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# SPECTRUM OF CENTRAL NERVOUS SYSTEM INFECTIONS IN ADULTS AT RIMS RAIPUR

KEYWORDS: CNS infections,Prognosis

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**ABSTRACT**

Aim of our study was to determine prospectively the causative pathogens of central nervous system (CNS) infections in patients admitted to RIMS RAIPUR.From May 2014 to December 2015, cerebrospinal fluid (CSF) samples from 352 adults with suspected meningitis or encephalitis underwent routine testing, staining (Gram, Ziehl-Nielsen, India ink), bacterial culture and polymerase chain reaction targeting *Neisseria meningitidis*, *Streptococcus pneumoniae, S. suis, Haemophilus influenzae* type b, *Herpes simplex* virus (HSV), Varicella Zoster virus (VZV), enterovirus, and 16S ribosomal RNA. Blood cultures and clinically indicated radiology were also performed. Patients were classified as having confirmed or suspected bacterial (BM), tuberculous (TBM), cryptococcal (CRM), eosinophilic (EOM) meningitis, aseptic encephalitis/meningitis (AEM), neurocysticercosis and others.352 (male: 66%) patients were recruited: median age 34 years (range 13–85). 95/352 (27.3%) diagnoses were laboratory confirmed and one by cranial radiology: BM (n = 62), TBM (n = 9), AEM (n = 19), CRM (n = 5), and neurocysticercosis (n = 1, cranial radiology). *S. suis* predominated as the cause of BM [48/62 (77.4%)]; *Listeria monocytogenese* (n = 1), *S. pasteurianus* (n = 1) and *N. meningitidis* (n = 2) were infrequent. AEM viruses were: HSV (n = 12), VZV (n = 5) and enterovirus (n = 2). 5 patients had EOM. Of 262/352 (74.4%) patients with full clinical data, 209 (79.8%) were hospital referrals and 186 (71%) had been on antimicrobials. 21 (8%) patients died: TBM (15.2%), AEM (10%), and BM (2.8%).352 (male: 66%) patients were recruited: median age 34 years (range 13–85). 95/352 (27.3%) diagnoses were laboratory confirmed and one by cranial radiology: BM (n = 62), TBM (n = 9), AEM (n = 19), CRM(n = 5), and neurocysticercosis (n = 1, cranial radiology). *S. suis* predominated as the cause of BM [48/62 (77.4%)]; *Listeria monocytogenese* (n = 1), *S. pasteurianus* (n = 1) and *N. meningitidis* (n = were infrequent. AEM viruses were: HSV (n = 12), VZV (n = 5) and enterovirus (n = 2). 5 patients had EOM. Of 262/352 (74.4%) patients with full clinical data, 209 (79.8%) were hospital referrals and 186 (71%) had been on antimicrobials. 21 (8%) patients died: TBM (15.2%), AEM (10%), and BM (2.8%).

**INTRODUCTION:-**

Central nervous system (CNS) infections encompass a wide range of pathogens and are an important cause of morbidity and mortality worldwide.We have identified *Streptococcus suis* as the leading cause of bacterial meningitis (BM), accounting for ~40% of BM cases. Other bacteria were *S. pneumoniae* (~23%), *N. meningitidis* (~8%), *Klebsiella pneumoniae* (~3%), and ~2.5% each for *Escherichia coli, Haemophilus influenzae* and *Staphylococcus aureus*. Recently, three adults were diagnosed with cerebrospinal fluid culture (CSF) culture positive *Listeria monocytogenes* meningitis. Older data from Vietnam have documented *N. meningitidis*, *Yersinia pestis* and *Pseudomonas pseudomallei* as causes of meningitis.Japanese B encephalitis virus (JEV), an important cause of acute paediatric encephalitis and was the most commonly detected virus (26%) in a prospective series of 194 children. Other isolated viruses were enteroviruses (9.3%), dengue (4.6%) and 0.5% each for *Herpes simplex*, Cytomegalovirus and influenza A/H5N1. More than half of these patients lacked a confirmed diagnosis.Accurate estimates of the contribution of meningitis due to *Mycobacterium tuberculosis* (TBM) are hampered by the difficulty of confirming the diagnosis. In HCM, TBM is thought to account for about one third of admitted meningitis patients. A diagnostic algorithm, developed by data from HCM, can distinguish TB from bacterial meningitis with a high degree of confidence using clinical and laboratory criteria. Patients were eligible for the study if they had clinical evidence of a CNS infection, based on the judgment of the admitting doctor, and they or a legal guardian provided written informed consent. Exclusion criteria included: (i) patients with a known pre-existing neurological condition e.g. cerebral tumour, receiving antibiotics for a cerebral abscess, cerebrospinal fluid (CSF) shunt *in situ*, and neurosurgery within the previous two months. Patients were managed by hospital doctors following routine clinical practice i.e. history, physical examination, haematology, biochemistry, blood culture, and lumbar punctures (LP), and radiology. The research team supplied LP manometers to measure CSF opening pressures, ophthalmoscopes and tuning forks (Rinné and Weber tests). HIV testing was not part of the study protocol but was done as clinically indicated. The study protocol mandated, *inter alia*, the taking of a blood culture on admission, and a preLP cranial CT scan if there was evidence of raised intracranial pressure or a focal neurological sign.Physicians were encouraged to take at least 5 mL of CSF. All CSF specimens were processed immediately for testing or storage at −80°C for later analysis. Testing was done in batches at least once per week. Routine CSF testing involved: (i) Gram stain for bacteria, (ii) ZN stain for mycobacteria/acid fast bacilli (AFB), (iii) India ink stain in HIV positive patients for suspected *Cryptococcus neoformans*, (iv) bacterial culture, (v) glucose and total protein, and (vi) total and differential white cell count (WCC). Further bacterial identification was done according to standard microbiologic techniques, including biochemical tests. Mycobacterial culture was only done if the treating physician requested it for patients with suspected TBM.PCR tests were done according to previously published methods for selected bacteria and viruses, with the following targets: (i) *Streptococcus suis* (ii) *S. pneumoniae* (iii) *Neisseria meningitidis* (iv) *Haemophilus influenza* type b The viruses tested were: (i) enterovirus (EV) (ii) HSV 1 and 2 and (iii) VZV Subsequently, selected negative CSF samples were tested for (i) Nipah virus (n = 81) in patients with non-purulent meningitis and (ii) bacteria by 16S rRNA in patients with suspected bacterial meningitis (n = 63).A microbiologically confirmed diagnosis was one in which any of the microbiological investigations (i.e. stain, culture, PCR) was positive for a pathogen that was consistent with the clinical picture. If patients had evidence of more than one CNS pathogen, the clinical diagnosis was made according to the dominant clinical picture and CSF findings. *Post hoc*, a diagnostic cranial CT scan for neurocysticercosis was considered sufficient to confirm that diagnosis. Diagnostic categories were: bacterial (BM), tuberculous (TBM), cryptococcal (CRM), eosinophilic (EOM) meningitis, aseptic encephalitis/meningitis (AEM), neurocysticercosis and

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miscellaneous. An eosinophilic meningitis of presumed parasitic aetiology was diagnosed if the CSF contained >10 eosinophils/mm3 and/or eosinophils accounting for >10 percent of CSF leukocytes. Clinically suspected diagnoses were made by the treating physicians based on all the clinical information i.e. clinical picture, CSF findings, radiology (chest×rays, brain imaging), and the response to treatment.Disability was assessed using the Modified Rankin score (MRS) from 0 to 6 (i) 0 = no symptoms, (ii) 1 = no significant disability despite symptoms; able to carry out all usual duties and activities, (iii) 2 = slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, (iv) 3 = moderate disability; requiring some help, but able to walk without assistance, (v) 4 = moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance, (vi) 5 = severe disability; bedridden, incontinent and requiring constant nursing care and attention, and (vii) 6 = Dead.

**RESULTS:-**

A confirmed etiological diagnosis was made in 96 of 352 (27.3%) patients. The three main confirmed diagnoses were cBM, 62/96 (64.6%), followed by cAEM, 19/96 (19.8%), and cTBM, 9/96 (9.4%).The 262 patients had a median age of 34.5 (range 13–85) years; 92 (35.1%) were females. 100 (38.2%) patients (72 male, 28 female) had a potential, occupational exposure pigs or pork; 95 were farmers (37.1%), 3 butchers, one each a cook and pig seller. This potential occupational exposure was significant (p = 0.01) in the cBM 32/55 (58.2%) vs. sBM 17/51 (33.3%) patients and (p = 0.028) in the combined (com) BM [49/106 (46.2%)] patients compared to the comTBM patients [19/65 (29.2%)].Preadmission illnesses lasted a median of 7 days, range 0 to 92. The majority of patients, 209/262 (79.8%), were referred from another hospital and 186/262 (71%) were already taking antimicrobial drugs: 4 on oral acyclovir, 6 anti-TB treatment and 176 on antibiotics. 27 patients reported they were HIV positive of whom 16 were in the comTBM group (3 confirmed, 13 suspected). Overall, fever (252/262, 96.9%) and headache (252/262, 96.2%) were the most commonly recorded symptoms. Neck pain (36.2%, n = 95), convulsions (14.1%, n = 37), and reduced hearing (8.8%, n = 23) were reported less frequently. Photophobia (4.2%, n = 11) was uncommon. Median vital signs parameters were within normal limits and similar between the groups (data not shown). 116/259 (44.8%) patients had a normal Glasgow Coma Score (GCS) of 15; 22 (8.5%) had unrousable coma, GCS ≤8. A stiff neck (218/262, 83.2%) and Kernig's sign (175/262, 66.8%) were common. A minority of patients had neurological signs e.g. oculomotor (n = 5) and abducens (n = 2) nerve palsies, hemiparesis (n = 12), monoparesis (n = 5), or paraplegia (n = 3). Profound hearing loss (inability to hear tuning fork) was detected in 12 patients, 7 on admission and in 5 new patients by discharge. Their diagnoses were: 7 *S. suis*, 1 *S. pneumoniae*, 3 sBM and 1 with cTBM.The majority of patients, 247/262 (90.5%), had LPs done either on admission (n = 208, 79.4%) or by the next day (n = 29), on median illness day 8 (range 0 to 100). Opening pressures were raised (>20 cm CSF) in 82 of 163 (50.3%) patients. *S. suis* (n = 48) was the most commonly identified bacterium in the BM group, followed by *S. pneumoniae* (n = 7). *N. meningitidis* (n = 2), *L. monocytogenes* and *S. pasteurianus* . HSV (n = 12) and VZV (n = 5) were the most commonly detected viruses in the AEM group; EV was detected in 2 patients. *M. tuberculosis* was confirmed in 9 patients. PCR had an important impact on diagnostic confirmation . Standard staining of CSF detected: (i) Gram positive cocci in 22 of 53 (41.5%) cBM and 23 of 94 (24.5%) cBM patients (Gram stain), (ii) no patients with acid fast bacilli (ZN stain), and (ii) 5 patients with cryptococcus (India ink).A history of preadmission antibiotic use did not affect significantly (p = 0.4) the Gram stain positivity rate in the cBM group: 37.8% (14/37) vs. 50% (8/16 not on antibiotics) but did (p = 0.02) for a confirmed diagnosis of BM: 39/83 (46.9% on antibiotics) vs. 19/26 (73.1% not on antibiotics).

**DISCUSSION:-**

Our study has documented the range of pathogens causing CNS infections in patients admitted to RIMS RAIPUR. A confirmed diagnosis was made in just over a quarter of patients and most often in the patients with confirmed bacterial meningitis. When combining the confirmed and suspected diagnoses, bacterial meningitis remained the principal diagnostic group followed by TBM and AEM.The low proportion of confirmed diagnoses is similar to other clinical series and is a consequence of previous antibiotic use, natural clearance of virus, targeting a preselected number of pathogens for PCR, late lumbar punctures , and the low sensitivity of diagnostic tools currently available for confirming TB. Indeed, the CSF findings in the sBM group were significantly different to the cBM group and were consistent with partially treated meningitis.The sensitivity of the Gram stain in our setting was low, ~25% for comBM and ~40% for cBM; other series have reported sensitivities of 60 to 90% in previously untreated patients and 40 to 60% in partially treated meningitis. Although a history of preadmission antibiotic use did not apparently affect our Gram stain results, according with some studies but not others, it certainly reduced our ability to confirm bacterial meningitis, a not unexpected finding. The reported sensitivity of ZN stain varies widely from lows of 5 to 13% to a high of 91%. A minimum of 6 mL of CSF for TB diagnosis alone is recommended and should be examined for at least 30 minutes. In the past, CSF volumes of 10–20 mL were taken routinely with good results and good tolerability by patients. As the normal rate of CSF fluid formation in adults is ~500 mL/day, there is no reason to collect insufficient volumes for proper microbiological diagnosis. The use of molecular analyses enhanced substantially our ability to diagnose patients. Indeed, PCR was the only diagnostic tool in our setting for viral pathogens. HSV and VZV were the two main viral pathogens detected and this diagnosis allowed appropriate treatment to be given.

**CONCLUSION:-**

Our study has identified bacterial meningitis caused by *S. suis* as the main cause of CNS infections in adults at our referral hospital in Hanoi. PCR was particularly helpful for the early diagnosis and treatment in the AEM group. The overall low rate of confirmed infections calls for better diagnostic tests.

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