Determination of pentraxin 3 levels in cerebrospinal fluid during central nervous system infections

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Abstract

Pentraxin 3 (PTX3) is an acute phase protein; its plasmatic levels significantly rise during severe infections. Data on PTX3 levels in cerebrospinal fluid (CSF) of patients with central nervous system (CNS) infections are lacking. We aimed (a) to assess the diagnostic potential of measuring CSF PTX3 levels in patients with CNS infections and (b) to establish CSF PTX3 cutoffs to distinguish between bacterial and aseptic meningoencephalitis (ROC curve). PTX3 levels were measured in CSF from 19 patients admitted to Trieste Hospital, Italy, with CNS infection. A diagnosis of bacterial infection and aseptic meningoencephalitis was made in 7 (37%) and 12 (63%) patients, respectively. Subjects with bacterial infections showed significantly higher PTX3 levels (13.5 vs 1.27 ng/mL in aseptic meningoencephalitis, $p = 0.010$). We identified two different CSF PTX3 levels cutoffs. (1) The best cutoff to maximise Youden's J was 9.6 ng/mL with a sensitivity, specificity, positive predictive value and negative predictive value (NPV) of 71.4%, 91.4%, 83.3%, 84.6%, respectively. (2) The cutoff with higher NPV (100%) was 3.6 ng/mL; a diagnosis of bacterial infections was obtained in 0% patients with CSF PTX3 levels < 3.6 ng/mL vs 58% of those with CSF PTX3 levels ≥ 3.6 ng/mL ($p = 0.017$). CSF PTX3 levels are higher in bacterial meningitis than aseptic meningoencephalitis. A cutoff of 3.6 ng/mL of CSF PTX3 has a high NPV and can be used to exclude bacterial CNS infections.

Keywords Pentraxin3 · Central nervous system infections · Meningitis · Etiology

Introduction

Pentraxin 3 (PTX3) is a 45 kDa acute phase protein, prototype of the long pentraxin subfamily [1] and is expressed by various cells: monocytes, endothelial cells, dendritic cells and neutrophils during inflammatory processes [2]. This protein is a multifunctional pattern recognition molecule, and studies reported that plasma PTX3 levels significantly increased in several conditions including infectious diseases, cardiovascular, kidney, and female reproductive system diseases, as well as severe traumatic brain injury [1, 3–5]. Moreover, high levels of PTX3 in plasma have been reported to be associated with the severity of infection, especially in sepsis [6, 7]. Indeed, in a recent review, plasmatic levels of PTX3 were significantly higher in critically ill patients and those with blood culture-positive bacteremia compared with healthy controls, and higher levels of PTX3 were associated with the development of severe sepsis and septic shock [7, 8].

Central nervous system (CNS) infections are life-threatening and may be caused by bacteria, viruses or fungi.

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Their prompt recognition and treatment is crucial for patients' outcome [9]. CNS infection diagnosis still represents a challenge because of CNS anatomy and pathophysiology that outline a "compartmentalized" infection, with different levels of inflammation in and out of the CNS. Indeed, currently, cerebrospinal fluid (CSF) analysis has been considered the gold standard for diagnosing CNS infections, and biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) have an ancillary role.

PTX3 is not constitutively expressed in the brain; however, following exposure to proinflammatory signals, it may be produced centrally [10, 11]. Some studies report a correlation between levels of PTX3 in CSF and several CNS disorders such as subarachnoid haemorrhage, stroke, traumatic brain injury, epilepsy, multiple sclerosis and neurodegenerative disorders (i.e. Parkinson disease) [4, 12]. However, the potential role of CSF PTX3 determination in the setting of CNS infections is lacking so far.

The aim of our study was to investigate the diagnostic potential of measuring CSF PTX3 levels in patients with CNS infections. In particular, we aimed to evaluate if PTX3 levels could be a marker able to distinguish bacterial from aseptic meningitis or meningoencephalitis.

Methods

Patients

Patients admitted to the University Hospital of Trieste, Italy, with suspected meningitis or meningoencephalitis undergoing lumbar puncture from January 2016 to September 2018 were retrospectively investigated. Those patients were treated according to international guidelines for meningitis [13, 14].

Clinical history, laboratory tests on plasma and CSF during hospital stay and the clinical outcome were retrieved by chart review. We included in the analysis only subjects with a final diagnosis of CNS infection which has been obtained through the patient's history, clinical presentation and laboratory findings (CSF analysis and biomarkers) together with the direct or indirect identification of the etiological agent and the exclusion of other infection sites.

Patients were classified as affected by bacterial meningitis if bacteria were isolated from CSF by culture and/or molecular amplification techniques or, if CSF analysis showed characteristics consistent with bacterial infection (such as a CSF cell count ≥ 250 cells/mmc with a predominance (≥ 60%) of polymorphonuclear neutrophils and low glucose CSF/serum ratio). In case of death, the diagnosis of bacterial infection was made by macroscopic pathological findings. The diagnosis of aseptic meningoencephalitis was made by using molecular amplification and serological testing.

This study was exempt for approval by our Ethic Committee since patient characteristics were irreversibly anonymised prior to be reported in an electronic database. For this type of retrospective non-interventional study, generic consent to the processing of personal de-identified data for scientific purpose is sufficient in Italy.

CSF sampling

CSF was collected by lumbar puncture performed within 2 h from hospital admission. For each patient, four samples of CSF were collected for obtaining these data: (1) leukocyte count, glucose and total protein levels; (2) culture and molecular amplification (using FilmArray®, BioFire™ Diagnostics, Inc., Salt Lake City, UT, USA); (3) real-time PCR for Herpesvirus (HSV 1-2), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella zoster virus (VZV), West Nile Virus (WNV), enteroviruses (Elitech Molecular Diagnostic, Torino, Italy), Tick-borne encephalitis virus (TBEV) and Mumps virus (MuV); and (4) PTX3 levels. The latest samples were first stored at − 80 °C and then analysed in duplicate using a home-made sandwich ELISA as previously described [15]. The samples were centrifuged at 1500–3000 rpm for 10 min before being analysed. All samples were frozen freshly collected and thawed at the time of the test twice as the analysis was repeated. The assay has a lower limit of detection of 100 pg/ml, with 8–10% inter-assay variability. No cross-reaction with human CRP or serum amyloid P component was observed for antibodies used to detect PTX3. The optical density was read at 450 nm with an automatic plate reader (Thermo Labosystems, Chantilly, VA). The concentrations were calculated by converting the optical density readings against a standard curve made with recombinant human PTX3.

Statistical analysis

Descriptive statistics (number, proportion, median, interquartile range (IQR)) were used to describe the baseline characteristics of patients. Categorical variables were compared between groups (bacterial infections versus aseptic meningoencephalitis) using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the non-parametric Mann–Whitney U test. Correlation analyses were performed using the Spearman correlation test. Receiver operating characteristic (ROC) curves were used to identify a cutoff of PTX3 concentration and cell numbers in the CSF and plasma CRP that could predict bacterial meningitis, and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the identified cutoff were calculated. Only p values < 0.05 were considered to be significant. All analyses were performed using the SPSS version 18.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Patients

Nineteen patients were investigated, and their main characteristics are reported in Table 1. Overall, 11 (57.9%) subjects were male and median age was of 47 years (IQR 34–62) and median Charlson comorbidity index was 1 (0–5) [16]. Lumbar puncture was performed after a median of 4 days (IQR 2–6) from symptoms onset and 6/19 (31.6%) patients had received antibiotic therapy before the procedure.

A diagnosis of bacterial infection and aseptic meningoencephalitis was obtained in 7 (36.8%) and 12 (63.2%) patients, respectively. Among subjects with bacterial infections, aetiological diagnosis was obtained in 4 individuals (two with *Listeria monocytogenes*, one with *Escherichia coli* and one with *Klebsiella pneumoniae*), while in the other 3 cases (one post neurosurgical meningitis, one culture negative meningitis and one case confirmed by macroscopic pathological examination), no agents were identified. Among subjects with aseptic meningoencephalitis, viral infection was diagnosed by molecular or serological tests in 3 patients (one HSV-2, one mumps virus, one Coxsackievirus).

At the time of lumbar puncture, the main demographic and clinical characteristics of patients affected by bacterial or aseptic meningitis and meningoencephalitis did not significantly differ between themselves, except for a higher prevalence of previous neurological diseases in the former group of patients

Table 1 Population's characteristics at the time of lumbar puncture: comparison between bacterial infections and aseptic meningoencephalitis

	Total ($n = 19$)	Bacterial ($n = 7$)	Aseptic ($n = 12$)	p
Demographic and clinical characteristics				
Age, years	47 (34–62)	59 (37–88)	45 (31–57)	0.108
Male gender	11 (57.9)	4 (57.1)	7 (58.3)	1.000
Comorbidities				
Diabetes	2 (10.5)	2 (28.6)	0	0.123
Heart diseases	3 (15.8)	2 (28.6)	1 (8.3)	0.523
Neurological diseases	5[a] (26.3)	4 (57.1)	1 (8.3)	*0.038*
Immunosuppression	2 (10.5)	2 (28.6)	0	0.123
Any comorbidity	7 (36.8)	4 (57.1)	3 (25.0)	0.236
Charlson score	1 (0–5)	5 (0–9)	0 (0–2)	0.073
Days from symptoms onset	4 (2–6)	4 (2–5)	4 (1–6)	0.864
Recent antibiotic therapy	6 (31.6)	2 (28.6)	4 (33.3)	1.000
Body temperature, °C	38.5 (38.0–39.0)	39.0 (37.0–39.2)	38.5 (38.2–38.9)	0.668
Fever (> 37 °C)	16 (84.2)	5 (71.4)	11 (91.7)	0.523
Glasgow coma scale	15 (13–15)	13 (12–15)	15 (14–15)	0.052
Blood tests				
WBC, cells/mmc	10,415 (8985-13,198)	13,330 (12,000-17,500)	9000 (8890-10,830)	*0.018*
CRP, mg/L	26.3 (1.3–118.3)	103.0 (17.0–197.0)	8.1 (1.3–65.1)	*0.026*
CSF characteristics				
Cells/mmc	312 (80–824)	997 (541–1581)	164 (67–348)	*0.028*
PMN (%)	47 (0–85)	88 (47–90)	1 (0–59)	*0.023*
Mononuclear cells (%)	53 (15–100)	12 (10–53)	99 (41–100)	*0.023*
Glucose, mg/dL	55 (37–64)	35 (2–65)	56 (52–63)	0.091
Protein, mg/dL	114 (89–219)	110 (89–405)	128 (74–204)	0.800
PTX3, ng/mL	4.70 (0.50–13.50)	13.5 (4.70–19.80)	1.27 (0.50–6.21)	*0.010*
Outcome				
Death	2 (10.5)	2 (28.6)	0	0.123
Sequelae	2/16 (12.5)	2/5 (40.0)	0/11 (0)	0.083

Significant values are shown in italic

Values are expressed as number (percentage) or median (interquartile range). *WBC*, white blood cells; *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *PMN*, polymorphonuclear neutrophils; *PTX3*, pentraxin 3

[a] Two cases of dementia, one epilepsy, one miastenia gravis, one neurotoxoplasmosis

(57.1% versus 8.3%, $p = 0.038$). However, as expected, blood tests revealed higher white blood cell count (median 13,330 versus 9000 cells/mmc, $p = 0.018$) and higher C-reactive protein levels (median 103 versus 8.1 mg/L, $p = 0.026$) in patients with bacterial meningitis (Table 1).

No patient with aseptic CNS infection died during the hospital admission. Among bacterial meningitis, the in-hospital mortality was 10.5% including 2 patients, the first one with *Escherichia coli* meningitis and another one with probable meningitis by macroscopic pathological examination.

CSF characteristics

The CSF characteristics of the overall population and the subgroups of patients with bacterial or aseptic meningitis and meningoencephalitis are reported in Table 1. Subjects with bacterial infections showed a higher number of CSF cells (median 997 versus 164 cells/mmc, $p = 0.028$) with a prevalence of polymorphonuclear neutrophils (88% versus 1%, $p = 0.023$).

PTX3 levels were significantly higher in patients with bacterial infections (median 13.5 versus 1.27 ng/mL in aseptic meningoencephalitis, $p = 0.010$) (Fig. 1).

The performance of different cutoff for the prediction of bacterial infections is detailed in Table 2. To investigate the role of PTX3 levels for prediction of bacterial infections, a ROC curve was developed; the area under the curve (AUC) was 0.857 (95% confidence intervals 0.683–1.000, $p = 0.011$) (Fig. 2a). The best cutoff to maximise Youden's J was 9.6 ng/mL, corresponding to a sensitivity, specificity, PPV and NPV of 71.4%, 91.4%, 83.3%, 84.6%, respectively; a diagnosis of bacterial infections was performed in 5/6 (83.3%) subjects with PTX3 levels ≥ 9.6 ng/mL versus 2/11 (15.4%) of those with PTX3 levels < 9.6 ng/mL ($p = 0.010$). Moreover, a cutoff of 3.6 ng/mL could be chosen to maximise NPV (sensitivity, specificity, PPV and NPV of 100%, 58.3%, 58.3%, 100%, respectively); a diagnosis of bacterial infections was obtained in 0/7 (0%) patients with PTX3 levels < 3.6 ng/mL versus 7/12 (58.3%) of those with PTX3 levels ≥ 3.6 ng/mL ($p = 0.017$) (Table 2).

We also investigated if CRP and CSF cells could be also helpful in distinguishing the two groups of patients. For plasmatic CRP, the AUC in the ROC curve was 0.818 (95% CI 0.593–1.000, $p = 0.026$) while for CSF cells was 0.810 (95% CI 0.532–1.00, $p = 0.028$) (Fig. 2b, c). Regarding the CRP levels in plasma, we found that the best cutoff (Youden's J) and best NPV was 10 mg/L (sensitivity, specificity, PPV and NPV of 100%, 54.5%, 58.3%, 100%, respectively) while 103 mg/L was the cutoff with the best PPV (sensitivity 57.1%, specificity 90.9%, PPV 80% and NPV 76.9%). Concerning the CSF cells, our analysis rules out that 541 cells/mmc was the best cutoff (Youden's J) (sensitivity 85.7%, specificity 83.3%, PPV 75% and NPV 90.9%) and best NPV and 997 cells/mmc, the one with the best PPV (sensitivity 57.1%, specificity 100%, PPV 100% and NPV 80%) (Table 2). PTX3 levels did not significantly correlate with the number of total cells ($r = 0.273$, $p = 0.259$), polymorphonuclear neutrophils ($r = 0.322$, $p = 0.179$), glucose ($r = 0.016$, $p = 0.948$) or protein levels ($r = 0.039$, $p = 0.873$) in the CSF.

Compared with plasma CRP and CSF cells, the CSF PTX3 levels present a slightly better AUC in the ROC curve and the two cutoffs we identified (3.6 ng/mL and 9.6 ng/mL) have similar sensitivity and specificity than the other biomarkers.

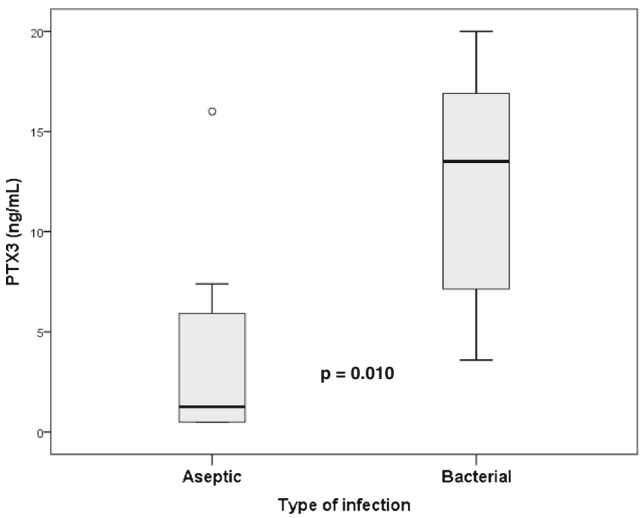

Fig. 1 Pentraxin 3 levels in the cerebrospinal fluid of patients with bacterial infections versus aseptic meningoencephalitis. Bold lines represent median values, the shaded area represents the interquartile range, and the lines above and below the bars represent 95% confidence intervals. Circles represent pentraxin 3 measurements outside 95% confidence level

Discussion

In the present study, we tried and demonstrated that PTX3 is detectable in the CSF of patients with infections of the CNS. In detail, CSF PTX3 levels were found to be higher in bacterial meningitis than in aseptic meningitis or meningoencephalitis.

As on murine model and clinical settings, PTX3 is not detectable in the brain in normal conditions, but its expression in the CNS is significantly induced in several neuropathological conditions [4, 10, 12, 17, 18]. However, only few studies investigated the correlation between PTX3 and central nervous system infections.

Sprong et al. found that plasma concentrations of PTX3 were significantly higher in subjects with septic shock due to meningococcal meningitis compared with those without shock; however, intrathecal PTX3 levels were not analysed in such series [19]. On the other hand, upregulation of PTX3 transcript was observed in the brain of mice during *Candida albicans* or *Cryptococcus neoformans* meningoencephalitis

Table 2 Performance of different cutoff in PTX3 and cell numbers in CSF and in plasma CRP for the prediction of bacterial infections

	Bacterial infections if <cutoff vs ≥ cutoff	*p*	Sensitivity	Specificity	PPV	NPV
CSF PTX3 cutoff						
≥3.6 ng/mL	0% vs 58.3%	0.017	100%	58.3%	58.3%	100%
≥9.6 ng/mL	15.4% vs 83.3%	0.010	71.4%	91.4%	83.3%	84.6%
CSF cells cutoff						
≥541 cells/mmc	9.1% vs 75%	0.006	85.7%	83.3%	75%	90.9%
≥997 cells/mmc	20% vs 100%	0.009	57.1%	100%	100%	80%
Plasma CRP* cutoff						
≥10 mg/L	0% vs 58.3%	0.038	100%	54.5%	58.3%	100%
≥103 mg/L	23.1% vs 80%	0.047	57.1%	90.9%	80%	76.9%

*CRP was available in 18/19 patients

[10], and in the CNS of horses during West Nile Virus infection [20].

To the best of our knowledge, our study is the first one to evaluate the role of PTX3 levels in CSF in the setting of CNS infections in humans. It demonstrated that bacterial meningitis can be associated with higher levels of PTX3 when compared with aseptic meningoencephalitis. In particular, we found the two following different cutoffs. (1) First, the PTX3 level of 9.6 ng/mL in the CSF is the best cutoff to predict a bacterial infection with a specificity of 91.4%; nevertheless, the sensitivity (71.4%) is not satisfactory. (2) Second, the PTX3 level of 3.6 ng/mL corresponds to a cutoff with a high negative predictive value showing that PTX3 levels in CSF under the latter cutoff are most likely suggestive for non-bacterial infections of CNS. This finding may help to identify patients with CNS infections not requiring antibiotic therapy.

Considering other biomarkers analysed in the present study, we confirm that both the CSF cell numbers and plasmatic CRP are important elements to confirm the diagnosis of bacterial meningitidis as previously reported [21]. It is interesting to note that CSF levels of PTX3 not only have good sensitivity and specificity but also are comparable with those of other biomarkers.

PCT is another marker that has been evaluated with regard to its usefulness in distinguishing between the possible causative organisms (bacterial or viral) also for SNC infections, both when measured in plasma and in CSF [22, 23]. Unfortunately, we did not perform PCT determination neither in plasma nor in CSF in the present study; therefore, we could not compare PTX3 with PCT for diagnosis of SNC infections.

This study has several limitations. First of all, the retrospective design of the study and the small number of patients from a single centre do not allow to generalise these results. Secondly, plasma determination of PTX3 levels was not available. Whether PTX3 reached the CSF due to increased permeability of the blood brain barrier or it was produced intrathecally remained to be confirmed. However, since PTX3 levels did not correlate with protein levels in the CSF, the hypothesis of an intrathecal production could be plausible.

Finally, we did not evaluate PTX3 levels in a control group of patients not affected by CNS infections in order to validate our data.

In conclusion, we demonstrated that CSF PTX3 levels are higher in bacterial meningitis than aseptic meningitis or meningoencephalitis. Moreover, we identified a PTX3 cutoff with a high NPV that could be used during the diagnostic process of CNS infections to identify those subjects with a very low probability of bacterial infection. Further studies are needed to validate our findings and to confirm the potential diagnostic role of PTX3 measurement in the CSF, especially

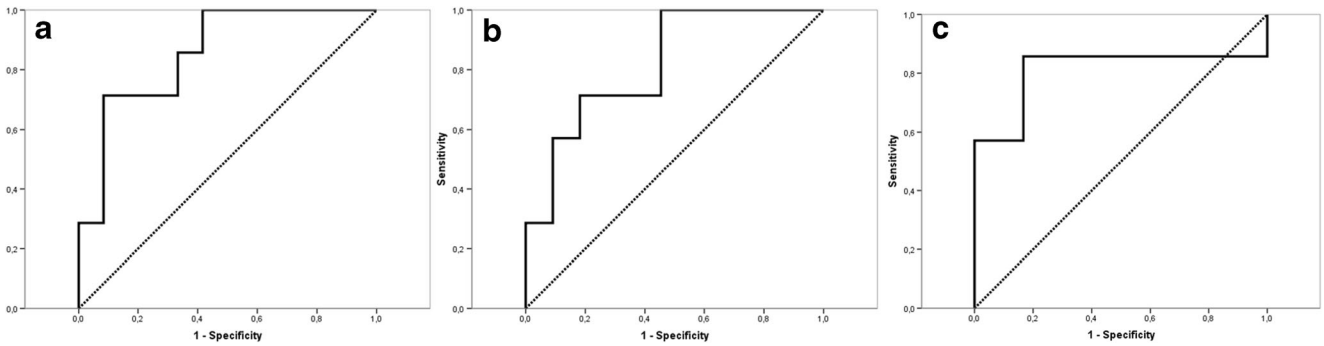

Fig. 2 Receiver operating characteristic (ROC) curve for the prediction of bacterial infections. **a** PTX3 levels. **b** Plasma CRP. **c** CSF cells

in those patients with meningitis that have been treated with antibiotics before the lumbar puncture.

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