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Epidemiology, clinical characteristics, and outcomes of patients having central nervous system infections in Almaza fever military hospital: A retrospective study

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Abstract

Objective: This study aimed to describe the epidemiology, clinical characteristics, management, and treatment outcomes of patients diagnosed with central nervous system (CNS) infections at a tertiary care hospital in Egypt.

Methods: A retrospective analysis was conducted on 104 patients admitted with suspected CNS infections between July 2021 and October 2023. Data extracted from hospital records included patient demographics, clinical features, laboratory and neuroimaging results, treatment regimens, and final outcomes.

Results: The median patient age was 50 years, with a male predominance (71.2%). The most common diagnoses were encephalitis (45.2%) and meningitis (41.3%). A causative pathogen was identified in only 42.3% of cases, with *Streptococcus pneumoniae* being the most frequent (13.5%). No etiology was found in 57.7% of cases. Diabetes was the most frequent comorbidity (27.9%). The universal clinical feature was disturbed consciousness, followed by fever and headache. The most used empirical treatment was a combination of ceftriaxone, vancomycin, and acyclovir (57.6%). The overall cure rate was 80.7%, and the mortality rate was 5.7%. All cases of cryptococcal meningitis and 10% of cerebral malaria cases were fatal.

Conclusion: In this cohort, CNS infections primarily affected older adults, with a high rate of unknown etiology. The use of empirical broad-spectrum therapy was associated with a favorable overall outcome. However, the findings highlight an urgent need for enhanced diagnostic methods to identify pathogens, especially in fatal fungal and parasitic infections, to guide targeted treatment and potentially improve survival.

Keywords: Central nervous system infections; Meningitis; Encephalitis; Epidemiology; Treatment outcomes; Egypt

1. Introduction

Central nervous system (CNS) infections represent a critical challenge in medicine due to their severe consequences and the imperative for prompt recognition, diagnosis, and treatment to save lives. These infections encompass distinct clinical syndromes like acute bacterial meningitis, viral meningitis, and encephalitis, alongside focal infections such as brain abscesses, subdural empyema, and infectious thrombophlebitis. Often, these conditions initially present with non-specific prodromal symptoms like fever and headache. Crucial to early management is the urgent differentiation between these conditions, identification of the causative pathogen, and initiation of appropriate antimicrobial therapy.

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Global and Regional Burden of CNS Infections Globally, meningitis remains a formidable disease, causing an estimated 250,000 deaths in 2019 and leaving one in five affected individuals with severe long-term sequelae. Vaccination programs, such as Egypt's expanded national vaccination program against *Neisseria meningitidis* and the introduction of influenza, measles, mumps, and rubella vaccines, are expected to significantly reduce local incidence rates of these infections. Viral meningitis is more prevalent than bacterial meningitis, though typically less severe. A significant proportion (up to 70%) of encephalitis cases have unknown etiologies, and non-infectious processes can also cause the condition. CNS infections are clinically characterized by symptoms such as fever, headache, vomiting, seizures, loss of consciousness, altered sensorium, focal neurological deficits, and blurred vision, with variations depending on the etiology and brain involvement [1].

Low- and middle-income countries (LMICs) disproportionately bear the burden of CNS infections. These infections can result from a wide range of viruses, leading to varied neurological manifestations. Common viral etiologies include enteroviruses, herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human immunodeficiency virus (HIV). *Cryptococcus* is the most common cause of fungal CNS infections, particularly in sub-Saharan Africa, where it is a leading cause of meningitis [1].

The global burden of disease reported a 21% reduction in deaths from CNS infections between 1990 and 2016, but an increase in incidence from 2.50 to 2.82 million cases during the same period. While viral meningitis is more common, bacterial meningitis is more serious if left untreated. Viral CNS infections range from 0.26 to 17 cases per 100,000 people, with incidence varying by age and other factors. In the U.S., viral meningitis incidence is approximately 0.7 cases per 100,000 people per year, and viral encephalitis is 1.7 cases per 100,000 people per year. Resource-limited settings face a particularly high burden of viral CNS infections, associated with high morbidity and mortality rates. For instance, acute encephalitis syndrome in sub-Saharan Africa has an estimated annual incidence of 4.3 cases per 100,000 people and a case-fatality rate of up to 45% in some regions [1].

Fungal CNS infections contribute significantly to morbidity and mortality globally, especially in immunocompromised individuals. Cryptococcosis, the most common fungal infection affecting the CNS, accounts for an estimated 223,100 cases and 181,100 deaths annually worldwide. Among people living with HIV, approximately 152,000 cases of cryptococcal meningitis occur each year, with 112,000 deaths, predominantly in sub-Saharan Africa. Other fungal pathogens like *Aspergillus* and *Candida* species also cause significant morbidity and mortality, particularly in immunocompromised patients. Mycobacterial infections, especially CNS tuberculosis, are common in Southeast Asia, accounting for 1% of all TB cases and being the most frequent form of CNS TB [1].

Immune Responses in CNS Infection: The CNS has an "immune privilege" status due to local tissue barriers and immunosuppressive microenvironments, restricting the flow of cells, infections, or macromolecules. Key physical barriers include the blood-brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier, and arachnoid barrier. Under pathological conditions, peripheral immune cells can cross the BBB. CSF transport through skull channels and into marrow cavities suggests a mechanism for pathogens to induce immune cell release in response to inflammation [2].

T-cell-mediated immune regulation involves resident microglia and perivascular macrophages inhibiting foreign bodies. T cells are crucial for eradicating viral and intracellular bacterial infections, often clearing viral infections non-cytolytically. Activated T cells can move from blood vessels to the subarachnoid space via the choroid plexus stroma. Both CD4+ and CD8+ T lymphocytes are found in meninges, choroid plexus, parenchyma, and naïve brain. Myeloid cells as antigen-presenting cells (APCs) activate and recruit antiviral T cells [2].

Immune responses in the CNS are divided into innate and adaptive. The initial strong innate response throughout the CNS provides antimicrobial defense, followed by adaptive immune responses if infection persists. Microglia, astrocytes, and other APCs express Major Histocompatibility Complex (MHC) class II and co-stimulatory molecules, activating T-cell subtypes and stimulating humoral immune responses (antibody production by B cells). B lymphocytes reside primarily in the meninges, particularly the dura mater layer, and gut-sensitized B cells may contribute to CNS humoral immunity when pathogens breach the blood-brain barrier [2].

Neurotropism is the ability of microorganisms to invade and reside in neural tissue. Neurotropic viruses vary in their neurovirulence and neuroinvasiveness; for example, herpes simplex viruses are highly neuroinvasive but weakly neurovirulent toward the peripheral nervous system. Viral genomic makeup, biological location, host immunological state, and environmental factors determine CNS viral infections. Flavivirus infections affect specific brain regions like anterior horn neurons, substantia nigra, thalamus, and neocortex. Flavivirus neuroinvasion is influenced by envelope protein glycosylation, which enhances axonal and transepithelial transport, and entry into host cells is facilitated by various cellular attachment factors. Flaviviruses also increase BBB permeability by disrupting tight junctions. CD8+ T

cells are vital for clearing West Nile virus-infected cells from the CNS. SARS-CoV-2 can enter the CNS via axonal transport through cranial nerves or by crossing the BBB/blood-CSF barrier after viremia. Future SARS-CoV-2 variants could exacerbate CNS issues, and immunization may affect CNS complications [2].

Immunosuppressive Effects of Pathogens: Some pathogens cause immunosuppression by impeding hemopoiesis or antigen presentation. Measles virus infection leads to temporary immunosuppression, depleting lymphocytes during acute infection. However, increased adaptive immune responses eventually eliminate the virus. HIV primarily targets helper T cells, leading to their depletion and Acquired Immunodeficiency Syndrome (AIDS), and can cause APC abnormalities. CMV infection suppresses hemopoiesis, affecting bone marrow stromal cells or directly infecting progenitor cells. Measles, HIV, and CMV cause systemic immunosuppression through various mechanisms: altering cytokine equilibrium, impairing macrophage and dendritic cell activities, inhibiting hemopoiesis, and generating immunosuppressive proteins. *Aspergillus fumigatus*, an airborne fungus, causes high mortality in immunodeficient persons and produces gliotoxin, which hinders neutrophil function and innate immunity by reducing LTB4 formation, interfering with neutrophil phagocytic activities [2].

Infection-Induced Autoimmune Responses: Infections can trigger autoimmune responses when the immune system reacts to self-antigens, often due to inherent deficiencies in peripheral self-tolerance, genetic defects, or other factors. Multiple sclerosis (MS) is a prevalent CNS autoimmune illness. Viruses or bacterial infections are often the root causes of autoimmune diseases, with viruses potentially initiating autoimmune reactions by influencing immune cells for self-defense. Molecular mimicry is a basic mechanism by which normal immune responses can shift to autoimmune responses following an infection [2].

Diagnosis of CNS Infections: Diagnosis typically involves clinical presentation, blood tests, blood culture and is confirmed by cerebrospinal fluid (CSF) analysis and neuroimaging. Lumbar puncture for CSF analysis is almost always performed when CNS infection is highly suspected. However, diagnostic methods lack consistent results globally, and variations in studies exist. Challenges in diagnosing meningitis/encephalitis include varied clinical presentations with overlapping symptoms such as fever, headache, neck stiffness, altered consciousness, seizures, and focal neurological findings, which can be associated with diverse infectious agents [3]. Furthermore, an etiology is not always identified due to a lack of targeted testing, the vast number of potential infectious causes, and the fact that about 10% of suspected cases are eventually found to have non-infectious origins. Routine CSF parameters can suggest the type of infection (bacterial, viral, or fungal) but are not specific. Bacterial meningitis cultures, while useful, take 2–5 days and can yield false negatives due to fastidious organisms, prior antibiotic treatment, or improper specimen handling. For non-bacterial ME, clinical suspicion is necessary to order the correct viral agent testing. Delays in diagnosis and treatment can occur when laboratories, especially in smaller or rural areas, rely on reference laboratories for CSF testing. In Egypt, bacterial septic meningitis (73.0%) is predominantly caused by *Streptococcus pneumoniae* (43.0%), with viral septic meningitis (22.0%) primarily attributed to HSV (32.8%) and enteroviruses (24.5%) [3].

Clinical Presentation and Diagnosis: Patients with CNS infections can present with a range of symptoms, including headache, fever, focal neurological deficits, seizures, acute confusion, lethargy, neck pain, photophobia, back pain, nausea, vomiting, syncope, coma, and dermatological manifestations. Constitutional symptoms like lymphadenopathy, arthralgias, and myalgias may also occur.

Meningitis: Acute meningitis, an infection of the meninges, is the most common infectious disease of the CNS. The classic triad includes fever, neck stiffness, and altered mental status, with 99–100% of meningitis patients presenting with at least one component. *S. pneumoniae* meningitis can lead to rapid clinical decline and death, although pneumococcal vaccines have reduced mortality. *Listeria monocytogenes* should be suspected in infants and elderly patients, and *Neisseria meningitidis* is concerning due to its epidemic potential [3].

Encephalitis: Patients with encephalitis can exhibit symptoms ranging from subtle deficits to unresponsiveness, including neurological manifestations seen in meningitis and seizures. A hallmark is acute onset of febrile illness (fever above 38°C within 72 hours). Meningeal symptoms may be absent. Altered mentation can range from confusion to obtundation. The presentation often reflects the causative agent's predilection for certain CNS cells; for example, herpes simplex virus infections affecting the temporal lobe can lead to aphasia, anosmia, temporal lobe seizures, and focal neural deficits [3].

In conclusion, CNS infections are a diverse and critical group of medical conditions requiring swift and accurate diagnosis and treatment. Their varied etiologies, complex immune interactions, and diverse clinical presentations underscore the ongoing challenges in management and prevention worldwide.

2. Materials and methods

- **Aim of the work:** Improve clinical management and treatment outcome by identifying epidemiologic features and factors affecting treatment and outcomes.

2.1. Objectives of the Study

- To determine the most common causes of central nervous system infections.
- To find out the factors affecting clinical management and treatment outcome.
- To determine the impact of HIV on central nervous system infection.
- To know the impact of travelling history on central nervous system infection.
- To know the effect of the new method of diagnosis of central nervous system infection on clinical outcomes.

Study Design: A descriptive retrospective study.

Study Settings: Almaza fever military hospital.

Study Population: All patients admitted to Almaza Fever Military Hospital intensive care unit with clinical presentation suggesting of a central nervous system infection.

Inclusion criteria: Patients with case definitions of central nervous system infections involving infection of the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membranes. It includes:

- Meningitis: An illness with sudden onset of fever (>38.5°C rectal or >38.0°C axillary) and one or more of the following: neck stiffness, altered consciousness, other meningeal irritation signs or petechial or purpureal rash.
- Meningoencephalitis: is an inflammation of the brain parenchyma with or without involvement of the meningeal structures.
- Encephalitis: is defined as inflammation of the brain parenchyma associated with neurologic dysfunction
- Parasitic infection of the brain.
- Patients who included were admitted to Almaza Fever Military Hospital from July 2021 to October 2023 and were included in the study.
- Suspected or clinically diagnosed cases in all age groups would be included.

2.2. Exclusion criteria

- All those patients whose diagnosis was uncertain and inconclusive were excluded from the study.
- Patients would be excluded from the study, like pregnant women and post-traumatic.
- Patients had contraindications to CSF lumbar puncture.
- Patients had incomplete data records.

2.3. Sample selection

All patients admitted to the intensive care unit at Almaza Military Fever Hospital who met the criteria for central nervous system infection in the period from July 2021 to October 2023.

2.4. Methods

Registered data in hospital databases and the procedures had been done for all cases included. Registration data for all the patients included in the study will be retrieved from hospital records and collected in a pre-prepared sheet.

2.5. Statistical Analysis

The collected data will be coded, revised, and entered into the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non-parametric distribution.

3. Results

Table 1 Demographic data among studied patient

		No	%
Gender	Male	74	71.2%
	Female	30	28.8%
Residence	Rural	39	62.5%
	Urban	65	37.5%
Age	Mean ±SD	44.14	20.08
	Range	4	82
	Median	50	
	0-18 years old	11	10.5%
	18-50 years old	40	38.46%
	Over 50 years old	53	50.9%

Most of the studied patients (n =74) were male. The median age of the studied patients ranged from 4 to 82 years old with median 50 years old; 50.9% (n =53) of all the studied patients were over 50 years old. and 10.5% (n =11) of the studied patients were under 18 years old.

Table 2 Medical history among studied patients (n = 104)

		No	%
	Diabetes	29	27.9%
	Hypertension	18	17.3%
	Travel history to endemic area	10	9.6%
	Urinary tract infection	8	7.7%
	Upper respiratory tract infection	5	4.8%
	Ischemic heart disease	4	3.8%
	HIV	2	1.9%
	Postsurgical intervention	2	1.9%
	Meningitis	2	1.9%
	Benign breast tumor excised	1	1.0%
	Parotitis	1	1.0%
	Polio	1	1.0%
	Right benign brain tumour	1	1.0%
Hospital stay	Mean ±SD	11.77	5.32
	Range	2	22
	Median	11	

The hospital stay duration of the studied patients ranged from 2 to 22, with median 11. From the various comorbidities measured. 27.88% of patients (n=29) were diabetic, 17.3% (n=18) of patients were hypertensive, 3.6% (n=4) of patients had ischemic heart disease, and 1.9% (n=3) of patients had HIV infections.

Table 3 Suspected diagnosis among studied patients (n = 104)

		No	%
Final diagnosis	Encephalitis	47	45.2%
	Meningitis	43	41.3%
	Cerebral malaria	10	9.6%
	Focal brain lesion	4	3.9%

From the final diagnosis, encephalitis was the most common final diagnosis that was found in 47 patients (45.2%), followed by meningitis, which was found in 43 patients (41.3%).

Table 4 Culture results among studied patients or CSF BioFire (n = 104)

		No	%
Culture	No growth	60	57.7%
	Streptococcus pneumonia (S pneumonia)	14	13.5%
	Herps simplex virus (HSV)	10	9.6%
	Positive blood film for malaria	10	9.6%
	Neisseria meningitis (N. meningitidis)	2	1.9%
	Klebsiella pneumoniae (K. pneumoniae)	2	1.9%
	Escherichia coli (E. coli)	2	1.9%
	Staphylococcus aureus (S. aureus)	2	1.9%
	Cryptococcus neoformans (C. neoformans)	2	1.9%

The results were as follow:

57.7% (No=60) of studied patients had undetected etiology. Streptococcus pneumoniae was the most commonly detected, found in 14 patients (13.5%), followed by a positive blood film for malaria, which was found in 10 patients (9.6%), and the same herpes simplex virus was found in 10 patients.

Table 5 Main presenting symptoms & signs among studied patients (n = 104)

		No	%
Disturbed conscious level	Yes	104	100%
Fever	Yes	94	90.4%
	No	10	9.6%
Headache	Yes	65	62.5%
	No	39	37.5%
Convulsion	Yes	32	30.7%
	No	72	69.2%
neck rigidity	Yes	27	26%

	No			77	74%
Vomiting	Yes			19	18.2%
	No			85	81.7%
	Fever	Headache	convulsion	Vomiting	Neck rigidity
C. neoformans	(2)100%	(2)100%	(2)100%	(2)100%	(2)100%
E. coli	(2)100%	(2)100%		(2)100%	
HSV	(8)80%	(6)60%	(2)20%		
K. pneumoniae	(2)100%				
N. meningitidis	(2)100%				(2)100%
S. pneumonia	(14)100%	(12)85.7%	(10)71.4%	(2)14.3%	(8)57.1%
S. aureus	(2)100%				
Cerebral malaria	100%(10)	70%(7)	30%(3)	10%(1)	%(0)
Undetected	(52)86.7%	(35)65%	(15)25%	(12)20%	(15)25%
X2	103.99	56.027	180.211	126.805	144.595
P value	0.001	0.001	0.001	0.001	0.001

Disturbed conscious level was the main symptom that was found in 104 patients (100%), followed by fever that was found in 94 patients (90.4%), followed by headache that was found in 65 patients (62.5%), followed by convulsion that was found in 32 patients (30.7%). Two (100%) patients with cryptococcal meningitis had fever, headache, convulsion, vomiting, and neck rigidity. Patients with HSV infections: 14 patients (100%) had fever, 12 patients (85.7%) had headache, 10 patients (71.3%) had convulsion, 2 patients (14.3%) had vomiting, and 8 patients (57.4%) had neck rigidity.

Table 6 Glasgow Coma Scale among studied patients (n = 104)

GCS	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**
	10.69	2.19	5	14	11
		No		%	
	Above 11	49		47.12%	
	Below 11	55		52.88%	
	Below 11			11 and over 11	
Meningitis	18			25	
	41.8%			58.2%	
Encephalitis	15			32	
	40%			60%	
Focal brain lesion	2			2	
	50%			50%	
Cerebral malaria	6			4	
	60%			40%	
	Below 11			11 & over 11	

C. neoformans	(2)100%	
E. coli		(2)100%
HSV	(3)30%	(7)70%
K. pneumoniae	(1)50%	(10)50%
N. meningitidis		(2)100%
S. pneumonia	(5)35.6%	(9)64.4%
S. aureus		(2)100%
Undetected	(24)40%	(36)60%
X2	103.99	56.027
P value	0.001	0.001

The median GCS of the studied patients ranged from 5 to 14, with a mean of 10.69 and a median was 11. 52.88% (No=55) of studied patients were below 11. 2 patients (100%) with cryptococcal infection showed GSC below 11; 3 (30%) patients with HSV infection showed GSC below 11; 1 (50%) patient with Klebsiella infection showed GSC below 11; 10 (50%) patients with malaria infection showed GSC below 11; 5 (35.6%) patients with streptococcal infection showed GSC below 11; and 24 (40%) patients with unknown infection showed GSC below 11.

Table 7 The results of laboratory investigations among studied patients (n = 104)

White blood cells (WBC)/ Complete blood count (CBC)	**Mean**	**SD**	**Minimum**	**Maximum**	**Median**
	14.15	9.08	3	56	12
		No		%	
	Above 12	45		43.26%	
	Below 12	59		56.74%	
White blood cells/CSF	Mean	SD	Minimum	Maximum	Median
	815.74	1685.28	4	10000	135
		No		%	
	Above 135	51		49.03%	
	Below 135	53		50.97%	
		No		%	
COVID swab	No	104		100.0%	
	WBC in CBC			WBC in CSF	
	Below 12	12 and over 12		Below 135	Above 135
Meningitis	17	26		10	34
	39.5%	60.5%		23.2%	67.85
Encephalitis	26	21		31	16
	55.3%	44.7%		70%	30%
Focal brain lesion		4			4
		100%			100%
Cerebral malaria	7	3		10	0

	70%	30%	100%	
C. neoformans	0	2	0	2
	0	100%	0	100%
E. coli	2	0	0	2
	100%	0	0	100%
HSV	8	2	8	2
	80%	20%	80%	20%
N. meningitidis	0	2	0	2
	0	100%	0	100%
K. pneumoniae	0	2	0	2
	0	100%	0	100%
S. pneumoniae	2	12	0	14
	14.3%	85.7%	0	100%
S. aureus	2	0	2	0
	100%	0	100%	0
Undetected aetiology	29	31	32	28
	48.33	51.66%	53.33%	46.66%
Chi Square test	X^2			
	35.693		12.968	
	P value			
	0.003		0.113	

WBC/CBC of the studied patients ranged from 3 to 56, with a mean of 14.15 and a median was 12. 43.26% (No=45) of studied patients were above 12. WBC/CSF of the studied patients ranged from 4 to 10000, and 49.03% (N = 51) were over 135. 67.7% of patients with meningitis had white blood cells in CSF above 135, while in encephalitis 70% were below 135.

2 (100%) patients with cryptococcal infections had elevated WBC above 12000 in CBC, 2 (20%) patients with HSV had elevated WBC above 12000 in CBC, 12 (85.7%) patients with streptococcal infections had elevated WBC above 12000 in CBC, and 31 (51.6%) patients with unknown infections had elevated WBC above 12000 in CBC.

2 (20%) patients with HSV had elevated WBC above 135 in CSF, 14 (100%) patients with streptococcal infections had elevated WBC above 135 in CSF, and 28 (46.66%) patients with unknown infections had elevated WBC above 135 in CSF.

Table 8 CT lung and brain among studied patients (n = 104)

CT lung	**No**	**%**
Free	83	79.8%
Consolidation	11	10.5%
Consolidation+ ground glass opacity	6	5.7%
Ground glass opacity	4	3.9%
CT/ MRI brain among studied patients	**No**	**%**

Free	51	49.03%
Oedema and inflammation	25	24.03%
Age related changes	19	17.3%
Focal cerebral lesion	5	4.8%
Herpetic encephalitis	2	1.90%
Old infarction	2	1.90%

From the CT lung examined, consolidation was the most common finding that was found in 11 patients (10.5%). From the CT/MRI brain, free brain CT was the most common finding, followed by 24.03% (N = 25) of patients having cerebral edema and inflammatory changes. Then age-related changes were found in 17.3% of patients, and lastly, focal cerebral lesions were found in 5 patients (4.8%).

Table 9 Treatment provided to the studied patients (n = 104)

Drug provided to the studied patients		**No**	**%**
Treatment	Ceftriaxone + vancomycin+ acyclovir	60	57.6%
	Ceftriaxone + linezolid + acyclovir	10	9.6%
	Quinine	6	5.8%
	Ceftriaxone + acyclovir	6	5.8%
	Artemisinin combination therapy	4	3.8%
	Meropenem + vancomycin + acyclovir	4	3.9%
	Ceftriaxone + linezolid+ meropenem	2	1.9%
	Ceftriaxone + vancomycin + acyclovir + remdesivir	2	1.9%
	Meropenem + vancomycin + acyclovir + remdesivir	2	1.9%
	Meropenem + linezolid + acyclovir	2	1.9%
	Ampicillin/sulbactam +amikacin	2	1.9%
	Vancomycin + cefotaxime + remdesivir + acyclovir	2	1.9%
	Linezolid + meropenem + levofloxacin+ acyclovir + remdesivir	2	1.9%

Regarding the drug provided to the studied patients, ceftriaxone + vancomycin + acyclovir was the most common type of treatment used, which was found in 60 patients (57.6%), followed by ceftriaxone + linezolid + acyclovir, which was found in 10 patients (9.6%). Quinine combination therapy was found in 6 patients (5.8%). Artemisinin combination therapy was found in 4 patients (3.9%).

Table 10 Outcome and complication among studied patients (n = 104)

Outcome	**No**	**%**
Cure	84	80.7%
Cure + behaviour changes	8	7.7%
Death	7	5.7%
Referral for need of surgical intervention	3	2.9%
cure+ loss of memory	2	1.9%

Reversible renal impairment	5	4.8%
Central retinal artery occlusion	1	1.0%
Reversible diminished hearing	1	1.0%
Rupture spleen	1	1.0%

Complete cure was the most common outcome that was found in 84 patients (80.7%), followed by cure + behavior changes, which was found in 8 patients (7.7%). Death was reported in 6 patients (6.7%). From the complication measured, reversible renal impairment was the most common complication that was found in 5 patients (4.8%).

Table 11 Demographic characteristics according to microbiological diagnosis

	Sex		**Residence**		**Age group**		
	Male	Female	Urban	rural	0-18	18-50	Over 50
C. neoformans	100%		100%			100%	
E. coli	100%		100%				100%
HSV	100%		20%	80%		80%	20%
K. pneumoniae	100%			100%			100%
N. meningitidis	100%		100%			100%	
positive blood film for malaria	100%		40%	60%		100%	
S. pneumonia	71.4%	28.6%	42.9%	57.1%	28.2%	14.1%	57.3%
S. aureus		100%	100%				100%
Unknown	60%	40%	75%	25%	10%	33%	57%
P value	0.001		0.002		0.113		

Cryptococcus neoformans patients were 2 patients, male, urban, and from 18 to 50 years old. HSV patients were 10 males, 20% urban, 80% from the age group 18-50 years, and 20% of patients were over 50. Streptococcal pneumonia patients were 14, 10 males (71%), 6 urban (43%), and 8 patients (57%) from the age group over 50.

Patients with unknown causes: 60% of them were male (No=36), 75% were urban (45), and 57% were above 50.

Table 12 Comparison between microbiological diagnosis and final diagnosis

	Encephalitis	**Meningitis**	**Focal brain lesion**	**Meningitis +pneumonia**	**Encephalitis + pneumonia**
C. neoformans		100% (2)			
E. coli	100% (2)				
HSV	40% (4)	40% (4)			20% (2)
K. pneumoniae					100% (2)
N. meningitidis		100% (2)			
S. pneumonia		85.7% (12)		14.3% (2)	
S. aureus		100% (2)			
Unknown	58.3% (35)	28.3% (17)	6.6% (4)	3.3% (2)	3.3% (2)

P value	0.0001

Cryptococcus neoformans patients were diagnosed clinically as having meningitis. E. coli patients were diagnosed clinically as encephalitis. HSV patients were 10 patients; 6 (40%) were diagnosed clinically as meningitis, and 6 (60%) were diagnosed clinically as encephalitis. Neisseria meningitis patients were diagnosed clinically as meningitis. Streptococcal pneumonia patients: 14 (100%) patients were diagnosed clinically as having meningitis. Patients of unknown etiology: 37 of them (61.6%) were diagnosed clinically as encephalitis, and 19 (31.6%) patients were diagnosed clinically as meningitis.

Table 13 Radiological investigation with clinical diagnosis

	Ct chest			**Ct brain**				
	Consolidation	**GGO**	**GGO+ consolidation**	**Oedema**	**Age related**	**Herpetic encephalitis**	**Infarction**	**FBL**
Meningitis	6	2	2	14	12	0	2	1
	13.9%	4.3%	4.3%	32.5%	27.9%		4.3%	2.3%
Encephalitis	6	0	4	8	8	2	0	0
	12.8%		8.4%	16.8%	16.8%	4.2%		
Focal brain lesion		2						4
		50%						100%
Cerebral malaria	1			3				
	10%			30%				

Patients with meningitis, 32.5% of them, had cerebral edema, while 16.8% of patients with encephalitis had cerebral edema.

Table 14 Treatment according to microbiological diagnosis

	C. neoformans		**E. coli**	**HSV**		**K. pneumoniae**	**N. meningitidis**		**S. pneumonia**		**S. aureus**		U	
Ceftriaxone + vancomycin + acyclovir	1	50%		8	80%		2	100%	6	42.90%			45	75%
Ceftriaxone + linezolid + acyclovir	1	50%							2	14.3%	2	100%	3	5%
Ceftriaxone + acyclovir													2	3.3%
Meropenem + linezolid + acyclovir													2	3.30%
Ceftriaxone + vancomycin + acyclovir + remdesivir													2	3.3%
Ceftriaxone + acyclovir													6	10%

Ceftriaxone + linezolid + meropenem									2	14.3%		
Linezolid + meropenem + levofloxacin + acyclovir + remdesivir				2	20%							
Meropenem + vancomycin + acyclovir									4	28.60%		
Unictam + amikacin			2	100%								
Vancomycin + claforan + remdesivir + acyclovir						2	100%					

It showed that 8 patients (80%) with HSV infections were treated with ceftriaxone + vancomycin + acyclovir, 2 patients (50%) with HSV infections were treated with linezolid + meropenem + levofloxacin + acyclovir + remdesivir, 2 patients (100%) with Klebsiella infections were treated with vancomycin + Claforan + remdesivir + acyclovir.

It showed that 6 patients (42.3%) with streptococcal infections were treated with ceftriaxone + vancomycin + acyclovir, 2 patients (14.1%) with streptococcal infections were treated with ceftriaxone + linezolid + acyclovir, 2 patients (14.1%) with streptococcal infections were treated with ceftriaxone + linezolid + meropenem, and 4 patients (28.2%) with streptococcal infections were treated with meropenem + vancomycin + acyclovir.

It showed that 45 patients (75%) with unknown infections were treated with ceftriaxone + vancomycin + acyclovir, 3 patients (5%) with unknown infections were treated with ceftriaxone + linezolid + acyclovir, 2 patients (75%) with unknown infections were treated with ceftriaxone + acyclovir, 2 patients (75%) with unknown infections were treated with meropenem + linezolid + acyclovir, 2 patients (75%) with unknown infections were treated with ceftriaxone + vancomycin + acyclovir + remdesivir, and 6 patients (75%) with unknown infections were treated with ceftriaxone + acyclovir.

Table 15 Outcome according to clinical diagnosis

			Encephalitis			**meningitis**		**Cerebral malaria**		**Focal brain lesion**		
Cure			95.7%			90.4%		90%		50%		
Death			4.3%			9.6%		10%				
Referral										50%		
	C. neoformans	E. coli	HSV		K. pneumoniae	N. meningitidis	Cerebral malaria	S. pneumonia	S. aureus	U	X2	P
Cure		100%(2)	100% (10)			100%(2)	80% (8)	85.7% (12)	100%(2)	80%(48)	114.135	0.001
cure+ behaviour changes				100%(2)						6%(10)		

Cure+ loss of memory							14.3%(2)				
Cure+ rupture spleen						10%(1)					
Cure + referral to hepatology hospital									1.7%(1)		
Death	100% (2)					10% (1)			5% (3)		
Referral									3.3 %(2)		

It showed that death had occurred in 5 patients and was caused by 2 cryptococcal infections (100%), 1 cerebral malaria (10%), and 3 unknown infections (5%).

It showed that cures with behavior changes occurred in 8 patients and were caused by 2 Klebsiella cases (100%) and 6 cases of unknown causes (10%).

4. Discussion

Our present study included all patients admitted to Almaza Fever Military Hospital with CNS infections in the period from July 2021 to October 2023. In this study, patients in all age groups were included; the most affected age group was over 50 years, representing 50.3%, followed by youth (18 - 50 years), representing 38.46% of patients included in this study.

There is dramatic change in the epidemiology of CNS infections that leads to incomplete understanding of its pathogenesis, which interferes with the initiation of effective empirical antimicrobial treatment. There is a growing need for more research to uncover these changes. The aim of the study is to assess the most common causes of central nervous system infections and to find out the factors affecting clinical management and treatment outcome.

Unrecognized demographic, environmental, or socioeconomic factors could also contribute to the change in the epidemiology of central nervous system infections. Changes in the use or availability of antimicrobial agents could also affect the ability to recover organisms from the CSF, thus having an apparent drop in the disease incidence. Although antimicrobial agents can be purchased in Egypt without a prescription, leading to patients frequently receiving therapy before being evaluated, this practice is unchanged.

This descriptive study analyzed 104 patients admitted to Almaza Fever Military Hospital with central nervous system (CNS) infections, focusing on demographic characteristics, clinical presentation, microbiological etiology, treatment outcomes, and complications. The findings provide valuable insights into the epidemiology and management of CNS infections in a tertiary care setting, particularly in a military hospital context. There are a lot of tables showing things like gender distribution, age ranges, common symptoms, types of infections, treatment regimens, and outcomes like cure rates and complications.

4.1. Demographics

Demographic data in our study has a higher male predominance (71.2% male) compared to Sabry's study [4] (58.9%). The age distribution is also different: our study had a median age of 50, with 50.9% over 50 years old, while Sabry's study had more children and adults (35.7% adults 25-64 years). This could indicate different population focuses or disease manifestations in different age groups. This reflects an older population, possibly due to the inclusion of encephalitis cases, which are more common in adults. Sabry's focus on pediatric and adult bacterial meningitis aligns with global trends.

Male predominance (71.2%) agrees with many other studies conducted in Egypt documenting that males were more affected than females; for example, a study in Menoufia Governorate in Egypt [5] stated that the male-to-female ratio in all suspicious cases was approximately 1.27:1. But the male-to-female ratio in positive cases for bacterial meningitis

was 1.75:1 and agrees with a study done in Nepal in 2022 where the ratio for central nervous infections in males was 58.9% [6].

In this study, CNS infections were more common in urban areas (62.5%). This was attributed to the location of Almaza Fever Military Hospital in Cairo, and it receives cases from all over the Republic for all members and families of the armed forces, and it is the only qualified hospital within the armed forces to receive these types of cases. Most of the studied patients were living in urban areas (59.7%); this also agrees with a study conducted by Sabry [4].

The median age of the studied patients was 50, not comparable with a study conducted in Australia [7], which stated that the median age of patients was 26 and the infant patients were 26.5%, also not comparable with a study conducted in India [8], which stated that the median age of studied patients was 35.

4.2. Clinical Presentation

Clinical presentations in our study reported disturbed consciousness in 100% of patients, fever in 90.4%, and headache in 62.5%. Sabry's study (2019) [4] mentions convulsions in 77.6% and disturbed consciousness in 87.7%, but fever in only 57.6%. The difference in fever prevalence might be due to different disease etiologies (more bacterial in the Sabry study vs. mixed in ours) or different diagnostic criteria. The universal disturbed consciousness in our study likely reflects encephalitis's neurological impact. Higher convulsion rates in Sabry's study had correlated with bacterial meningitis severity. Fever prevalence differences might stem from diagnostic timing or etiology (viral vs. bacterial).

Universal symptom: disturbed consciousness (100%), followed by fever (90.4%) and headache (62.5%). Neck rigidity (26%) was less frequent, contrasting with classical meningitis presentations [9].

Severity indicators: 52.88% of patients had a Glasgow Coma Scale (GCS) <11, correlating with poorer outcomes [10].

Diabetes (27.9%) and hypertension (17.3%) were the most common comorbidities, aligning with global studies linking metabolic disorders to increased susceptibility to infections [11].

4.3. Diagnosis Distribution

The most common diagnosis in our study was encephalitis (45.2%), followed by meningitis (41.3%) and cerebral malaria (9.6%), which was not comparable with the Nepal study [6], which had stated that meningoencephalitis (46.3%) was followed by meningitis (36.8%) and encephalitis (16.8%).

4.4. Microbiological Etiology

Causative organisms were another key area. Our study found undetected etiology in 57.7% of cases, with Streptococcus pneumoniae (13.5%), HSV (9.6%), and malaria (9.6%) as identified causes. Sabry's study [6] reports S. pneumoniae as the main bacterial cause (42%), followed by N. meningitidis (15%) and TB (10%). Viral causes like HSV and enterovirus accounted for 22%. The high rate of undetected etiology in our study might be due to limited diagnostic tools compared to Sabry's use of PCR. The high undetected rate likely stems from reliance on culture-based diagnostics, whereas Sabry used PCR for pathogen identification. Malaria's prominence in our study suggested travel history with no regional endemicity, while Sabry's focus on bacterial pathogens aligns with global meningitis epidemiology.

Undetected etiology (57.7%): dominated, possibly due to prior antibiotic use or limitations in diagnostic tools. This was very high and not comparable with the India study [8], which stated also that 9% were of undetected etiology and comparable with a study conducted in Laos [12], which had 42.3% undiagnosed. The high rate of undetected pathogens aligns with challenges in low-resource settings [13], emphasizing the need for advanced diagnostics like multiplex PCR or metagenomics.

Streptococcus pneumoniae (13.5%) and herpes simplex virus (9.6%) were most prevalent, consistent with global trends [14]. Cryptococcal infections (1.9%) were rare but associated with HIV comorbidity (100%), underscoring immunodeficiency as a critical risk factor.

Bacterial pathogens dominated: Streptococcus pneumoniae (13.5%) was the main known cause in our study, which is not comparable with a study in Nepal that stated that the main cause of CNS infections was tubercular CNS infection due to Nepal's TB-endemic context [6], also not comparable with an India study by [8] that stated also that the main cause was tuberculosis.

Viral pathogens were 9.6% and fungal pathogens were 1.9% in our study, which was not comparable with a study conducted in Australia [7], which stated that viral pathogens were 41.2%, bacterial 24.1%, and fungal 4.8%.

Undetected etiologies in our study highlight the need for expanded diagnostics (e.g., multiplex PCR) to identify viral/atypical pathogens.

4.5. Treatment and Outcomes:

Our study used ceftriaxone + vancomycin + acyclovir in 57.6% of cases, likely covering both bacterial and viral etiologies. Sabry's study used various ceftriaxone-based regimens, with corticosteroids like dexamethasone reducing complications. Outcomes in our study show an 80.7% cure rate and 5.7% mortality, while Sabry's study [4] reports higher mortality (28.7% for septic meningitis), possibly due to more severe bacterial cases.

The empirical use of antivirals (acyclovir) and antimalarials reflected diverse etiologies (encephalitis, malaria) in our study, while Sabry stated corticosteroid use underscores bacterial meningitis management guidelines.

Lower mortality in our study might indicate milder cases or effective empirical treatment.

Empirical therapy: Ceftriaxone + vancomycin + acyclovir (57.6%) was the most used regimen, reflecting adherence to guidelines for bacterial and viral coverage, which was comparable with a study in Nepal that stated that ceftriaxone + vancomycin and anti-tuberculous treatment in all TB cases and another study conducted in Laos [12] that suggested ceftriaxone and doxycycline for broader coverage, possibly due to increased rickettsial infection incidence.

High complete cure rate (80.7%), but mortality (5.7%) occurred predominantly in cryptococcal (100% fatality) and cerebral malaria (10%) cases, highlighting the need for early pathogen-specific interventions.

4.6. Mortality and Comorbidities:

The mortality rate (5.7%) was lower than in similar studies (10–15% van de Beek [9] & 27% India study [8]), possibly due to prompt ICU care and empirical treatment efficacy.

The mortality rate (5.7%) was comparable with a study conducted in Australia [7], which stated that the mortality rate was 4.4% due to adherence to guidelines.

Mortality rate: 5.7%, linked to cryptococcal infections (100% mortality), which highlighted challenges in managing fungal CNS infections and cerebral malaria.

Mortality rates in a study conducted in Laos [12] reported 26.3%, and a study conducted in India [8] reported 21%, which was not comparable with our study's 5.7%.

The lower mortality in our study could be due to better treatment protocols, earlier diagnosis, early empirical treatment (e.g., ceftriaxone + vancomycin in 57.6% of cases), exclusion of severe comorbidities (e.g., only 1.9% HIV co-infection vs. 24.8% in Laos [12]), or differences in pathogen virulence. However, our study had a smaller sample size, which might affect reliability.

All studies emphasize early intervention to reduce complications.

5. Conclusion

This descriptive study provides a comprehensive overview of CNS infections managed at a tertiary military hospital in Egypt. The findings reveal a distinct epidemiological profile characterized by an older patient population and a high burden of encephalitis, contrasting with studies from other regions where bacterial meningitis dominates younger cohorts. The high rate of undetected etiologies (57.7%) highlights a significant diagnostic challenge, likely attributable to limitations in available microbiological testing and possibly prior antibiotic use.

Despite this diagnostic gap, the empirical treatment strategy primarily employing a combination of ceftriaxone, vancomycin, and acyclovir was associated with a high cure rate (80.7%) and a relatively low overall mortality (5.7%). However, the 100% mortality observed in cryptococcal meningitis cases signals an area for urgent improvement in the early recognition and management of fungal pathogens.

The study underscores several key points for clinical practice and future research:

- Enhanced Diagnostics: There is a pressing need to implement advanced diagnostic techniques, such as multiplex PCR and CSF antigen testing, to reduce the number of cases with unknown etiology and allow for pathogen-directed therapy.
- Vigilance for Specific Pathogens: Clinicians should maintain a high index of suspicion for herpes simplex virus encephalitis and cryptococcal meningitis in immunocompromised patients, ensuring timely and appropriate treatment.
- Age-Specific Considerations: The predominance of older adults with comorbidities like diabetes suggests that management protocols should be tailored to address the complexities of this demographic.

In conclusion, while empirical broad-spectrum therapy appears effective in this setting, optimizing outcomes for CNS infections in Egypt hinges on closing the diagnostic gap. Future efforts should focus on strengthening laboratory capacity and conducting prospective studies to better understand the evolving epidemiology and optimal management of these serious infections.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare no conflict of interest of any sort

Statement of ethical approval

Ethical approval was obtained from the Ethical Committee of medical military academy.

Statement of informed consent

Consent to extract data from hospital records obtained from the Almaza Military Fever Hospital administration. This data will not be used for any purpose other than this research study.

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