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Aetiologies of Central Nervous System Infections: A Study at Tertiary Care Hospital in Northern Punjab

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ABSTRACT

Objective: To identify demographic patterns and etiologies of CNS infections and to identify the clinical presentations, diagnostic accuracy, and clinical outcomes of various CNS infections in hospitalized patients in a tertiary care hospital.
Study Design: Cross sectional study.
Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi Pakistan, from Oct 2019 to Jun 2020.
Methodology: A total of 97 adult patients presenting with clinical features of Central Nervous System (CNS) infection were enrolled for this in-hospital study. Cerebrospinal fluid (CSF) was collected for a routine examination, bacterial culture, and viral Polymerase Chain Reaction (PCR) test. Human Immunodeficiency Virus (HIV) serology and neuroimaging were done in all cases. The diagnosis was established based on World Health Organization guidelines for infectious diseases. Infections were classified into four major categories for analysis purposes.
Results: Of 97 enrolled patients, the mean age was 38.8±18.5 years. CNS tuberculosis was the most common infection seen in 46(47.4%) cases, 25(25.7%) patients had viral encephalitis, and 17(17.5%) had bacterial meningitis. The rest of the patients (n=9) had fungal (3%) or parasitic infections (4%). In contrast, two patients were found to have focal cerebritis, one due to Brucella and the other due to Salmonella typhi.
Conclusion: Tuberculosis is the most common (CNS infection in this region. First, patients with CNS infections, especially chronic ones, present very late in our setting, leading to increased morbidity and mortality. Secondly, Molecular diagnosis is obtainable in only a small percentage of cases for various reasons.

Keywords: Central nervous system, Infection, Tuberculosis.

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INTRODUCTION

Central nervous system (CNS) infections are a major cause of morbidity and mortality in the developing world, though precise estimates have been difficult to establish.[1] Geographically, the burden of CNS infections is unequally distributed and predominantly impacts middle and low-income countries. According to a meta-analysis, LICs (Low-Income Countries) had an overall incidence of 726 cases/ 100,000 people and MICs (Middle-Income Countries) had 299/100,000 in contrast to HIC(High-Income Countries) with an annual incidence of 11.4 cases/ 100,000 population.[2]

A wide variety of pathogens, including bacterial, viral, fungal, and helminthic, are responsible for central nervous system infections resulting in meningitis, encephalitis, spinal and cranial abscesses and epilepsy. These infections can have acute and chronic presentations. Bacteria like Streptococcus pneumonae and Neisseria meningitides can cause acute meningitis.An array of organisms can cause chronic meningitis, but the most common pathogen causing chronic meningitis or meningoencephalitis in the region is Mycobacterium Tuberculosis.[3]

Most CNS infections are treatable with early diagnosis and timely initiation of the treatment; despite that, these infections remain poorly recognized and under-treated in developing countries.[1] Reasons are limited neurology services, lack of laboratory facilities and a significant lack of population-wide data.[4,5]

The main aim of this study was to characterize the common etiologies of CNS infections in this region, along with their common clinical presentations. Identification of causative organisms is crucial to provide a much-needed insight into local epidemiology. It will help improve local management guidelines and guide regional public health measures in the region. Availability of data and local guidelines will also sensitize the primary care physicians and emergency physicians to keep the index of suspicion high so that timely care can be provided to the patients.

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METHODOLOGY

It was a cross sectional study conducted in a 1200-bedded tertiary care hospital in Rawalpindi that covers an area of approximately 20,000 km^2 and a population of about 30 million, including northern Punjab, Kashmir, and the eastern part of Khyber Pakhtunkhwa province. The study was conducted between October 2019 and June 2020. The Ethics Committee of the Hospital approved the study (ERC No. A/28/160/EC).

Inclusion Criteria: All patients presenting in the Emergency or Outpatient Department, with the age of more than 18 years and having at least two signs and symptoms of neurological involvement, including fever >38F, headache, altered sensorium, seizures, or neck stiffness, were included in the study.

Exclusion Criteria: Patients already admitted to a hospital for any indication other than CNS infection who developed signs of CNS infection during the hospital stay were excluded from the study. Patients on long-term or acute immunosuppressive treatment such as chemotherapy, radiotherapy, chronic immunotherapy, or disease-modifying agents for chronic inflammatory diseases were also excluded.

Consecutive sampling was employed. The sample size that was adequate enough to determine the percentage of different types of CNS infections was calculated using the WHO sample size calculator.

CNS infections were diagnosed and classified according to the World Health Organization guidelines for infectious diseases.[6,7] Infections were categorized as "laboratory-confirmed, "probable", and "possible". The "possible" category applied only to the tuberculous infections.[8] Clinical diagnosis was based on clinical features, MRI findings, and CSF analysis in the absence of laboratory confirmation. The consensus opinion of local neurology and infectious disease experts was obtained in case of inconclusive laboratory findings with a clinical picture suggestive of a CNS infection. Patients with normal or inconclusive CSF results, unremarkable MRI Brain, or sufficient evidence of an alternative diagnosis were excluded after an expert panel review.

Lumbar Punctures (LP) were performed according to the hospital protocol. Cerebrospinal fluid (CSF) samples were analyzed for physical characteristics, cell count, proteins, glucose, viral PCRs, gram stain, and culture. Using Gene Xpert, CSF samples were also sent for Adenosine Deaminase levels and PCR for Mycobacterium tuberculosis. Autoimmune antibodies and fungal antigens were tested where appropriate. Other laboratory investiga-tions included thick and thin blood films stained with Giemsa stain for malarial parasites and Indian ink staining of CSF and Cryptococcal Antigen Latex Agglutination System for cryptococcal antigen. HIV1&2 Serology were performed using a serial algorithm of Determine HIV1/2 and HIV1/2 STAT-PAK. Blood and urine cultures and chest X-Rays were obtained for all febrile patients. Magnetic Resonance Imaging and CT scans of the brain were done in all cases.

The attending physician filled out detailed data forms that included patient demographics, history and examination findings, and relevant investigation results. Then, the primary investigator and supervisor reviewed the data to ensure case eligibility.

For analysis purposes, we classified CNS infections into three major groups; Bacterial meningitis, viral encephalitis/meningitis, and CNS tuberculosis. Fungal and parasitic central nervous system infections, the number being very small, were grouped as "others". Two cases of focal cerebritis, one due to Salmonella Typhi and the other one due to Brucella, were also included in this group, as these were very unusual focal presentations of systemic bacterial infections.

Informed consent was obtained from all patients included in the study. This study did not interfere with patients' routine management and did not require additional blood sampling. Therefore, it was permissible for the next of kin to consent on the patients' behalf if they could not do so owing to their impaired cognitive or conscious state. Separate consent was obtained for Human immunodeficiency virus (HIV) testing. Patient data were retrieved from hospital medical notes and stored in a password-protected electronic database.

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Quantitative variables were summarized as mean±SD and qualitative variables were summarized as frequency and percentages.Chi-square test was applied to find out the association.The *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Between October 2019 and June 2020, 172 patients fulfilled the inclusion criteria. Out of these, 75 patients were excluded-59 for alternate diagnoses and 16 for incomplete data. The final study sample comprised 97 patients with confirmed CNS infections based on the clinical picture, CSF parameters, routine laboratory investigations, neuroimaging, and consensus expert opinion. The mean age of our study population was 38.8±18.5 years, with 61(62.9%) male and 39(37.1%) female patients (Table-I). The meningeal signs were quite variable depending on aetiology, with as high as 88.2% of the patients with BM presenting with meningeal signs and 45.7% in patients with CNS tuberculosis.

Table-I: Baseline characteristics, Signs and Symptoms among Patients presenting with Central Nervous System (CNS) Infection (n=97)

Baseline features	n(%)
Age	38.8±18.5 years
Male Gender	61(62.9%)
Rural residence	81(83.5%)
Fever	70(72.2%)
Headache	84(86.6%)
Seizure	48(49.5%)
Neck stiffness	49(50.5%)
Altered sensorium	43(44.4%)

In contrast, only four patients with viral meningoencephalitis had signs of meningism on presentation. About 67% of the patients had a reduced conscious state, measured by the Glasgow Coma Scale (GCS), at some point during the hospital stay. The breakdown according to diagnosis was given in Table-II.

Table-II: Comparison of Clinical Parameters among the Major Groups(n=97)

Features	Bacterial Meningitis(n=17)	Viral encephalitis/ Meningitis (n=25)	Tuberculosis Meningitis (n=46)	Others (n=9)	*p*-value
Age(years) Mean(SD)	33.29(17.3)	36.68(18.42)	40.96 (19.8)	44.1 (11.98)	-
Male n(%)	5(29.4%)	16(64%)	30(65.2%)	8(88.9%)	0.052
Duration of illness (days) mean(SD)	5.29(3.40)	11.84(8.27)	37.13(39.9)	38.56(46.52)	-
Neck stiffness n(%)	15(88.2%)	4(16%)	21(45.7%)	3(33.3%)	<0.001
Fever n(%)	17(100%)	13(52%)	33(71.1%)	7(77.7%)	<0.001
Headache n(%)	17(100%)	19(76%)	39(84.7%)	9(100%)	0.261
Seizures n(%)	4(23.5%)	17(68%)	23(50%)	4(44.4%)	0.014
Altered sensorium n(%)	7(41.1%)	5(20%)	22(47.8%)	8(88.9%)	0.384
Findings on MRI Brain n(%)	13(76.47%)	11(44%)	41(89.13%)	4(44.4%)	<0.001
Illness resolved at hospital discharge n(%)	10(58.8%)	16(64%)	17(37%)	3(33.3%)	0.045
Mortality n(%)	0(0%)	3(12%)	10(21.7%)	4(44.4%)	0.022

Lumbar puncture was done in 97% of the patients. There were 2 cases of parasitic brain disease and one case of mucormycosis where LP was not performed due to the risk of brain stem herniation caused by the space-occupying lesions. Details of the CSF results were given in the Table-III. Of note, two patients with CNS tuberculomas lacked meningeal signs and had bland CSF. MRI brain was obtained in all cases within a mean of four days of admission, earlier if GCS was less than 8. MRI Brain was contrast-enhanced in all but six cases. Neuroimaging findings included hydrocephalus, leptomeningeal enhancement, infarcts and tuberculomas in the case of CNS tuberculosis.

Table-III: Cerebrospinal Fluid (CSF) Parameters among Patients with Clinically Diagnosed Central Nervous System Infections (n=97)

Cerebrospinal Fluid (CSF) Parameter	Bacterial meningitis (n=17)	Viral Encephalitis (n=25)	Tuberculosis Meningitis (n=46)
White blood cells (WBC)(cells/mm^3)	2873.0 (29-10000)	109.0 (10-400)	127.26 (1-364)
Neutrophils(%)	81.7% (40-90%)	29.6% (10-40%)	30.65% (0-80%)
Lymphocytes(%)	18.3% (10-60%)	70.4% (60-90%)	69.34% (20-100%)
Protein (mg/dl)	1782.8 (605-2901)	597.52 (179-1553)	1256.32 (398-2520)
Glucose (mg/dl)	3.91(1.0-7.4)	3.87(1.5-7.2)	3.53(0.8-7.9)
Adenosine Deaminase(ADA)	4.51(1.6-9.8)	4.21(1.5-9.2)	8.77(0.4-24.4)

Antibiotics were empirically administered to all our patients. Neurosurgical intervention was required in two cases. The first was a case of tuberculous meningitis, while the other was a case of Listeria meningitis, who developed progressive hydrocephalus despite antibiotics. The in-hospital mortality rate was 17.5%, with the highest mortality among patients with CNS tuberculosis (21.7%) out of the three major groups. Out of those who survived, 47.4% (n=46) of patients were discharged home without any neurological deficit, 23.7% (n=23) with a minor, and 11.4% (n=11) with a major neurological deficit.

DISCUSSION

The etiologies of different CNS infections presenting to a tertiary care hospital in Northern Punjab were investigated. The purpose was to analyze the pattern of CNS infections in this community. The most common aetiology was CNS Tuberculosis, which constituted 47.4% of the patients. It was followed by viral meningoencephalitis constituting 25.7% of cases. At the same time, bacterial meningitis was the least common CNS infection out of these three. However, a slightly higher incidence of CNS tuberculosis has been reported in other parts of Pakistan. For example, according to Awan *et al.* 65.3% of all the CNS infections presenting to tertiary care hospitals in Sindh were tuberculous meningitis, 17.7% were viral, and 12.9% were bacterial meningitis.[9] This is consistent with the epidemiology of infections in Pakistan, where tuberculosis is endemic, with an estimated 620,000 people having active tuberculosis, 410,000 getting infected, and 59,000 dying from the disease every year.[10]

A similar study done in North India by Kumar et al. reported that CNS tuberculosis was the most prevalent cause (51.5%) of CNS infections, followed by viral meningoencephalitis (13.9%), community acquired bacterial meningitis (9.7%), Cryptococcal meningitis (6.2%). Fungal infections and neurocysticercosis accounted for 1.7% of the cases each. The prevalence of Human Immunodeficiency Virus infection in this population was 11%.[11]

A study in Malaysia also shows a very high prevalence of tuberculous meningitis (48.8%) in all CNS infections. The rate of HIV co-infection was 15%, and the case fatality rate was 19%.[12] In another study done in Indonesia by Imran *et al.* the rate of co-infection with HIV was 54%, with in-hospital mortality of 32%.[13] However, in contrast to all of the above studies, the seroprevalence of Human Immunodeficiency Virus in the present study population was only 3%. Thus, compared to many other developing countries where CNS tuberculosis has a strong association with HIV,[13] here CNS tuberculosis was seen in immunocompetent, young and previously healthy people. Despite this, the mortality rate for CNS tuberculosis of 21.7% was as high as in other parts of the developing world.[14] The poor prognosis could be attributed to a significant delay in diagnosis,[15] which was a whooping 37±39.9 days. The most important reason for this late presentation is the lack of integrated health services in Pakistan.[16] As most of the health spending is out of pocket,[17] people cannot seek proper medical care in time. However, it was observed that 39(40%) patients had visited some health facility before presenting to tertiary care. However, lumbar puncture had been done in only 2(2%) patients, leading to a significant delay in diagnosing CNS infection.

Bacterial meningitis accounted for 18% of the cases of CNS infections. However, the precise pattern of bacterial etiologies could not be determined as CSF culture/gram stain was positive in only five (25%) cases. This has been corroborated in another study by Ahmed *et al.* from Sindh, Pakistan, where only 19% of all bacterial CNS infections were culture positive and 25% were gram-positive.[18] According to Afifi *et al.* only 8% of cases will be culture-positive if antibiotics were already administered.[19] Studies have shown that the incorporation of real-time PCR for identifying a specific bacterial pathogen increases diagnostic yield in such cases.[20]

Malaria is also endemic in Pakistan. According to an estimate, 500,000 cases of malaria arise each year.[10] However, only 2 cases of Cerebral Malaria were seen during the study period. One reason for this could be that malaria mainly involves CNS in children 1-5 years of age.[18] Another reason can be geographical diversity, as malaria is more common in the Indus basin of Sindh and parts of Balochistan.[10] Finally, a contributing factor could be the seasonality of the disease, as July and August were not included the study period.

Fungal infections (n=3) were least common, all presenting in immunocompromised patients. 2 cases of cryptococcal meningitis turned out to be HIV positive with CD4 count <100/microlitre, while one case with mucormycosis had poorly controlled diabetes. We had two patients with Parasitic infections, one with CNS hydatid disease and the other with CNS Cysticercosis.

CONCLUSION

From this pattern, we could conclude that CNS tuberculosis was the most common CNS infection in patients presenting to this tertiary care hospital, followed by viral and bacterial etiologies. There was a great delay in diagnosis, mainly due to late presentation, resulting in a poor outcome. Therefore the primary physician must always consider the possibility of CNS infection, particularly in the context of tuberculosis.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SS & WA: Conception, study design, drafting the manuscript, approval of the final version to be published.

AY & AH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

KHN & MAN: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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