Procalcitonin, Midregional Proenkephalin A and N-terminal Protachykinin A in cerebrospinal fluid to differentiate bacterial from viral meningitis

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Levels of procalcitonin (PCT) are elevated in many conditions leading to systemic inflammatory response syndrome (SIRS), as following bacterial infection (Assicot et al., 1993), pancreatitis (Rau et al., 1997), burns (Nylen et al., 1992) or polytrauma (Mimoz et al., 1998). However, the presence of PCT in cerebrospinal fluid is less well examined. A few studies focused on meningitis, where PCT in CSF was undetectable (Gendrel et al., 1997), elevated (Jereb et al., 2001; Kepa et al., 2005) or not different from control levels (Shimetani et al., 2001). In addition, a significant increase of PCT in CSF in patients with acute neuroinflammation (e.g. encephalitis and meningitis) was reported (Ernst et al. 2007).

Proenkephalin A (PENK A) and Protachykinin A (PTA) represent large peptide precursor sequences containing the neuropeptides methionin-enkephalin (Met-Enk)/leucine-enkephalin (Leu-Enk) and substance P (SP), respectively (Comb et al., 1982) (Nawa et al., 1984). However, enkephalins and SP are instable in vitro, possessing a half-life time of less than 15 and 12 min, respectively (Mosnaim et al., 1988) (Conlon and Sheehan, 1983). Therefore the reliable measurement of these peptides in biological fluids faces difficulties. To overcome this (pre-) analytical problem, we have developed sandwich immunoassays based on the chemiluminescence and coated tube technique for the detection of a midregional PENK A precursor fragment (MR-PENK A) (Ernst et al. 2006) comprising amino acids 119–159 and an N-terminal precursor fragment of PTA (NT-PTA) (Ernst et al., 2008) comprising amino acids 1–37. In contrast to the mature neuropeptides, MR-PENK A and NT-PTA are stable in vitro for at least 48 h at room temperature (Ernst et al., 2006) (Ernst et al., 2008). Enkephalins and SP were found to be altered in meningitis and encephalitis (Ciesla et al., 2005) (Qureshi et al., 2000). In addition Ernst et al. reported a significant decrease of MR-PENK A and NT-PTA, respectively in CSF of patients with acute neuroinflammation (e.g. meningitis and encephalitis) (Ernst et al. 2010).

In the present study we examined whether levels of PCT, MR-PENK A and NT-PTA in CSF can be used to differentiate bacterial from viral meningitis.
PCT, MR-PENK A and NT-PTA were measured as described elsewhere (Morgenthaler et al. 2001; Ernst et al. 2006; Ernst et al. 2008). Twenty-five patients were diagnosed to suffer from a viral meningitis and twenty patients were diagnosed to have a bacterial infection. Bacterial meningitis was defined as the acute onset of meningitis (CSF WBC count ≥7/µL) and documented bacterial infection in CSF (direct examination, culture, latex agglutination, or polymerase chain reaction) or blood culture. Viral meningitis was defined as the acute onset of meningitis and the absence of any bacterial meningitis criteria.

PCT concentrations were significantly elevated in CSF of patients with bacterial meningitis (median 0.216 ng/mL) when compared to patients with viral meningitis (median < 0.007 ng/mL (functional assay sensitivity) (p<0.0001). ROC plot analysis resulted in an area under curve (AUC) of 0.86 (95% CI:0.74-0.98, p<0.0001). In contrast, MR-PENK A concentrations were significantly decreased in CSF of patients with bacterial meningitis (median 3.4 nmol/L) when compared to patients with viral meningitis (median 16.9 nmol/L) (p<0.0001). ROC plot analysis resulted in an area under curve (AUC) for MR-PENK A of 0.91 (95% CI:0.83-0.99, p<0.0001). Similarly, NT-PTA concentrations were significantly decreased in CSF of patients with bacterial meningitis (median 630.6 pmol/L) when compared to patients with viral meningitis (median 243.6 pmol/L) (p<0.0001). ROC plot analysis resulted in an area under curve (AUC) for NT-PTA of 0.83 (95% CI:0.70-0.95, p<0.0001). MR-PENK A and NT-PTA were significantly correlated (Spearman r=0.85, p<0.0001), whereas there was no correlation between PCT and either MR-PENK A or NT-PTA (p>0.05).

As PCT increases in CSF of bacterial meningitis patients and both, MR-PENK A and NT-PTA, decrease, a combination of PCT with either MR-PENK A or NT-PTA resulted in an increased AUC of 0.96 (95% CI:0.90-1.0, p<0.0001) and 0.95 (95% CI:0.88-1.0, p<0.0001) in comparison to the single marker. A combination of MR-PENK A and NT-PTA resulted in an AUC of 0.88 (95% CI: 0.75-0.97) and not better as the single marker MR-PENK A alone. A combination of all three markers resulted in an AUC of 0.97 (95% CI:0.91-1.0, p<0.0001) and was not significantly different compared to the results of a two-marker-combination.

Our results show that PCT, MR-PENK A and NT-PTA are able to differentiate bacterial from viral meningitis. The results of the single markers are significantly improved when PCT is combined with either MR-PENK A or NT-PTA or both.
References


