

The challenge of treating central nervous system infections

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Central nervous system (CNS) infections produce large numbers of death and disability. For example, 17-33% of patients with bacterial meningitis die in spite of appropriate antibiotic therapy [1-3]. Case fatality rates can be as high as 44% in tuberculous meningitis (TBM) [4], and 20-30% in Japanese encephalitis (JE), the commonest viral encephalitis worldwide [5]. Many of the survivors are left with residual neurological sequelae; 30-54% after bacterial meningitis [3, 6], up to 47% after TBM [4, 7], and about 50% after JE [5]. CNS infections are of special concern to clinicians in developing countries, as they are commoner and produce more deaths and disability in these regions [8]. Early treatment is imperative. In bacterial meningitis, delays in treatment are associated with excess mortality and residual neurological deficits whereas early treatment has been shown to improve outcome [2, 9]. Recent advances in knowledge have helped guide treatment, especially in bacterial meningitis, but many questions remain.

Getting the diagnosis right – how useful are the clinical features?

Delivering appropriate treatment early depends on rapid and accurate diagnosis, but clinical diagnosis can be difficult. The clinical spectrum of CNS infections is wide (meningitis, encephalitis, brain abscess), the possible causes are diverse (bacterial, tuberculous, viral, fungal, etc), yet the clinical presentation is frustratingly similar, with a varying combination of fever, headache, nausea, vomiting, altered consciousness, seizures, focal neuro-logical deficits and meningism. Clinical findings are unhelpful in predicting the type of CNS infection [10]. In a meta-analysis, Attia *et al* found that typical symptoms had low sensitivity for detecting meningitis (headache- 50%, nausea and vomiting- 30%, altered mental state- 67%) [11]. The triad of fever, neck stiffness and altered mental state is seen in only 44-46% [1, 3,

11, 12]. Thomas *et al* observed that traditional signs of meningeal irritation were poor predictors of meningitis. The sensitivity was 30% for neck stiffness, and only 5% for Kernig's sign and Brudzinski's sign [13]. Other signs such as active neck flexion and jolt accentuation of headache, although less well known, are more sensitive for meningeal irritation [10, 11, 14]. The clinical features may be more useful in 'ruling-out', rather than 'ruling-in' a diagnosis of meningitis. Although the sensitivity is very low, the specificity for Kernig's sign and Brudzinski's sign is high at 95% [13]. At least one of the triad of fever, neck stiffness and altered mental state is seen in 99-100%, and the absence of all three virtually eliminates the diagnosis [1, 11].

Getting the diagnosis right – how useful are laboratory investigations?

As clinical clues are unreliable, establishing the diagnosis depends on laboratory investigations. Cerebrospinal fluid (CSF) analysis is the mainstay in diagnosis, and CSF cytology, biochemistry and staining provide the most helpful data in initial decision making. Independent predictors of bacterial meningitis on CSF analysis include CSF: blood glucose ratio less than 0.23, protein more than 2.2 g/L, leucocyte count more than 2000/cc, and a polymorphonuclear leucocyte count more than 1180/cc [15]. However, such changes reflect more severe infection, and are seen in only a minority of cases. CSF cytology can be negative in up to 10% with bacterial meningitis and importantly, these patients may have worse outcomes [12, 16]. Simple microbiological staining measures can be helpful but unreliable. Gram staining of CSF has good specificity in bacterial meningitis (up to 97%), but can be negative in 40-75% depending on the concentration of microorganisms [14]. In TBM, sensitivity of Ziehl-Nielsen staining for acid-fast bacilli is only 5-30% [17].

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Targeted treatment then requires isolation of the organisms in blood culture or CSF, but this is difficult in developing countries where it really matters, largely due to inadequate diagnostic facilities. Blood cultures are positive in about two-thirds of patients with bacterial meningitis in developed countries [8, 12], but rates fall to less than one-third in the developing world [8, 18, 19]. CSF isolation rates are high (60-73%) in developed countries [1, 12, 15], but much lower (3-35%) in developing countries [8, 20, 21, 22, 23]. In a Sri Lankan study of 215 adults with suspected CNS infection, a definitive microbiological diagnosis was established in only one patient [24]. In another Sri Lankan study of children <5 years, an organism was isolated in only 2.3% of CSF specimens [21]. Previous antibiotic use may be an important reason for poor diagnostic yield, and high rates are reported from many parts of the developing world (Vietnam – 61%, Pakistan – >50%, Nepal – 26.7%, Sri Lanka – 32%) [18, 22, 23, 24]. This is in contrast to the low rates of prior antibiotic use (usually less than 10%) from developed countries [3].

Early diagnosis, therefore, requires tests that do not depend on the presence of live organisms. The advent of the polymerase chain reaction (PCR) based assays for nucleic acid detection has revolutionized microbiological diagnosis in CNS infection. They are rapid, more sensitive and specific, and are not affected by prior antibiotic treatment, thus improving timely and accurate diagnosis [25]. PCR based assays are especially important in viral infections, where traditional methods fail to confirm the causes. However, they are not readily available in developing countries, and their introduction in such settings has been shown to improve the diagnostic yield [26].

Getting the diagnosis right – Are we missing something?

Inadequate diagnostic facilities and prior antibiotic use, may not be the only reasons for poor diagnostic yields. A closer analysis of the literature reveals that between-study comparisons can be misleading. Most previous studies reporting high isolation rates are from case series with a selected syndrome (bacterial meningitis, viral encephalitis, etc.), with many of them being retrospective studies [1, 2, 3, 12]. Many such series describe only microbiologically proven cases [2, 3, 12], and would naturally show higher isolation rates. In contrast, studies of unselected patients with presumed CNS infection have produced much lower isolation rates, even from developed countries [27, 28, 29, 30]. Such data are more relevant for ‘point of care’ clinical decision making in the acute stage, as patients do not present with a diagnostic label of ‘bacterial meningitis’ or ‘viral encephalitis’, but with a diagnostically challenging clinical syndrome of febrile meningo-encephalopathy. In a multicentre study from UK, only 20% were found to have a CNS infection out

of 217 suspected patients, and CSF culture was positive in only 3 out of 199 samples [27]. In another study in UK, 60% of the cases were of unknown aetiology [30]. In the California Encephalitis Project, a confirmed or probable cause was found in only 16% of patients, and an aetiological agent was not found in 62% despite extensive testing [29]. Up to 85% of cases worldwide are reported to be due to undetected causes [28].

It is important to look beyond the usual suspects for such low diagnostic yields. Increasing global travel can introduce previously unseen organisms to new territories. We may well have been ignoring the possibility of a different spectrum of neurotropic organisms that are not detected by the traditional microbiological investigations. Several hitherto unsuspected agents, such as Bocavirus and Cyclovirus, have been recently isolated in CSF of Sri Lankan patients with CNS infections. [31, 32]. Furthermore, several non-infectious syndromes such as paraneoplastic and immune-mediated encephalitis are well described, and recent reports indicate that they may be at least as common as infectious causes [28, 33]. In a multicentre study of patients with encephalitis in UK, only 42% of cases were attributed to infections, and 21% had immune-mediated encephalitis [28]. In patients aged <30 years in the California Encephalitis Project, immune-mediated encephalitis due to anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies was commoner than those due to viral aetiologies [33].

Getting the treatment right

As laboratory diagnosis is difficult, and delays in treatment are unacceptable, urgent antimicrobial treatment has to be commenced on an empiric ‘best guess’ basis. The choice of drugs would ideally depend on local epidemiological data of prevalence of causative organisms and antibiotic sensitivity patterns. Such data, however, are lacking from developing countries. Current guidelines recommend the use of third generation cephalosporins in suspected bacterial meningitis, with the addition of vancomycin in areas of high levels of penicillin and cephalosporin resistance in *S. pneumoniae* [14, 15], but these recommendations are based on data from developed countries. In Sri Lanka, there are no prevalence data on the aetiology of CNS infections to guide empiric therapy. Previous published work have been largely confined to case series of specific syndromes [20, 21, 34, 35, 36]. Available data suggest alarmingly high rates of antibiotic resistance in Sri Lankan patients. Among pneumococcal isolates from children, penicillin resistance was seen in 91%, and cefotaxime resistance in 48% [20]. Addition of intravenous acyclovir to the antibiotic regimen is generally recommended in initial empiric therapy, and is routinely practiced by most clinicians [15]. However, acyclovir is effective in only Herpes simplex virus and

varicella encephalitis, and there is no evidence to support its routine use in all suspected cases. Uncertainty in early diagnosis therefore would lead to further uncertainty in early treatment, and add significantly to cost of care.

The mortality in bacterial meningitis is related to CNS inflammation, rather than direct effects of infection. Treatment induced bacterial lysis triggers a cascade of inflammatory events that includes release of inflammatory cytokines, excitotoxicity and oxidative damage, leading to cytotoxic and vasogenic oedema, increasing intracranial pressure and neuronal dysfunction and death [10, 14, 15]. Steroids have been shown to attenuate this inflammatory response, inhibit cytokine synthesis, decrease CSF outflow resistance and stabilize the blood-brain barrier [10, 14]. This knowledge has been translated into clinical trial benefits, with intravenous dexamethasone shown to be effective in reducing mortality and long term neurological sequelae [15, 37, 38]. There are, however, several issues related to steroid therapy in meningitis. Initial concerns included possible lack of benefit in non-*H. influenzae* meningitis in children, and poor CSF penetration of antibiotics (especially vancomycin) with stabilization of the blood-brain barrier [14], but these concerns have now being allayed [39]. Another concern is that steroids may have no value in treating meningitis in low income countries [39], but this assumption is based on the lack of efficacy seen in studies from areas of high HIV prevalence [19, 40]. Currently, intravenous dexamethasone, commenced before or with the first dose of antibiotic, is recommended for adults and children with community acquired meningitis [10, 15, 38, 39].

The place of steroids is less clear in other acute CNS infections. After initial skepticism, steroids are now recommended in TBM [41], based on several clinical trials showing reductions in death and disability [42, 43]. There is no evidence of benefit in using steroids in viral encephalitis. Therefore, accurate aetiological diagnosis is necessary in deciding on steroid use, but this is not usually possible in the first few hours when steroids should be started with the first dose of empiric antibiotic therapy.

The challenge for Sri Lanka?

Getting the treatment right in the critical first few hours depends on getting the diagnosis right. This is particularly challenging in developing countries like Sri Lanka where CNS infections are more prevalent, due to a combination of lack of rapid diagnostic facilities, widespread prior antibiotic use, and lack of epidemiological data. There is a clear need for research into the aetiology of acute CNS infections and local antibiotic sensitivity patterns. Searching beyond the traditional diagnostic paradigms for previously unsuspected infectious agents and non-infectious causes deserves more attention. Use of newer diagnostic tools and newer antibiotics would add to the

cost of care, but this would be money well spent, on minimising disability and saving lives.

Conflicts of interests

There are no conflicts of interest.

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