2 cytokines in the earliest lesion stages exists, with strong expression of IL-10 by cells of astrocyte morphology in the immediate vicinity of the perivascular infiltrates [17].

Moreover, in MS, it has not yet been possible to fully substantiate the concept of sequential Th1 disease-promoting activity and Th2 downregulatory activity as developed in EAE models, and therefore the validity of the Th1/Th2 concept as the basis for immunotherapy in MS has been challenged. Redundancy and the pleiotropic nature of cytokines, and their dual effects (pro- or anti-inflammatory) have limited their use in clinical practice and emphasise the need for cautious use of the Th1/Th2 concept derived from EAE studies. The understanding of how, where, and when, during the CNS immune response, do cytokines exert their effects (pro-inflammatory or pro-remyelinating) is crucial in planning future strategies for therapeutic intervention.

CONCLUSION

Finally, during recent years, attempts to correlate cytokines and MRI results, TNF-alpha expression and clinical evolution or between raised levels of NO and MRI activity or disease progression, have failed [16, 20]. A significant correlation between IL-10 levels and the IgG index, and the OB of IgG in the CSF of MS patients has been reported in a recent study [21]; we, however, have not observed this correlation. This is not surprising given the inherent heterogeneity observed with respect to the clinical, radiographic, genetic and morphological features of this disease [22]. More extensive studies are required to further confirm these observations.

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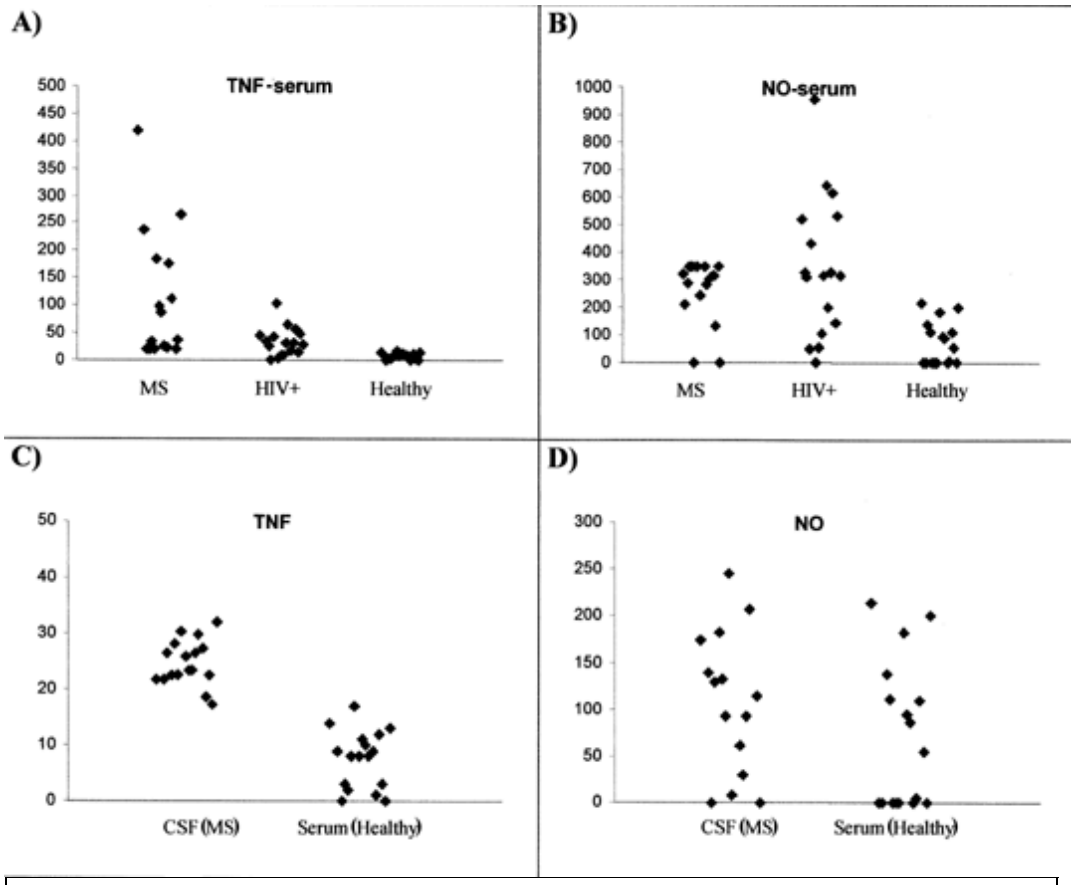


Figure 1

Comparison of individual concentration values of TNF and NO between groups: A: Serum TNF; **B:** Serum NO; **C:** TNF-alpha in CSF with respect to serum values in healthy individuals; **D:** NO in CSF with respect to serum values in healthy individuals.

Table 1
Demographic characteristics of the cohort of MS patients at the entry to the study

N° of patients	17
Age (mean ± SD)	33.35 ± 2.44
Gender	
Male/Female	9/8
Diagnosis	
MS-RR	8
MS-Progresive	1
MS-first bout	8

SD: standard deviation; MS: multiple sclerosis; RR: relapsing remitting.

Table 2
Cytokine and NO levels in serum and CSF of MS patients and controls (VIH⁺ C and Healthy C)

	TNF_{SERUM}	$IL\text{-}10_{SERUM}$	NO_{SERUM}	TNF_{CSF}	$IL\text{-}10_{CSF}$	NO_{CSF}
Acute MS (n = 17)	185 ± 79.5	16.6 ± 1.5	511.3 ± 252.1	24.7 ± 0.98	16.9 ± 2.1	719.2 ± 560.2
HIV⁺ C (n = 17)	32.9 ± 5.1	U.D.	344.9 ± 61.4	–	–	–
Healthy C (n = 17)	7.5 ± 1.2	U.D.	70.35 ± 18.9	–	–	–
Acute MS *versus* HIV⁺ C	$p < 0.05$	–	N.S.	–	–	–
Acute MS *versus* Health C	$p < 0.001$	–	$p < 0.005$	$p < 0.001$*	–	$p < 0.05$*

TNF-α and IL-10 concentrations are expressed as pg/ml ± standard error of mean (SEM), and NO in nM ± SEM (U.D.: undetectable at assay sensitivity determined to be 2 pg/ml; N.S.: not significant).
*Acute MS (CSF values) *versus* healthy controls (serum values).

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