



## Short Communication

## Central nervous system infections in the absence of cerebrospinal fluid pleocytosis



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## ABSTRACT

Previous multicenter/multinational studies were evaluated to determine the frequency of the absence of cerebrospinal fluid pleocytosis in patients with central nervous system infections, as well as the clinical impact of this condition. It was found that 18% of neurosyphilis, 7.9% of herpetic meningoencephalitis, 3% of tuberculous meningitis, 1.7% of Brucella meningitis, and 0.2% of pneumococcal meningitis cases did not display cerebrospinal fluid pleocytosis. Most patients were not immunosuppressed. Patients without pleocytosis had a high rate of unfavorable outcomes and thus this condition should not be underestimated.

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## Introduction

The normal white blood cell (WBC) count in the cerebrospinal fluid (CSF) of adults is between 0 and  $5 \times 10^6$  cells/l (Tunkel, 2015). CSF pleocytosis is important in establishing the diagnosis of central nervous system (CNS) infections such as meningitis, encephalitis, and meningoencephalitis. However, the absence of pleocytosis represents a diagnostic challenge to clinicians when suspecting a CNS infection. Under this particular circumstance, can the possibility of meningitis, encephalitis, or meningoencephalitis be excluded? Accordingly, the examining physician should know the frequency, clinical characteristics, and outcomes of different CNS infections that may present with an absence of CSF pleocytosis. Data on this subject in the literature appear to be very limited.

## Methods

The Infectious Diseases International Research Initiative (ID-IRI) study group has been performing large multicenter/multinational studies since 2008, with studies on tuberculous meningitis (Erdem et al., 2015a; Erdem et al., 2014a), herpetic meningoencephalitis (Erdem et al., 2015c), Brucella meningitis (Erdem et al., 2015b), pneumococcal meningitis (Erdem et al., 2014b), and neurosyphilis (Ozturk-Engin et al., 2016). Strengths of all of these studies include the large numbers of patients involved, microbiological confirmation for all patients enrolled, and the inclusion of both patients with and without CSF pleocytosis. Additionally, the first three studies are the largest series published to date in the literature: tuberculous meningitis ( $n = 507$ ), herpetic meningoencephalitis ( $n = 496$ ), Brucella meningitis ( $n = 294$ ), pneumococcal meningitis ( $n = 306$ ), and neurosyphilis ( $n = 141$ ).

In this study, the data of ID-IRI studies were investigated to identify patients without CSF pleocytosis (WBC count of  $\leq 5 \times 10^6$  cells/l). Their clinical presentations, laboratory findings, and outcomes were assessed to provide an insight into this particular condition for the treating clinician.

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## Results

The characteristics of the patients with CNS infections (pneumococcal meningitis, tuberculous meningitis, Brucella meningitis, neurosyphilis, herpes simplex virus (HSV) meningoencephalitis) without CSF pleocytosis are presented in Table 1. According to the data, 32 of 141 patients (18%) with neurosyphilis, 39 of 496 patients (7.9%) with herpetic meningoencephalitis, 19 of 507 patients (3%) with tuberculous meningitis, five of 294 patients (1.7%) with Brucella meningitis, and one of 306 patients (0.2%) with pneumococcal meningitis did not present with CSF pleocytosis. These 96 patients were included in this study.

The mean CSF protein in all five CNS infections was elevated, with some patients also having hypoglycorrhachia (CSF to serum glucose ratio  $\leq 0.5$ ). The mean CSF protein was higher and the mean CSF to serum glucose ratio was lower in those with tuberculous meningitis than in those with herpetic meningoencephalitis ( $p < 0.05$ ). The mean age was  $\geq 49$  years in all groups, and 55 (57%) patients were male. Forty (42%) of the patients had a fever and only seven (7.3%) had the classic meningitis triad. A stiff neck was seen more frequently in tuberculous meningitis (63%) than in the other infections. Immunosuppressive conditions that could predispose to the absence of pleocytosis were not detected in

pneumococcal meningitis or in Brucella meningitis. Furthermore, they were relatively infrequent in neurosyphilis (37%), tuberculous meningitis (15.8%), and herpetic meningoencephalitis (12.8%). A total of 51 (53%) patients had neurological sequelae or died.

## Discussion

This appears to be the largest study evaluating the frequency, clinical characteristics, and outcomes of patients without CSF pleocytosis in five types of CNS infection. Previous studies have described case series of patients without CSF pleocytosis in relation to bacterial meningitis, herpes simplex encephalitis, and enteroviral meningitis (Saraya et al., 2016; Hui Tan et al., 2016; Lin et al., 2016). The lack of CSF pleocytosis in bacterial meningitis is rare, but this can be seen more commonly in viral infections. In this study, the mean values of protein and CSF/blood glucose suggested the probable presence of a CNS infection despite the absence of CSF pleocytosis, stressing the importance of considering the total CSF profile when ruling out a CNS infection. Even though a significant proportion of patients had fever, headache, and altered mental status, only seven of the 96 patients (7.3%) had the classic meningitis triad. In contrast, although neck stiffness was detected in two-thirds of tuberculous meningitis cases, it was seen

**Table 1**  
Characteristics of patients with a CNS infection with no CSF pleocytosis.<sup>a</sup>

|                                            | Pneumococcal meningitis | Tuberculous meningitis          | Brucella meningitis  | Neurosyphilis              | HSV meningoencephalitis |
|--------------------------------------------|-------------------------|---------------------------------|----------------------|----------------------------|-------------------------|
| ID-IRI study                               | Erdem et al. (2014b)    | Erdem et al. (2015a)            | Erdem et al. (2015b) | Ozturk-Engin et al. (2016) | Erdem et al. (2015c)    |
| Number                                     | 306                     | 507                             | 294                  | 141                        | 496                     |
| CSF analysis                               |                         |                                 |                      |                            |                         |
| Pleocytosis absent, <i>n</i>               | 1                       | 19                              | 5                    | 32                         | 39                      |
| Pleocytosis absent, %                      | 0.2%                    | 3%                              | 1.7%                 | 22%                        | 7.9%                    |
| Protein (mg/dl), mean $\pm$ SD             | 1446                    | 305.5 $\pm$ 457.63 <sup>b</sup> | 89.2 $\pm$ 363.43    | 74.9 $\pm$ 114.7           | 77 $\pm$ 48.89          |
| CSF/blood glucose, mean $\pm$ SD           | 0.1                     | 0.45 $\pm$ 0.16 <sup>c</sup>    | 0.51 $\pm$ 0.89      | 0.63 $\pm$ 0.13            | 0.68 $\pm$ 0.57         |
| Demographic and clinical parameters        |                         |                                 |                      |                            |                         |
| Age (years), mean $\pm$ SD                 | 68                      | 49.15 $\pm$ 17.03               | 55.4 $\pm$ 20.27     | 52.15 $\pm$ 14.09          | 57 $\pm$ 20.99          |
| Sex, male, <i>n</i> (%)                    | 1                       | 9 (47%)                         | 2 (40%)              | 26 (81%)                   | 17 (44%)                |
| Fever $>38^{\circ}\text{C}$ , <i>n</i> (%) | 38.2 $^{\circ}\text{C}$ | 13 (68%)                        | 3 (60%)              | 4 (12%)                    | 19 (49%)                |
| Neck stiffness, <i>n</i> (%)               | (–)                     | 12 (63%)                        | 1 (20%)              | 6 (18%)                    | 6 (15%)                 |
| Headache, <i>n</i> (%)                     | (+)                     | 6 (31%)                         | 4 (80%)              | 13 (40%)                   | 22 (56%)                |
| Mental changes                             | (+)                     | 13 (68%)                        | 1 (20%)              | 13 (40%)                   | 33 (85%)                |
| Classic triad <sup>d</sup>                 | (–)                     | 1 (5%)                          | 1 (20%)              | 1 (3%)                     | 4 (10%)                 |
| GCS                                        | 5                       | 10.13 $\pm$ 3.99                | 15 $\pm$ 2.38        | 14.26 $\pm$ 1.45           | 11 $\pm$ 3.92           |
| Potential immunosuppressive conditions     |                         |                                 |                      |                            |                         |
| HIV-positive                               | (–)                     | 2                               | (–)                  | 7 <sup>e</sup>             | (–)                     |
| Diabetes mellitus                          | (–)                     | (–)                             | (–)                  | 3                          | (–)                     |
| Immunosuppressive drugs                    | (–)                     | 1                               | (–)                  | (–)                        | 4 <sup>f</sup>          |
| Solid tumor                                | (–)                     | (–)                             | (–)                  | (–)                        | 1                       |
| Drug addiction                             | (–)                     | (–)                             | (–)                  | 3                          | (–)                     |
| Number (%)                                 | 0 (0)                   | 3 (15.8%)                       | 0 (0)                | 12 (37%)                   | 5 (12.8%)               |
| Outcome                                    |                         |                                 |                      |                            |                         |
| Sequelae, <i>n</i> (%) <sup>g</sup>        | (–)                     | 6 (31%)                         | 1 (20%)              | 12 (37%)                   | 15 (39%)                |
| Death, <i>n</i> (%)                        | Died                    | 5 (26%)                         | (–)                  | 3 (9%)                     | 8 (21%)                 |

CNS, central nervous system; CSF, cerebrospinal fluid; HSV, herpes simplex virus; ID-IRI, Infectious Diseases International Research Initiative; SD, standard deviation; GCS, Glasgow coma scale score.

<sup>a</sup> Pleocytosis: number of patients with  $\geq 5 \times 10^6$  leukocytes/l in the CSF.

<sup>b</sup> Mean CSF protein higher compared to HSV meningoencephalitis by analysis of variance analysis ( $p < 0.05$ ). No differences seen when comparing Brucella meningitis and neurosyphilis to HSV meningoencephalitis ( $p > 0.05$ ).

<sup>c</sup> Mean CSF glucose lower compared to HSV meningoencephalitis ( $p < 0.05$ ). No differences seen when comparing Brucella meningitis and neurosyphilis to HSV meningoencephalitis ( $p > 0.05$ ).

<sup>d</sup> Classic triad: symptoms of fever, headache, and altered mental status.

<sup>e</sup> One patient had co-existing diabetes and HIV infection.

<sup>f</sup> Immunosuppressive medications (cyclosporine, methotrexate, cyclophosphamide, and systemic steroids) for kidney transplantation, chronic inflammatory demyelinating polyneuropathy and intestinal adenocarcinoma, pemphigoid, and Takayasu arteritis.

<sup>g</sup> Focal neurological deficits, seizures, and hydrocephalus.

infrequently in Brucella, herpetic, and syphilitic CNS diseases. The low frequency of meningismus in this study could possibly be explained by the fact that meningeal irritation disappears in the absence of CSF inflammation. Furthermore, tuberculous meningitis had higher rates of hypoglycorrhachia and elevated CSF protein.

The absence of pleocytosis was relatively infrequent but not rare in these CNS infections. Patients without CSF pleocytosis appeared to have a high rate of unfavorable outcomes, including sequelae and death. A recent study of 175 children with bacterial meningitis (Lin et al., 2016) identified the lack of CSF pleocytosis as a prognostic factor in the multivariable analysis. The examining clinician should not underestimate the presence of a CNS infection despite the lack of CSF pleocytosis for a patient with a suspicion of meningitis or encephalitis. In particular, other clues related to the clinical presentation or abnormalities in CSF analyses should be carefully considered as a whole, and microbiological clues pointing to a CNS infection should be pursued when necessary.

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### Conflict of interest

RH is a consultant for bioMérieux and a speaker for Pfizer, Merck, Medicines Company, and BioFire. The remaining authors have no competing interests to declare.

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