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Adults with suspected central nervous system infection: A prospective study of diagnostic accuracy

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Summary *Objectives:* To study the diagnostic accuracy of clinical and laboratory features in the diagnosis of central nervous system (CNS) infection and bacterial meningitis.
Methods: We included consecutive adult episodes with suspected CNS infection who underwent cerebrospinal fluid (CSF) examination. The reference standard was the diagnosis classified into five categories: 1) CNS infection; 2) CNS inflammation without infection; 3) other neurological disorder; 4) non-neurological infection; and 5) other systemic disorder.
Results: Between 2012 and 2015, 363 episodes of suspected CNS infection were included. CSF examination showed leucocyte count $>5/mm^3$ in 47% of episodes. Overall, 89 of 363 episodes were categorized as CNS infection (25%; most commonly viral meningitis [7%], bacterial meningitis [7%], and viral encephalitis [4%]), 36 (10%) episodes as CNS inflammatory disorder, 111 (31%) as systemic infection, in 119 (33%) as other neurological disorder, and 8 (2%) as other systemic disorders. Diagnostic accuracy of individual clinical characteristics and blood tests for the diagnosis of CNS infection or bacterial meningitis was low. CSF leucocytosis differentiated best between bacterial meningitis and other diagnoses (area under the curve [AUC] 0.95) or any neurological infection versus other diagnoses (AUC 0.93).
Conclusions: Clinical characteristics fail to differentiate between neurological infections and other diagnoses, and CSF analysis is the main contributor to the final diagnosis.

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Introduction

Neurologists, emergency care and infectious diseases specialists are often called on to rule out central nervous system (CNS) infection. In most cases the patient is febrile, confused and complaining of headache, and the question revolves around the need for a lumbar puncture to exclude bacterial meningitis.[1] When an alternative diagnosis is not so obvious after general physical and neurological examination, and doubt remains about the possibility of CNS infection, lumbar puncture is mandatory, as it is in almost every patient who is thought to have a CNS infection.[2] The differential diagnosis in patients with suspected CNS infection can be broad, ranging from life-threatening conditions such as bacterial meningitis, herpes simplex encephalitis or septic encephalopathy to rather benign self-limiting conditions such as aseptic (viral) meningitis, sinus infection or an "ordinary" flu.[1]

Studies on diagnostic accuracy can provide guidance in the diagnostic dilemmas in patients with suspected CNS infection, but almost all consist of retrospective studies comparing patients diagnosed with bacterial meningitis to those with aseptic meningitis, disregarding other diagnoses included in the differential diagnosis of suspected bacterial meningitis.[1] One prospective study including 297 adults with suspected meningitis, in which 27% of patients were diagnosed with CNS infection and only 1% with culture-proven bacterial meningitis, determined the diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity for meningitis, and concluded that these signs have low sensitivity and rather high specificity in the diagnosis of meningitis.[3] We performed a prospective study of diagnostic accuracy on clinical and laboratory features in the diagnosis of CNS infection and bacterial meningitis in patients presenting with suspected CNS infection.

Methods

In a single centre study (Academic Medical Center, Amsterdam, The Netherlands), we prospectively included adult episodes (age $>$ 16 years) presenting to the emergency department or inpatients with suspected CNS infection who underwent cerebrospinal fluid (CSF) examination. Episodes were identified during morning rounds or reported to the investigators by the treating physician. Physicians could contact the investigators 24/7 to include patients. To assure no episodes were missed, an overview of all CSF samples analysed by the hospital laboratory was checked and all episodes fulfilling the inclusion criteria were also included.

Episodes in which patients developed an infection within one month of neurosurgery or traumatic brain injury as well as those who had a neurosurgical device in situ were subsequently excluded. Online case record forms were used to collect data on medical history, clinical characteristics on presentation and results of ancillary investigations including blood tests, cerebrospinal fluid analysis, microbiological examination and radiological imaging. Type, dose and duration of antibiotic and antiviral treatment were recorded. Furthermore, neurological status at discharge was recorded and graded according to the Glasgow Outcome Scale (GOS). The scale rates outcomes from 1 to 5, where a score of 1 indicates death; 2 indicates vegetative survival; 3 indicates severe disability); 4 indicates moderate disability; 5 indicates mild or no disability.[4] A score of 5 on the GOS was considered a favourable outcome and a score of 1—4 was considered unfavourable. All patient data was rendered anonymous and the study was carried out in accordance with Dutch privacy legislation. The study was approved by the medical ethical committee of the Academic Medical Centre, Amsterdam, The Netherlands.

We categorized whether the patients were suspected for community-acquired disease or hospital-acquired meningitis defined as meningitis during hospitalization or within one week after discharge. Patients admitted to the ICU or ward in whom CSF examination was performed within 48 h of admission were considered to have community-acquired disease. Patients were considered to be immunocompromised if they were taking immunosuppressive drugs, had undergone splenectomy or if their previous medical history was positive for diabetes mellitus, alcoholism, cancer or human immunodeficiency virus (HIV) infection.

Diagnostic classifications

The reference standard was a diagnostic classification into five categories: 1) central nervous system infection, 2) nervous system inflammation without infection, 3) non-infectious non-inflammatory neurological disorder, 4) non-neurological infection and 5) other systemic disorder. Rationale for choosing the reference standard was pragmatic clinical applicability. Episodes were classified as a nervous system infection if there was microbiological evidence of infection by culture, gram stain, polymerase chain reaction (PCR) or other microbiological test of cerebrospinal fluid. For all episodes with cerebrospinal fluid pleocytosis ($>$4 leukocytes/ml) but no microbiological proof of infection in cerebrospinal fluid two clinicians (UK, MB) independently classified the episodes as being due to infection, inflammatory disease or another neurological disorder. Inter-rater agreement was assessed by calculation of the kappa coefficient (kappa 0.76). Differences were resolved by discussion and consultation of a third clinician (DvdB). Episodes were classified as other neurological disease when a non-infectious, non-inflammatory disease of the CNS was diagnosed. When physical or ancillary showed evidence of a focus of infection outside the CNS and no evidence of central nervous system infection, patients were classified as having systemic infection without neurological involvement. Patients with a clinical diagnosis of fever or sepsis with unknown origin were also included in this category. When neither an infection nor a neurological diagnosis was established, episodes were classified as systemic non-infectious disease. Subsequently, we made subcategories of the central nervous system infections consisting of 1) bacterial meningitis, 2) viral meningitis, and 3) other central nervous system infections. Episodes due to spirochaetal infection (either neuroborreliosis, neurosyphilis or neuroleptospirosis) and tuberculous meningitis were included in the other central nervous system infections category.

Analyses

Power calculation was done for testing sensitivity of a single diagnostic test. Using an α of 0.05, β of 0.20,