Total lactate dehydrogenase in cerebrospinal fluid for identification of bacterial meningitis

Bacterial meningitis (BM) is a medical emergency and needs treatment without delay (Kim, 2010). Early diagnosis and appropriate treatment of patients presenting with signs of meningitis or encephalitis are important factors in determining their prognosis. Cerebrospinal fluid (CSF) analysis for cell count, protein, lactate, Gram and other stains, and glucose is routinely used as a diagnostic tool to distinguish between bacterial and non-bacterial causes of meningitis (Knight et al., 1981), but results may be inconclusive leading to diagnostic uncertainty and delayed treatment. In resource-constrained settings laboratory facilities for CSF analysis, culture or PCR are not always available. Clinical signs and symptoms, such as fever, neck stiffness and photophobia, are important diagnostic tools, but may be difficult to assess. Total lactate dehydrogenase (LDH) in CSF is a potentially useful biomarker of BM. A number of studies have found increased levels of LDH in CSF in children with BM (Nussinovitch et al., 2009; Neches & Platt, 1968), but data in adults are limited. The aim of the present study was to investigate if total LDH is increased in CSF samples from adult patients with BM compared to aseptic meningitis and controls.

We tested stored CSF samples (at −80 °C) from adult patients diagnosed with acute bacterial meningitis (ABM), tuberculous meningitis (TBM) and viral (aseptic) meningo-encephalitis and included control samples from patients without meningitis and with normal CSF admitted between June 2007 and October 2008 at the National Hospital for Tropical Diseases (NHTD) in Hanoi, Vietnam (Taylor et al., 2012). This study was ethically approved by the Oxford Tropical Ethical Review Committee and the Scientific Committee of NHTD. The CSF samples collected on admission were tested for white blood cell (WBC) count with differential, glucose and protein. The samples were also analysed with culture, PCR and direct microscopy to detect bacterial and viral pathogens. From the original study, 69 CSF samples were selected from 40 patients with ABM, 10 with viral (aseptic) meningo-encephalitis, nine with TBM and 10 with normal CSFs (controls). All of these had confirmed diagnosis with culture or PCR. The 69 samples were thawed and total LDH activity was measured using standard laboratory equipment (Olympus AU and Hitachi Modular). See the supplementary material for the analytical methods.

Bacterial pathogens detected were *Streptococcus suis* (32 cases), *S. pneumoniae* (six cases) and *Neisseria meningitidis* (two cases, see Table S1). Detected viruses were herpes simplex virus (nine cases) and varicella-zoster virus (one case). The median (interquartile range (IQR)) LDH activity in each group was 104 (52–238) U l⁻¹ for ABM, 83 (35–351) U l⁻¹ for aseptic meningitis, 61 (33–98) U l⁻¹ for TBM and 11 (9–30) U l⁻¹ for controls. Median (IQR) WBC was 1750 (285–6300) for the bacterial meningitis group, 391 (250–442) for the tuberculous group and 14 (9–40) for the controls (see Fig. 1). One-way analysis of variance (ANOVA) showed that the difference between the different forms of meningitis and controls was statistically significant (*F*=7.93, *P*<0.0001). The post hoc analysis showed that the level of LDH activity in cases of ABM was significantly higher than that of the controls (*P*<0.0001), while no significant difference to cases of aseptic meningitis (*P*=0.777) and TBM (0.089) was seen. Controls had significantly lower levels of LDH activity than the bacterial (*P*<0.0001) and the aseptic groups (*P*=0.007), but did not differ significantly compared to the tuberculous cases (*P*=0.189). Any difference in LDH between cases of aseptic meningitis and TBM was not seen (*P*=0.248). See supplementary material for analysis of WBC.

LDH activity differs significantly between patients with both viral meningitis and ABM compared to patients without meningitis. Therefore, LDH is a potential complementary biomarker to WBC, which differs significantly between bacterial and aseptic meningitis while showing overlap.

![Fig. 1. LDH in frozen CSF samples from patients with acute bacterial, viral (aseptic) or tuberculous meningitis, and from controls (69 patients in total).](image-url)
between no meningitis and viral meningitis. The clinical usefulness of LDH as a complement to WBC for diagnosing different aetiologies of meningitis needs to be assessed in larger prospective studies.

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Abbreviations: BM, bacterial meningitis; CSF, cerebrospinal fluid; IQR, interquartile range; LDH, lactate dehydrogenase; NHTD, National Hospital for Tropical Diseases; TBM, tuberculous meningitis; WBC, white blood cell.

Supplementary material is available with the online version of this paper.