Review Article

A study on Bacterial Infections Associated with Central Nervous System in Pakistani Population

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Abstract

Objective: This paper reviews the evolving trends and epidemiology of CNS infections in Pakistan over four decades, exploring pathophysiology, diagnostic criteria, and treatment approaches through systematic review and meta-analysis.
Methodology: A comprehensive research study was conducted from August 2021 to May 2022 at the Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore. It involved a literature review and meta-analysis of CNS infections in Pakistan from 1980 to 2022. This study estimates the burden of CNS infectious diseases, analyzing 183 articles. Approximately 100 studies used cerebrospinal fluid as a diagnostic specimen, while 83 studies used extra ventricular drainage, meeting inclusion criteria.
Results: The highest numbers of studies were conducted in 2009, 2011, 2014, 2015, 2017, 2019, 2020, and 2021, indicating an increasing focus on this area. Karachi had the highest publication rate. Bacterial agents accounted for 69% of cases, affecting both children (60%) and adults (72.2%). Males comprised 65% of the affected population. Low to middle in come patients with limited education were prevalent. Common symptoms included headache, nausea, neck stiffness, fever, seizures, and photosensitivity. *Meningitis* was the most prevalent type (55%), followed by subdural empyema (51.4%) and brain abscesses (41%). Major pathogens included *Streptococcus pneumoniae, Acinetobacter bauma nii, Enterobacter cloacae, Enterococcus faecium, and Haemophilus influenzae,* Viruses, fungi, and parasites were also involved. Many patients exhibited stages 3 and 4 on the MRC Breathlessness scale. These trends emphasize the importance of understanding CNS infections in Pakistan, focusing on causes, clinical presentations, and pathogens involved.
Conclusion: This review highlights the need for improved training, resources, and high quality care. Bacterial CNS infections continues to remain a significant challenge in the country.

Keywords: *Meningitis*, Subdural Empyema, Brain abscesses, Cerebrospinal fluid, Extraventricular drain

Introduction

When bacteria invade the central nervous system (CNS), comprising the brain, spinal cord, and nerves, it causes infections of CNS. The severity stems from the vital functions performed by this essential organ.[1] Bacteria invade the brain and meninges through various routes, causing meningitis and inflammation of the surrounding membrane.[2] Two primary meningitis types exist: leptomeningitis involving the pia and arachnoid, and patchy meningitis affecting the outer arachnoid and dura mater layers.[3] Thes pecific region of infection and severity depend on the anatomical location within the brain and meninges. Empyema, the accumulation of infected cerebral fluid, may occur in the epidural and subdural region.[4] The blood-brain barrier acts as a critical defense against bacterial invasion. Additionally, CNS infections can result from intracellular bacteria and be triggered by brain injuries, compound skull fractures, or neurosurgical procedures.[5] CNS infection symptoms include severe headache, convulsions, back pain, stiff neck, confusion, weakness, fever, seizures, high pitched crying, paralysis, loss of appetite, nausea, vomiting, light sensitivity, and more.[6] Diagnosis involves collecting specimens like cerebrospinal fluid (CSF) through a spinal tap or drain, blood samples, and imaging techniques such as CT or MRI. This research focuses on specimen collection, specifically CSF and extra ventricular drainage, and the necessary steps for diagnosing CNS infections.[7] CNS infection s result from various microorganisms, including bacteria, fungi, parasites, or viruses. Meningitis can be acute if caused by bacteria or viruses, or subacute when caused by parasites or fungi. Treatment typically involves medication.[8] CNS infections can lead to conditions like encephalitis and brain abscesses. Different bacterial species target specific age groups: *Listeria monocytogenes, Escherichia coli,* and Group B *streptococcus affect neonates, while E. coli, Neisseria meningitidis, and Haemophilus influenzae* affect children, and *Streptococcus pneumoniae* and *Neisseria meningitidis* affect adults. In the CNS, macrophages, and microglia have inflammasomes that detect infectious agents.[9] Bacterial proteins, such as IbeA, IbeB, AsIA, YijiP, OmpA, PilC, and InIB, aid in bacterial invasion of the brain.[10,11] Neisseria meningit dis, a human opportunistic pathogen, spreads through close contact and can cause meningitis and sepsis. Vaccines targeting Group B Neisseria meningitidis are available to combat its infection.[12]

Haemophilus influenza is associated with *Haemophilus meningitis,* characterized by fever, nausea, neck stiffness, and neurological disorders. Vaccines like "Hib" have been developed to reduce its incidence.[13] *Escherichia coli* are a common cause of neonatal *meningitis* and has a high mortality rate. It crosses the blood-brain barrier using various virulence factors, leading to inflammation of the meninges. Vaccines are available to protect against severe *E. coli meningitis*.[14] *Klebsiella pneumonia* is an uncommon source of bacterial meningitis, often observed in post neurosurgical and nosocomial infections. Its polysaccharide capsule and other factors contribute to its resistance and high morbidity and mortality rates.[15] Serratia marcescens is an opportunistic pathogen that can cause meningitis, pneumonia, and wound infections. It can cross the blood brain barrier and affect the brain parenchyma, leading to fatal CNS meningitis, particularly in neonates and immunocompromised individuals.[16] *Salmonella typhimurium* rarely causes meningitis but is associated with systemic infections. It affects neonates and infants more severely, potentially resulting in severe neurological complication.[17] *Acinetobacter baumannii-is* an opportunistic pathogen commonly linked to nosocomial infections. It is challenging to treat due to its virulence patterns and antibiotic resistance mechanisms. *Acinetobacter meningitisis* often fatal, particularly in neurological settings.[18] *Pseudomonas aeruginosa*, known for causing severe pulmonary diseases, can also lead to *Pseudomonas meningitis,* especially in patients who have undergone neurosurgery. Its virulence factors weaken host cell defense mechanisms, contributing to high morbidity and mortality rates.[19] *Streptococcus pneumoniae* is a gram positive bacterium responsible for pneumococcal meningitis, particularly in young children. It can spread easily through respiratory droplets and has a high mortality rate. Vaccines are available to reduce pneumococcal infection.[20] *Listeria monocytogenes*, transmitted through contaminated food, commonly affect the central nervous system and cause meningitis. It has unique spreading mechanisms and can cross the blood-brain barrier, leading to cranial nerve involvement. Pregnant women are particularly at risk.[21] Other bacterial pathogens, such as *Clostridium tetani,* Streptococcus *agalactiae, Mycobacterium tuberculosis, Staphylococcus aureus,* and *Enterococcus faecalis*, also contribute to *meningitis* cases with their specific virulence factors and characteristics.[22] Prompt diagnosis of bacterial *meningitis* is crucial, often involving analysis of (CSF). Treatment includes specific antibiotics based on bacterial susceptibility, and in somecases, vaccines are available to prevent certain types of meningitis. Overall, understanding the diverse bacterial pathogens and their mechanisms in causing meningitis is essential for effective prevention, diagnosis, and treatment strategies to combat this life-threatening infection.[23] According to the World Health Organization (WHO), both the United States of America and Africa experience a high fatality rate from central nervous system infections, particularly meningococcal meningitis. The untreated fatality rate for this disease is 50%, with a 10% risk frequency. In Africa, the Meningitis Belt, spanning from Sub Saharan Africa to Senegal in the west and Ethiopia in the east, is known for its high incidence of meningtis among people living nearby. Annually, approximately 30,000 cases of meningitis are reported in Africa.[24] *Neisseria meningitidis* is the most commonly observed bacterial species causing meningitis in both regions, with 12 serotypes, six of which can cause epidemics. The disease shows seasonal variation, with higher case numbers during winter. Neonates and children un der five years of age are most affected, but cases among adults with a mean age of 39 years have also been reported.[25] The complexity of treatment arises from the various serotypes of the bacterium, which contribute to its pathogenicity.[26] According to the Global Burden of Disease, 400,000 deaths Report and ranked among the top 10 leading causes of death from communicable diseases in in 2020.[27] Serogroup-specific vaccines are now used for prevention and outbreak control, particularly in epidemic-prone regions of Africa. These vaccines are affordable, with prices ranging from US $0.60 to US $2.5-117.0 per dose. The use of vaccines has led to a significant reduction in meningitis cases, with a 58% decrease in the incidence rate and a 60% decline in the risk of epidemics.[28] In Pakistan, an underdeveloped country with a high population density, rapid disease spread is a challenge. Limited awareness and low literacy rates contribute to a lack of treatment, prioritizing illness over prevention and cure. The most common (CNS) infections in Pakistan are often caused by Streptococci bacteria.[29] Men being more susceptible than women. All four provinces of Pakistan face equal risk, although the northern areas, particularly Khyber Pakhtunkhwa, have a higher incidence.[30] The Aga Khan Institute in Karachi conducts extensive research on CNS infections, with a focus on cerebrospinal fluid and ventricular drain specimens. The availability of vaccines, antibiotics, and specialized medicines has significantly reduced the severity and occurrence of CNS infections in the Pakistani population.[31] This research project aims to conduct a comprehensive analysis of (CNS) infections in Pakistan. This includes enumerating the annual reported cases, assessing the effectiveness of treatments, evaluating the morbidity and mortality rates associated with CNS infections, planning appropriate diagnosis and treatment procedures, estimating the burden of these infections, and determining the current capacity of the neurosurgical workforce in managing them. Additionally, the research aims to identify geographic areas in Pakistan that require targeted improvement in neurosurgical capacity to better address the incidence of CNS infectious diseases.

Methodology

The research was conducted at the Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore from August 2021 to May 2022. A retrospective literature review of published articles on Central Nervous System Infections in Pakistan was performed. Data were collected about the prevalence of CNS infection in different regions of Pakistan, types, signs and symptoms, bacterial species and socio-demographic character of patients. Google Scholar (https://scholar.google.com/) and PRISMA (http://www.prisma-statement.org/) were used with a combination of keywords and controlled vocabulary representing the concepts "CNS infections in Pakistan", "meningitis", "brain abscesses", "subdural empyema" and "Prevalence of CNS infections in Pakistan". A total of "183" articles were collected. Out of these, 100 studies met the inclusion criteria already set for CSF as a specimen for diagnosis. While 83 studies met the inclusion criteria with EVD as a specimen for diagnosis, all studies were reviewed by title and abstract and then by full text.

All articles were published in Pakistan, in a good impact factor journal from 1980 to 2022. In this study, we did not include articles based on age and gender of patients. Thus, this literature review encompasses patients of all ages, including neonates. The review includes both immune-competent and immunosuppressed patient populations. Exclusion criteria involved CNS infections in animals (goats, mice, etc.) and infection that has an indirect route to CNS infection like tetanus, polio, etc. All the data were organized in a Microsoft Excel sheet. Data were categorized. These involve the author's name, the city in which the article was published, the year in which the article was published, the title of the article, the name of the journal in which the article has been published, the socio-demographic character of patients (education, occupation, and financial status), age of patients (neonates, 1year-10years, 10- 20years and 30 years above), the gender of patients (male and female), clinical signs, types, MRC stage, strain mentioned in the article, a specimen for diagnosis, number of citations of the article and impact factor of the journal. Two separate Excel sheets were made for each specimen, one for CSF and another for EVD as a specimen. The frequencies of each parameter were calculated using the software Prism (https://www.graphpad.com/features) and SPSS (https://www.ibm.com/spss). As the above methods involved extrapolating data from studies reported in the literature, the studies contained no personal data with no means to contact. It is a systematic observational review, so informed consent, patient consent for publication, Institutional Review Board approval, and Ethics Committee approval were not required.

Results

A comprehensive collection of articles from Google Scholar, PubMed, and PubMed Central yielded a total of 183 publications. The analysis employed conventional CSF tests and cutoffs to evaluate CNS inflammation and predict the etiology of community-acquired meningoencephalitis. Notably, CSF proved diagnostically useful in patients with recent CNS injury, surgery, or prior catheter usage (Table. 1).

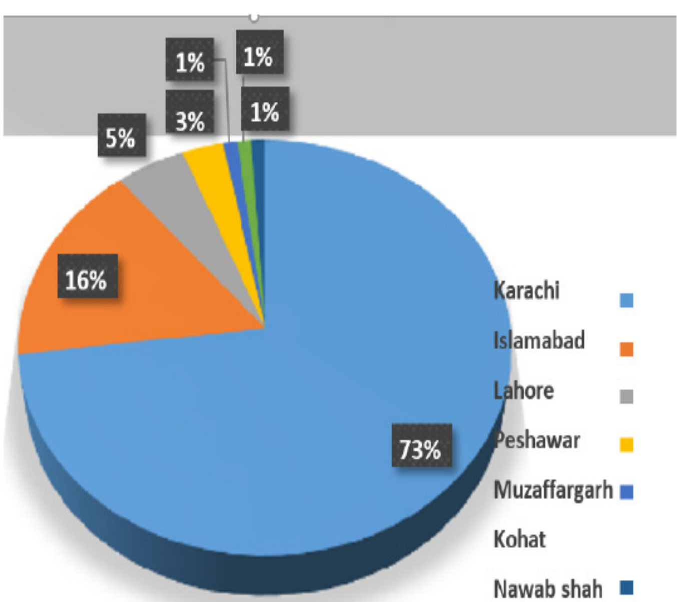

Figure 1: Percentage of studies conducted in different regions of Pakistan.

Table 1: Selection of articles with Cerebrospinal Fluid as Specimen

Sr. No	Year	Cities in which infection isstudied	Number of studies conducted (n=100)
1	2022	Karachi, Islamabad	4 (4)
2	2021	Karachi	6 (6)
3	2020	Islamabad	7 (7)
4	2019	Karachi	5 (5)
5	2018	Karachi	2 (2)
6	2017	Karachi, Islamabad	6 (6)
7	2016	Karachi, Lahore	4 (4)
8	2015	Karachi, Islamabad	7 (7)
9	2014	Karachi, Islamabad	6 (6)
10	2013	Karachi, Islamabad	7 (7)
11	2012	Karachi, Muzaffargarh	2 (2)
12	2011	Karachi, Islamabad, Peshawar, Kohat	5 (5)
13	2010	Karachi	3 (3)
14	2009	Karachi, Lahore, Islamabad	8 (8)
15	2008	Karachi, Islamabad	2 (2)
16	2007	Karachi	1 (1)
17	2006	Karachi Islamabad	3 (3)
18	2005	Karachi	2 (2)
19	2004	Karachi, Islamabad	2 (2)
20	2003	Karachi, Nawabshah	2 (2)
21	2002	Karachi, Peshawar	2 (2)
22	2001	Islamabad	1 (1)
23	2000	Karachi	1 (1)
24	1999	Karachi	1 (1)
25	1996	Karachi, Islamabad	2 (2)
26	1994	Karachi	1 (1)
27	1993	Karachi	1 (1)
28	1990	Karachi	1 (1)
29	1991	Karachi	1 (1)
30	1992	Karachi, Islamabad	2 (2)
31	1988	Karachi	2 (2)
32	1987	Lahore	1 (1)
33	1984	Karachi	1 (1)
34	1980	Karachi	1 (1)

In addition to the aforementioned findings, a distinct cohort of 83 research studies delved into the application of Sequential sampling from Exponential Viral Distributions (EVDs). The collective analysis of these studies revealed that such sampling practices emerged as a noteworthy indicator for central nervous system infection, as explicitly demonstrated in Table 2. This underscores the importance of Sequential sampling as a valuable diagnostic tool in identifying and assessing central nervous system infections across various clinical contexts.

Table 2: Selection of articles with extra ventricular Drainage as Specimen

Sr.No	Year	Cities	Number of studies conducted (n=83)
1	2022	Karachi	5 (6.02)
2	2021	Karachi	9 (10.8)
3	2020	Islamabad	9 (10.8)
4	2019	Karachi	8 (9.6)
5	2018	Karachi, Peshawar, Lahore	7 (8.4)
6	2017	Karachi	6 (7.2)
7	2016	Karachi	4 (4.81)
8	2015	Karachi	4 (4.81)
9	2014	Karachi, Peshawar	5 (6.02)
10	2013	Karachi	4 (4.81)
11	2012	Karachi	3 (3.61)
12	2011	Karachi	4 (4.81)
13	2010	Karachi	2 (2.4)
14	2009	Karachi	3 (3.61)
15	2008	Karachi	1 (1.2)
16	2007	Karachi	1 (1.2)
17	2006	Karachi	2 (2.4)
18	2005	Karachi	1 (1.2)
19	2004	Karachi	1 (1.2)
20	2003	Karachi	1 (1.2)
21	1997	Karachi	1 (1.2)
22	1993	Karachi	1 (1.2)
23	1980	Karachi	1 (1.2)

The distribution of these studies across various regions provides valuable insights into the prevalence and scope of CNS infections in different parts of Pakistan (Figure 1). A considerable proportion of studies examined patients between 1 month to 30 years or above (Table 3). In terms of gender distribution, the majority of studies included more males than females. Neonates and children had a substantial presence among the studied cases. Financially, the patients varied from low to middle class, and many of them had limited education, often up to the primary level. However, the occupation of the patients was not specified in any of the articles.

Table 3: Age of CNS infected patients.

Sr. No	Age of patients	Number of studies conducted (n =183)
1	1 month- 10 years	82 (44.8)
2	10-20 years	50 (27.3)
3	30years or above	96 (52.4)

Clinical signs play a significant role in diagnosing CNS infections (Figure 2).

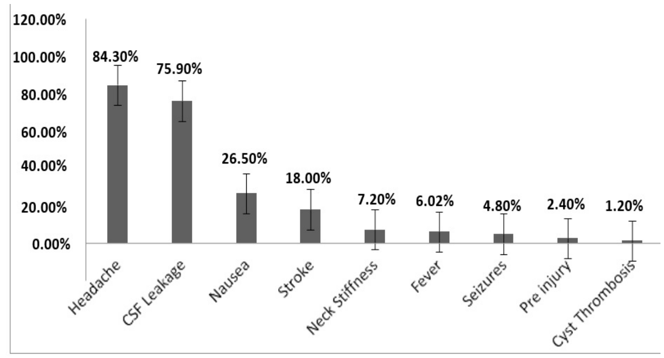

Figure 2: Clinical signs associated with CNS infections (%age)

The prevalence of CNS infections reveals meningitis as the most studied type, accounting for 45.3% of cases, while subdural empyema and brain abscesses represent 42.7% and 31.6% respectively.

Among the studies conducted, bacterial infections were the most commonly reported, followed by viral, parasite-origin, and fungal infections, in that order (Table 3). These findings underscore the diverse nature of CNS infections and the importance of conducting comprehensive research to better understand and address each specific type of infection. The MRC Breathlessness scale, specifically stages 3 and 4, was commonly observed in CNS infections, indicating the severity of the pathology (Table 4).

Table 4: Strains Causing CNS Infection

Sr. No	Strain	Number of studies conducted (%age)n =183
	Gram-negative bacterial strain	
1	*Acinetobacter baumannii*	59 (32.3)
2	*Enterobacter cloacae*	52 (28.4)
3	*Enterococcus faecium*	34 (18.5)
4	*Pseudomonas aeruginosa*	31 (16.9)
5	*Haemophilus influenza*	16 (8.7)
6	*Klebsiella pneumonia*	14(17.6)
7	*Stenotrophonas maltophilia*	11 (6.1)
8	*Neisseria meningitis*	9 (4.9)
9	*Escherichia coli*	6 (3.2)
10	*Haemophilus influenza type B*	4 (2.1)
11	*Helicobacter pylori*	3 (1.6)
12	*Salmonella typhi, Salmonellaparatyphi*	2 (1.09)
13	*Campylobacter jejuni*	1 (0.54)
14	*Rhinocladiella mackenziei*	1 (0.54)
	Gram Positive Bacterial Strains	
15	*Streptococcus pneumonia*	36 (19.6)
16	*Mycobacterium tuberculosis*	17 (9.2)

Sr. No	Strain	Number of studies conducted (%age)n =183
17	*Micrococcus spp*	10 (5.4)
18	*Staphylococcus aureus*	9 (5.2)
19	*Staphylococcus epidermidis*	2 (1.09)
20	*Streptococcus pyogenes*	2 (1.09)
21	*Listeria monocytogenes*	2 (1.09)
22	*Propionibacterium acnes*	2 (1.09)
23	*Actinomyces*	2 (1.09)
24	*Clostridium tetani*	1 (0.54)
25	*Nocardia*	1 (0.54)
Fungi, Parasites, and viruses		
26	*Naegleria floweri*	9 (5.2)
27	*Aspergillus*	7 (3.8)
28	*Herpes simplex virus*	3 (1.6)
29	*Japanese Encephalitis Virus*	2 (1.09)
30	*Rubella virus*	2 (1.09)
31	*Toxoplasma gondii*	2 (1.09)
32	*Enterovirus*	2 (1.09)
33	*Candida albicans*	1 (0.54)
34	*Arbovirus*	1 (0.54)
35	*Epstein Barr Virus*	1 (0.54)
36	*Varicella zooster virus*	1 (0.54)
37	*Dengue virus*	1 (0.54)
38	*Measles virus*	1 (0.54)
39	*Mumps virus*	1 (0.54)
40	*Plasmodium falciparum, P. vivax*	1 (0.54)
41	*Ramichloridium mackenziei*	1 (0.54)
42	*Wangiella dermatitidis*	1 (0.54)
43	*Rhinocladiella mackenzeiei*	1 (0.54)
44	*Bipolaris*	1 (0.54)

Discussion:

A systematic literature review and meta-analysis were conducted to analyze studies published from 1980 to 2022 in Pakistan, providing comprehensive estimates of the burden of CNS infectious diseases. The findings highlight regional disparities, pathogens involved, clinical signs, and socio-demographic factors. The limited healthcare workforce and resources in Pakistan, combined with the high burden of CNS infections, underscore the urgent public health concerns in the country. Unlike developed regions with better diagnosis and treatment, Pakistan faces a high prevalence of CNS infections, resulting in significant morbidity and mortality. The lack of access to timely diagnosis and treatment contributes to untreated cases and preventable deaths. Raising awareness about early diagnosis and treatment is crucial to reduce the impact of CNS infections in Pakistan.[32] There was a consensus on sampling for diagnostic procedures. Two such sampling methods were studied one being the CSF while the other being the EVD. For diagnostic and therapeutic purposes, surgical drainage is required to obtain cultures of bacterial, mycobacterial, fungal, parasitic, and viral origin for guidance in medical treatment. The sampling for diagnosis of CNS infection was done based on differential diagnostic recommendations.[33]

The highest number of studies were conducted in Pakistan in the years 2009, 2011, 2014, 2015, 2016, 2017, 2018, 2019, 2020, and 2021, with increasing incidence rates over time due to improved awareness and understanding of CNS infectious diseases.[34] Karachi had the highest number of published articles (73%), likely because it is the largest city in Pakistan and has several medical universities actively involved in research. Bacteria were found to be the most common causative agent of CNS infections, with a 69% incidence rate. Similarly, research conducted in the United States in 2021 also identified bacteria as the primary causative organism in most CNS cases.[35]

In terms of age distribution, CNS infections were predominantly observed in children aged 1 month to 10 years, accounting for 82% of cases. Research conducted in the United Kingdom in 2022 also highlighted the higher incidence and morbidity of neonatal meningitis compared to other age groups.[36] Adults aged 30 years and above accounted for 96% of CNS infection cases. Similar studies conducted in Thailand and the United States in 2022 reported mean ages of 40 years and 35.8 years, respectively. The reason behind this might be firstly, as individuals age, their immune systems may weaken, making them more susceptible to infections, including those affecting the CNS. Secondly, older adults may have underlying health conditions or chronic illnesses that compromise their immune function, increasing the risk of CNS infections. Lastly, lifestyle factors such as travel, exposure to new environments, and medical procedures become more common with age, potentially leading to increased opportunities for pathogen exposure and infection. Male patients were more commonly affected, with a prevalence of 65%. Males being more affected by central nervous system (CNS) infections can result from a combintion of biological and behavioral factors. One key contributor may be differences in immune responses, as females often exhibit stronger immune defenses against certain infections. Addtionally, specific risk behaviors or occupational exposures may increase the likelihood of CNS infections in males, leading to a gender-based discrepancy in infection rates. This aligns with research conducted in the United States (Pennsylvania) in 2020, which reported that 60-78% of CNS infection patients were male.[37]

The financial status of CNS-infected patients in Pakistan ranged from low to middle income. While most of the patients were illiterate or had an education status till primary, in 2022 research was conducted in the US and India, revealing that the highest cases of CNS infections are reported in low-income countries, because of poor vaccination facilities provided by the government in low-income countries.[38] The most common clinical sign of CNS infection was headache (83%), Nausea (65%), Neck stiffness (60%), Fever (59%), Seizures (41%), and CSF Leakage (63%). Comparatively, in 2015 research conducted in the US (Pittsburgh) the major clinical signs observed were headache (58.9%), Nausea (47.1%), and photophobia (29.4%). Photophobia is not observed in either case in Pakistan.[39]

The most prevalent CNS infection was meningitis (45.3%), subdural empyema (42.7%), and brain abscesses (31.6%). Comparatively, in 2018 research conducted in India shows that bacterial meningitis occurs as 3 cases per 100,000 persons in developed countries, but it is more common ten times in underdeveloped countries, and brain abscesses have an incidence of 0.3-1.3 cases per 100,000 people per year.[40] Remarkably the most common bacterial species that causes CNS infection was gram-positive Streptococcus pneumonia with a 36% incidence. Similarly, research conducted in 2021 in the US shows that Streptococcus pneumonia and Neisseria meningitides are the cause of 80% of bacterial meningitis in cases reported per year.[41]

On the other hand, gram-negative bacteria are also involved in causing CNS infections that include Acinetobacter ba ma nii with 68.6% virulence, Enterobacter cloacae with 62.6% virulence, Enterococcus faecium with 40.9% virulence an Haemophilus influenza with 29% virulence. Similarly, research conducted in 2018 in the US shows that gram-negative bacilli are the common cause reported of CNS infections per year.[42] There are numerous viruses (*Epstein Barr Virus, Varicella zoster virus, Rubella virus, Dengue virus, Enterovirus, Herpes simplex virus, Measles virus, Mumps virus, Japanese Encephalitis Virus, etc.), fungi (Aspergillus flavus, Aspergillus fumigatus, etc.) and parasites (Plasmodium falciparum, P. vivax,* etc) involved in causing CNS infections. Comparatively, in 2022 two types of research conducted in the US revealed that *Enterovirus, Adenovirus, Herpes Simplex Varicella zooster virus* is the common cause of viral meningitis while fungal infections are caused by Aspergillus sp in most cases. MRC stage 3rd and 4th is mostly observed in patients with CNS infection.[43, 44]

Conclusion

In conclusion, bacterial meningitis with brain abscesses and subdural empyema is a common CNS infection all over Pakistan. These bacterial infections require early recognition and management. Moreover, a significant contrast between the incidences in different regions of Pakistan reinforces that CNS infections are primarily a disease in developing countries. Our results corroborate that CNS infections are a known public health problem. CNS infections are directly related to poor socioeconomic conditions, including hematogenous and direct spread from pneumonia. Meningitis, brain abscesses, and Subdural empyema are the common types of brain infections with prominent symptoms such as headache, fever, seizures, nausea, neck stiffness, and CSF leakage. CNS infections can occur in either gender and at any age of life. Mortality may increase when one is facing a dual health problem such as a head injury recently or is in an immuno-compromised state. All the diagnostic procedures should be used to identify the bacterial agent and then start the therapy accordingly. However, the vaccine is considered the best mechanism to reduce the burden.

Limitations

We recognized several limitations in this literature review. The disease estimations presented in this study are based on the widest-ranging and most comprehensive studies available till now. The major highlights of this study include the comprehensive literature research, a large number of included studies, and a great emphasis on the inclusion of data from different regions of Pakistan. To our knowledge, this is the largest review of available literature on CNS infections in Pakistan. However, the findings are not without limitations. While the three disease categories (meningitis, subdural empyema, and brain abscesses) are not comprehensive, they omit multiple diseases that lead to CNS infections such as HIV–related infections, Polio, AIDS, etc. However, less common diseases were omitted including cerebral schistosomiasis, prion disease, and neuroborreliosis, which are unlikely to greatly affect the estimated volume of CNS infections. Additionally, including data from the most significant possible number of regions in Pakistan was not practically possible. It was due to the missing data issue. In this study, we only identified the CNS infection cases that were present in the literature. However, we believe that CNS infection patients are still underreported, especially in rural areas of Pakistan. The exclusion of this vast body of data could have a significant impact on our approximations. This may result in overestimations or underestimations of incidence. While these limitations are substantial, they highlight the difficulty in obtaining high-quality epidemiological data on infectious diseases affecting the CNS, particularly in low-resource settings. Further research should specifically address these limitations, with a focus on population-based epidemiological studies in Pakistan.

Recommendations

To address the limitations of our study and advance research in this area, we propose several critical recommendations and future directions. These include expanding disease categories to encompass HIV-related infections and Polio, incorporating alternative data sources to enhance data completeness, improving rural data collection through collaborations and community engagement, employing statistical adjustments, prioritizing population-based studies in rural areas, collaborating with health organizations, conducting sensitivity analyses to assess data limitations, and advocating for future research aimed at enhancing data collection and reporting mechanisms. These measures collectively aim to reduce the burden of CNS infections in Pakistan and improve public health outcomes.

Authors' contribution: MA executed experimental design, collected data, and authored the paper. HA did collection of data and wrote the paper while TF did Contributed data and analysis tools, Contributed to article write-up. SM did whole paper analysis and proof reading, contributed to the revision of whole paper. .

Conflict of interest: The authors have no conflict of interest regarding this study.

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