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# **The cerebrospinal fluid CD4/CD8 ratio and interleukin-6 and -10 levels in neurosarcoidosis: a multicenter, pragmatic, comparative study**

Running title: Cerebrospinal fluid markers in neurosarcoidosis

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## **Abstract**

**Objectives:** Neurosarcoidosis is a rare inflammatory disorder of unknown cause. The aim of this study was to evaluate the value of T/B lymphocyte population counts and the concentrations of the cytokines IL-6 and 10 in the cerebrospinal fluid (CSF) of neurosarcoidosis patients.

**Methods:** We conducted a retrospective study of CSF biomarkers in patients with neurosarcoidosis who underwent CSF analysis between 2012 and 2017 as well as various control populations.

**Results:** We analyzed 43 patients with neurosarcoidosis, 14 with multiple sclerosis (MS), and 48 with other inflammatory disorders. The IL-6 levels were higher in sarcoidosis patients than in MS patients (median 8 versus 3 pg/mL,  $p=0.006$ ). The CD4/CD8 ratio was higher in sarcoidosis patients than in MS patients and in patients with other inflammatory disorders (median 3.18 versus 2.36 and 2.10, respectively,  $p=0.008$ ). The IL-6 level was higher in patients with active neurosarcoidosis than in non-active neurosarcoidosis patients (median 13 versus 3 pg/mL,  $p=0.0005$ ). In patients with neurosarcoidosis, a CSF IL-6 concentration  $>50$  pg/ml was associated with a higher risk of relapse or progression-free survival (Hazard Ratio 3.60; 95% Confidence Interval 1.78-23.14). A refractory neurosarcoidosis patient was treated with an anti-IL-6 monoclonal antibody that produced a complete neurological response.

**Conclusions:** The CSF CD4/CD8 ratio and IL-6 concentration are increased in neurosarcoidosis compared to MS and other inflammatory disorders. A CSF IL-6 concentration  $> 50$  pg/mL is associated with relapse or progression of neurosarcoidosis. IL-10 levels may be elevated in neurosarcoidosis.

	<b>Neuro-sarcoidosis n=43</b>	<b>Multiple sclerosis n=14</b>	<b>p**</b>	<b>Others n=48</b>	<b>p***</b>
<b>IL-6 (pg/mL), median (range)</b>	n=43 <b>8 (2-1158)</b>	n=13 <b>3 (2-17)</b>	0.006*	n=42 <b>5 (2-2037)</b>	0.012*
<b>IL-10 (pg/mL), median (range)</b>	n=43 <b>2 (2-132)</b>	n=13 <b>2 (2-2)</b>	0.069	n=42 <b>2 (2-436)</b>	0.092
<b>CD4/CD8, median (range)</b>	n=29 <b>3.18 (1.34-13.83)</b>	n=12 <b>2.36 (1.18-3.90)</b>	0.044*	n=29 <b>2.10 (0.78-5.44)</b>	0.008*
<b>CD19, % median (range)</b>	n=29 <b>1.00 (0.00-15.00)</b>	n=12 <b>1.00 (0.00-12.00)</b>	0.80	n=29 <b>2.00 (0.00-70.00)</b>	0.89

**Table 1. Cerebrospinal fluid lymphocyte population counts and interleukin (IL) concentrations**

\* statistically significant \*\* comparison between neurosarcoidosis and multiple sclerosis patients \*\*\* comparison between neurosarcoidosis, multiple sclerosis, and other patients

	<b>ePost&gt;0</b>	<b>ePost=0</b>	<b>p</b>
<b>IL-6 (pg/mL), median (range)</b>	n=26 <b>13 (2-1158)</b>	n=17 <b>3 (2-95)</b>	0.0005*
<b>CD4/CD8, median (range)</b>	n=21 <b>3.60 (1.34-13.83)</b>	n=8 <b>2.54 (1.49-5.21)</b>	0.12

**Table 2. Cerebrospinal fluid CD4/CD8 ratio and interleukin-6 level in neurosarcoidosis patients.**

Comparison between active (ePost>0) and non-active (ePost=0) patients.

\* statistically significant

Sarcoidosis is a multisystem disease characterized by the formation of noncaseating granulomas in various organs [1]. Central nervous system (**CNS**) involvement is clinically present in 5% of cases, and represents a major cause of disability [2].

Neurosarcoidosis is a challenging condition [3]. First, CNS localization of sarcoidosis may be the first manifestation of the disease and should be differentiated from a broad range of inflammatory, infectious and neoplastic conditions, such as multiple sclerosis, infectious meningitis, neoplasia (solid tumors and lymphoma), histiocytic disorders and other autoimmune conditions. Next, the diagnosis of sarcoidosis relies on the documentation of noncaseating granulomas, but the accessibility of the CNS for a biopsy is low [4]. Finally, the course of neurosarcoidosis involves frequent relapses despite treatment with glucocorticosteroids and immunosuppressive drugs [5].

We lack biomarkers for diagnosis and prognosis in neurosarcoidosis. Cerebrospinal fluid (**CSF**) analysis usually reveals lymphocytic meningitis, sometimes with low glycorrachia levels and specific oligoclonal bands [6]. However, all these biological findings have been reported in other inflammatory, infectious or neoplastic conditions. Typical sarcoidosis granulomas comprise histiocytic cells (epithelioid and multinucleated giant cells) and T CD4 lymphocytes. Therefore, patients with sarcoidosis harbor a blood T CD4 lymphopenia together with an enrichment of T CD4 lymphocytes in the organs. The CD4/CD8 ratio serves as a biomarker in the bronchoalveolar lavage (**BAL**); a value of this ratio greater than 3.5 has been demonstrated as a reliable marker for the diagnosis of sarcoidosis rather than other interstitial lung diseases [7]. The value of the CSF CD4/CD8 ratio has been evaluated in a small study of 7 patients; 2 of them had an elevation of the T CD4 lymphocyte subpopulation [8]. However, this study was too small to allow conclusions to be drawn.

CSF interleukin (IL)-6 and IL-10 levels have been used in various neurological conditions. In particular, the concentrations of these cytokines have been evaluated in cerebral lymphoma, multiple sclerosis, and Behcet disease (**BD**) with neurological involvement [9-13]. The CSF IL-6 is elevated in a broad spectrum of neurological diseases, including infectious diseases and neuro-BD. An elevated CSF IL-10 concentration seems to be a reliable marker of lymphoma, but the comparative groups in previous studies did not include patients with neurosarcoidosis [9, 14, 15]. Thus, we aimed to study the lymphocyte subpopulations counts and IL-6 and IL-10 levels in the CSF of patients with neurosarcoidosis, and compared the results with those of patients with other inflammatory disorders of the CNS.

## **Methods**

The lymphocyte population counts and IL-6 and 10 levels were analyzed from backup CSF samples obtained from patients with an inflammatory CNS disorder between 2012 and 2017 in one internal medicine department and 2 neurology departments at the Pitié-Salpêtrière Hospital (Paris, France). The study was approved by the ethics committee Comité de Protection des Personnes Ile de France VI, and was conducted in accordance with the Declaration of Helsinki.

Continuous variables are reported as the mean (standard deviation – **SD**) or median (interquartile range – **IQR**) and were compared using a Mann-Whitney test, Kruskal-Wallis test or Wilcoxon matched-pairs signed-rank test. Categorical variables are reported as the count (percentage) and compared using Fisher's exact test. Survival curves were built using the Kaplan-Meier method considering the time from the first IL-6 concentration measurement to relapse, progression or last follow-up. All of the tests

were two-sided, and a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad V6.0 (GraphPad, La Jolla, CA, USA). The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

## **Results**

### **Clinical characteristics**

Out of 192 patients who had at least one determination of CSF lymphocyte population counts or IL concentrations, 83 were excluded because they had no definite diagnosis of CNS involvement. Thus, we analyzed the results of 47 patients with neurosarcoidosis, 14 with MS and 48 with various CNS inflammatory disorders (including 10 L-group histiocytosis [16], 8 neurolupus, 7 R-group histiocytosis [16], 6 pSS, 4 neuro-BD, and 4 tuberculosis with CNS localization patients). In the neurosarcoidosis group, 3 patients were further excluded because CNS localization was not confirmed and 1 additional patient was excluded because she had both MS and neurosarcoidosis; therefore, 43 patients (19 women and 24 men, mean age at the time of the first concentration measurement 41 years – range: 19-58) were ultimately analyzed in this group. Among these patients, at the time of the first CSF lymphocyte population counts/IL concentration measurement, 26 patients had an ePOST score >0 and were considered “active neurosarcoidosis”, whereas 17 were “non-active”. In the MS group, there were 7 men and 7 women, and the median age at the time of the first CSF analysis was 36 (range 17-58). Eleven patients had remitting-relapsing subtype, and 3 had primary progressive disease. Two patients had only brain localizations, whereas 12 had brain and spine localizations. Eight patients had no treatment at the time of lumbar puncture, one was receiving corticosteroids, 2 were receiving azathioprine, 2 glatiramere acetate,



and one was receiving interferon-beta. In the “others” group, there were 26 men and 22 women, and the median age at the time of the first measurement was 48 (range: 18-86).

### **CSF lymphocyte population counts**

The results of the CSF lymphocytes population counts analysis are shown in **Table 1**.

The CD4/CD8 ratio significantly differed between the 3 groups. Moreover, the CD4/CD8 ratio was higher in neurosarcoidosis patients than in MS patients. Eleven patients had a CD4/CD8 ratio >5: 9 patients with neurosarcoidosis (8 with active and 1 with non-active disease), 1 patient with pSS and 1 patient with neuro-BD. No patient with MS had a CD4/CD8 ratio >5 (the highest ratio in this group was 3.90). The receiver operating characteristic (**ROC**) curves for CD4/CD8 ratio are shown in the **Figure 1**. With a CD4/CD8 cut-off of 3.9, the sensitivity was 28.57% and the specificity 100.0 %, when comparing sarcoidosis versus MS. With a CD4/CD8 cut-off of 3.9 the sensitivity was 28.57% and the specificity 87.18% when comparing sarcoidosis with MS and others. CSF CD19 percentages were low in all groups, except in 4 patients with R-group histiocytosis. CSF CD19 percentages did not differ between the groups. We observed the presence of CD19 lymphocytes in the CSF of 6/12 (50%) MS, 19/29 (66%) neurosarcoidosis, and 15/29 (52%) other patients.

### **CSF IL concentrations**

The CSF IL concentrations are shown in **Table 1**. The CSF IL-6 concentration differed between the 3 groups. The IL-6 level was higher in the neurosarcoidosis and other inflammatory disorder groups than in the MS group. Sixteen patients had an IL-6 level > 20 pg/mL: 13 patients with neurosarcoidosis and 3 patients with R-group histiocytosis. The IL-6 concentration was higher in neurosarcoidosis patients with active disease

compared with those with non-active disease (**Table 2**). The ROC curves are shown in the **Figure 1**. With an IL-6 cut-off of 19.5 pg/mL the sensitivity was 28.95 and the specificity 100.0 %, comparing neurosarcoidosis to MS. With an IL-6 cut-off of 25 pg/mL the sensitivity was 26.32 and the specificity 91.23% comparing neurosarcoidosis versus MS and others. All MS patients had IL-6 levels  $\leq 20$  pg/mL. In the group with no sarcoidosis and no-MS diagnosis, called "others", IL-6 and IL-10 levels did not differ between active and non-active patients. The CSF IL-10 concentration was generally low but sometimes elevated in neurosarcoidosis and other inflammatory disorders, although never in MS. There were no differences between IL-10 concentrations between groups. There were no differences in IL-6 (8.00 for treated and 6.00 for non-treated,  $p=0.60$ ) and IL-10 (2.00 versus 2.00,  $p=0.21$ ) levels between treated and non-treated patients at the time of the analysis, among patients with neurosarcoidosis.

### **Outcomes of neurosarcoidosis**

We studied the outcomes of the 43 patients with neurosarcoidosis. The median duration of their disease since the diagnosis of neurosarcoidosis was 15 months (range: 0-141). At the time of the first CSF lymphocyte population counts and/or IL determination, 28 patients were receiving treatment for neurosarcoidosis (corticosteroids for 27 and/or immunosuppressive drugs for 19, including 8 patients treated with infliximab, an anti-tumor necrosis factor (TNF)- $\alpha$  monoclonal antibody). The IL-6 concentration was measured repeatedly in 28 patients (all treated with steroids, 5 with a first line immunosuppressive drugs, and 23 with a combination of infliximab and low-dose methotrexate in addition to steroids) and decreased under treatment (median at baseline 10, at last determination 6 pg/mL,  $p=0.015$ ). The patients with an IL-6 concentration at baseline  $> 50$  pg/mL had a worse progression or relapse-free survival

than those with IL-6  $\leq$  50 pg/mL (**Figure 2**,  $p=0.0054$ , hazard ratio 3.60; 95% confidence interval 1.78-23.14). The time course of IL-6 is shown in **Figure S1**. The median follow-up was 12 months (range 3-84 months).

Additionally, a 43-year-old woman who had a past history of multiple sclerosis received a diagnosis of multiorgan sarcoidosis with CNS involvement. She was treated with tocilizumab, an anti-IL-6 receptor monoclonal antibody, because of the progression of the neurological localization of sarcoidosis despite treatment with steroids and cyclophosphamide. Additionally, the anti-TNF- $\alpha$  monoclonal antibody, which can be used in refractory neurosarcoidosis, was contraindicated because of her history of multiple sclerosis. The oral prednisone daily dose was not increased, and the patient received the first infusion of tocilizumab in December 2016. After 3 administrations, her brain MRI showed a disappearance of all gadolinium-enhanced lesions (**Figure 3**). The treatment was maintained until July 2018 without side effects. Her prednisone dosage was tapered to 5 milligrams/day.

## **Discussion**

In this study, we report the results of CSF biomarkers in neurosarcoidosis, MS and other inflammatory CNS disorders. We showed that the CD4/CD8 ratio and IL-6 levels were significantly higher in sarcoidosis than MS. We also showed that the IL-6 concentration was significantly higher in neurosarcoidosis patients with active disease compared to those with non-active disease. A high CSF IL-6 concentration ( $>50$  pg/mL) was associated with a shorter time to relapse or progression of neurosarcoidosis. Moreover, a patient with refractory neurosarcoidosis improved after treatment with tocilizumab, which is an anti-IL-6 monoclonal antibody.

### **CSF CD4/CD8 ratio as a diagnostic marker in neurosarcoidosis**

Neurosarcoidosis is challenging to diagnosis and can mimic a broad range of inflammatory diseases. Various CSF biomarkers, e.g., CSF angiotensin conversion enzyme (**ACE**), have been studied for diagnostic and prognostic purposes but yield low reliability [17]. In our study, a CD4/CD8 ratio >5 was highly suggestive of neurosarcoidosis (9 out of 11 patients) and was never observed in MS patients. Moreover, a CSF CD4/CD8 ratio >5 was suggestive of active neurosarcoidosis (8 patients out of 9). The CD4/CD8 ratio has been previously evaluated in the lung for pulmonary manifestations of sarcoidosis [18], in the aqueous humor of sarcoid uveitis patients [19, 20], and in the CSF in a small study of neurosarcoidosis and yielded variable reliability [21]. In our larger study, we demonstrated that CSF CD4/CD8 ratio could be useful for diagnostic and prognostic purposes in neurosarcoidosis patients.

### **CSF IL-6 level as a prognostic marker in neurosarcoidosis**

The CSF IL-6 concentration was elevated in neurosarcoidosis and other inflammatory disorders. In neurosarcoidosis patients, the CSF IL-6 concentration significantly decreased with treatment. Moreover, a CSF IL-6 concentration > 50 pg/mL was associated with a higher risk of relapse and progression. IL-6 expression has been found to be upregulated in granulomas [22]. Moreover, IL-6 is essential for the differentiation of Th17 cells, an IL-17-producing helper CD4+ T cell subset that is involved in sarcoidosis pathogenesis [23]. The CSF IL-6 concentration may be elevated in other inflammatory disorders. In neurosarcoidosis, an elevated CSF IL-6 level seems to be associated with a higher risk of relapse and worse progression-free survival.

### **Targeting IL-6 in neurosarcoidosis**

Neurosarcoidosis is a challenging condition. Glucocorticoids are the cornerstone of treatment for neurosarcoidosis, but they have cumulative toxicity. Immunosuppressive drugs have been used with variable efficacy [5]. Infliximab, a chimeric monoclonal antibody directed against tumor necrosis factor- $\alpha$ , has emerged as a therapeutic option [24, 25]. However, infliximab may have serious adverse effects, and patients have high relapse rates (36-50%) after treatment interruptions. Thus, there is a need for new therapeutic options in neurosarcoidosis. Here, we found that tocilizumab, an anti-IL-6 receptor monoclonal antibody, which was used without increasing the daily steroid dose, was efficacious for treating one neurosarcoidosis patient for whom infliximab was contraindicated. Tocilizumab has been used to treat uveitis, an inflammatory condition that shares pathogenic mechanisms with sarcoidosis [26]. Tocilizumab should probably be investigated in patients with sarcoidosis who are refractory to conventional therapy.

### **Limitations**

Our study has several limitations. The clinical characteristics of the patients were assessed retrospectively. However, this allowed definite diagnoses, since in the setting of neuroinflammatory disorders, the diagnoses might be modified after several months of evolution. The number of samples did not allow multivariate analyses. Finally, we did not obtain CSF samples from patients without neurological diseases.

In conclusion, in this multicenter comparative study, we showed that the CSF lymphocyte population counts and IL-6/IL-10 concentrations were useful diagnostic and prognostic markers. Moreover, IL-6 was found to be an interesting target for the treatment of neurosarcoidosis.



## **Figure legends**

### **Figure 1. Receiver Operating Characteristics (ROC) curves of cerebro-spinal fluid**

**interleukins levels and CD4/CD8 ratio.** A. ROC curve of IL-6 levels between sarcoidosis versus multiple sclerosis and other patients. B. ROC curve of IL-6 levels between sarcoidosis versus multiple sclerosis patients. C. ROC curve of CD4/CD8 ratio between sarcoidosis versus multiple sclerosis and other patients. D. ROC curve of CD4/CD8 ratio between sarcoidosis versus multiple sclerosis patients.

**Figure 2.** Relapse/progression-free survival in neurosarcoidosis patients depending on their cerebrospinal fluid interleukin-6 level.

**Figure 3.** Magnetic resonance imaging (T1-weighted imaging with gadolinium) before and 3 months after tocilizumab treatment (steroid dosage was not increased). The disappearance of multiple leptomeningeal gadolinium-enhanced lesions is shown.

**Figure S1. Time course of IL-6 levels in neurosarcoidosis patients (pg/mL)**

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