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Abstract: Background/Objectives: Diagnosis of encephalitis is a challenging problem due to the heterogeneity of clinical presentations and the myriad of aetiology. The objective was to determine the aetiology, clinical features, laboratory parameters, radiological findings and in-hospital outcome of acute encephalitis syndrome (AES) cases in Myanmar. **Methods:** A prospective analytic study was conducted at Neuromedical Ward of Yangon General Hospital during March to August 2023. 81 AES cases were enrolled and cerebrospinal fluids (CSF) samples were collected. Qiastat ME Panelwas used to detect viral, bacterial and fungal pathogens. **Results**: 17 out of 81 (21%) cases were non-encephalitis with alternative definite diagnosis. Among the remaining 64 encephalitis cases, the exact infectious and immune aetiologies were identified in 31/64 (48.4%); 26/31 cases (83.9%) were infectious causes and 5/31 patients (16.1%) were immune encephalitis. Among the infection causes, six Herpes Simplex Virus-1, one bacteriologically confirmed and seven probable *Mycobacterium tuberculosis*, three *Haemophilus influenzae,* two *Streptococcus pneumoniae*, one *Streptococcus pyogenes,* one Varicella-Zoster Virus (Ramsay Hunt Syndrome with meningoencephalitis), two *Cryptococcus neoformans infected patients* and rare causes such as *Listeria monocytogenes, Burkholdelria cepacia, Sphingomonas paucimobilis* and *Aspergillus* were identified. One case was dual infection with *Haemophilus influenzae and Cryptococcus neformans*. Abnormal protein levels and CSF pleocytosis were significantly higher among bacterial causes (P<0.05). 6.45% (2/31) of encephalitis patients with identified causes and 12.12% (4/33) of those without organism identified had bad outcome. **Conclusions:** Herpes encephalitis and tuberculous meningoencepalitis were the commonest. This study highlighted that molecular testing with multidisciplinary approach is required to ensure the right treatment on time.

Keywords: acute encephalitis syndrome; infectious cause; autoimmune encephalitis; adult; Myanmar; 2023

1. Introduction

Encephalitis is a complex clinical problem due to myriad of aetiologies and pathogenesis with high mortality rate. It is often complicated by prolonged and permanent neurologic deficits. Not only infectious but also immune mediated causes can present with encephalitis. The incidence of the disease can vary depending on the economic status of the country but it is generally between 3.5 and 7.4 per 100,000 patient per year [1]. The incidence of the disease in the population is not high but the

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morbidity and mortality rate is high, Thus, it is still a public health problem worldwide. The mortality rate of the encephalitis cases ranges from 3.8% to 7.4% [2].

The aetiologies of encephalitis are mainly classified into two groups such as: infectious and immune mediated causes. Although infectious causes are the commonest causes, the reported number of autoimmune encephalitis cases were increased in both adults and pediatric patients nowadays due to the availability of the diagnostic facilities and treatment options [3]. There are various types of autoimmune encephalitis and for young adults, particularly women, anti-N-methyl-D-aspartate receptor antibody (anti-NMDAR Ab) encephalitis was common and in late adulthood, anti–leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis, are the most prevalent autoimmune encephalitis [4] Diagnosis is essential for the autoimmune encephalitis cases for the prompt start of effective and correct treatment [5].

Among the infectious group, viral causes are the commonest and both Deoxyribonucleic Acid (DNA) and Ribonucleic acid (RNA) viruses can present with encephalitis[6]. Herpes virus group, Varicella-Zoster Virus (VZV), Japanese Encephalitis (JE), Zika (ZKV), Dengue (DENV), Chikungunya (CHIKV), Influenza, Adeno and Human Immunodeficiency (HIV) viruses are common viruses that can cause encephalitis. Some bacterial infections, *Haemophilus influenzae, Escherichia coli, Streptococcus pneumoniae, Streptococcus pyogenes, Neisseria meningitidis*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Listeria monocytogenes*, *Leptospira* and *Salmonella typhi,* can also present as encephalitis. *Cryptococcus neoformans* and *Aspergillus* should also be considered in the aetiology of encephalitis. The common cause of microorganisms can vary with the seasons, geographical regions and immunity of the patients.

Even in developed countries, diagnostic and management guidelines are based on the prevalence of the diseases causing encephalitis. Genetic backgrounds, immunization status, geographical location are the essential and crucial facts to consider for making diagnostic and management guidelines such as adding of ampicillin in the empiric antibiotic therapy for the high prevalence areas of *Listeria monocytogenes*, arboviral screening tests at the tropical countries. To make the priority lists of laboratory tests, surveillance was conducted to identify the aetiology, clinical profiles, laboratory investigations and outcomes of the encephalitis patients admitted at Neuro-medical Ward, Yangon General Hospital during 2023 in Myanmar.

2. Materials and Methods

A prospective analytic study was conducted at a tertiary care center, Neuro-medical Ward, Yangon General Hospital (YGH) during March to August, 2023.

2.1. Patients' Recruitment

Acute encephalitis syndrome (AES) is defined as a patient with acute onset of fever (>38°C) in the preceding 7 days with one or more of the following clinical features: altered mental status or seizure [7]. All patients presenting with AES admitted to the Neuro-medical ward during the study period were recruited.

2.2. Study Procedures

Demographic profiles, clinical presentations, outcome of the patients at discharge from the hospital, immunocompromised or not, electroencephalogram (EEG), neuroimaging (Computed Tomography (CT) / Magnetic Resonance Imaging (MRI)) findings were recorded. CSF samples were analyzed for molecular tests, and biochemical and microscopic investigations. If the results were negative for infectious diseases, anti-NMDAR Ab were checked.

2.3. Laboratory Tests

Total eight bacterial pathogens (Neisseria meningitis, Haemophilus inflenzae, Streptococcus pneumoniae, Streptococcus agalactiae, Sterptococcu pyogens, Listeria moncytogenes, Escherichia coli and Mycoplasma pneumoniae), six viral pathogens (Herpes simplex virus 1 (HSV-1), Herpes

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Simplex Virus (HSV-2), Human Herpes Virus 6 (HHV-6), Entero virus Human Parechovirus and Varicella Zoster Virus (VZV) and one fungal pathogen (Cryptococcus neoformans) were checked on CSF specimens by Real-time PCR based QIAstat-Dx ME Panel (Qiagen, Germany) using QIAstat-Dx Analyzer 1.0.To identify four arboviruses (Japanese Encephalitis, West Nile, Dengue and Chikungunya Viruses), viral RNA was extracted from CSF sample using Qiagen Mini Viral RNA extraction kits (Qiagen, Germany) according to the manufacturer's instruction. Conventional one step Reverse Transcription RT-PCR (Takara one step RT-PCR, Takara, Japan) was done to detect JEV, DENV, ZIKV and CHIKV genome using specific primers. All the experiments were done according to the procedures described in previous studies [8–10]. The molecular tests were done at Pathology Research Division, Department of Medical Research, Yangon.

In this study, laboratory confirmed, probable and possible diseases were defined according to the criteria for the diagnosis of acute encephalitis by an infectious agent [6]. For the diagnosis of autoimmune encephalitis, cell based indirect immunofluorescence (EUROIMMUNE, Lubeck) assay for anti-NMDAR Ab was measured from either serum or CSF samples[11]. Statistical analysis

Data entry was done using Microsoft excel and analysis was done using STATA Software, Version 15 (STATA Corp., College Station, TX, USA). Descriptive statistics for demographic features, clinical findings, CSF analysis and radiological features were presented as frequencies and percentages. The classification of causes of acute encephalitis were presented using proportions and 95% confidence intervals. Differences in demographic profiles, clinical presentations, laboratory parameters and neuroimaging results were compared by classification of causes of acute encephalitis using chi-square test. Univariable analyses were applied to identify the factors associated with survival of patients with encephalitis. A p-value of <0.05 was considered statistically significant.

3. Results

In this study, total 81 AES cases were enrolled, and 40/81 (49.4%) cases were males and 41/81 (50.6%) cases were females. Among 81 cases, 29 patients (35.8%) were less than 35 years old, 32 were (39.5%) were 35-59 years old and 20 cases (20.7%) were more than 60 years old. Of 81 total patients, 17 cases turned out non-encephalitis with a definite alternative diagnosis such as metabolic encephalopathy, septic encephalopathy, cerebral malaria, stroke, epilepsy, brain metastasis.

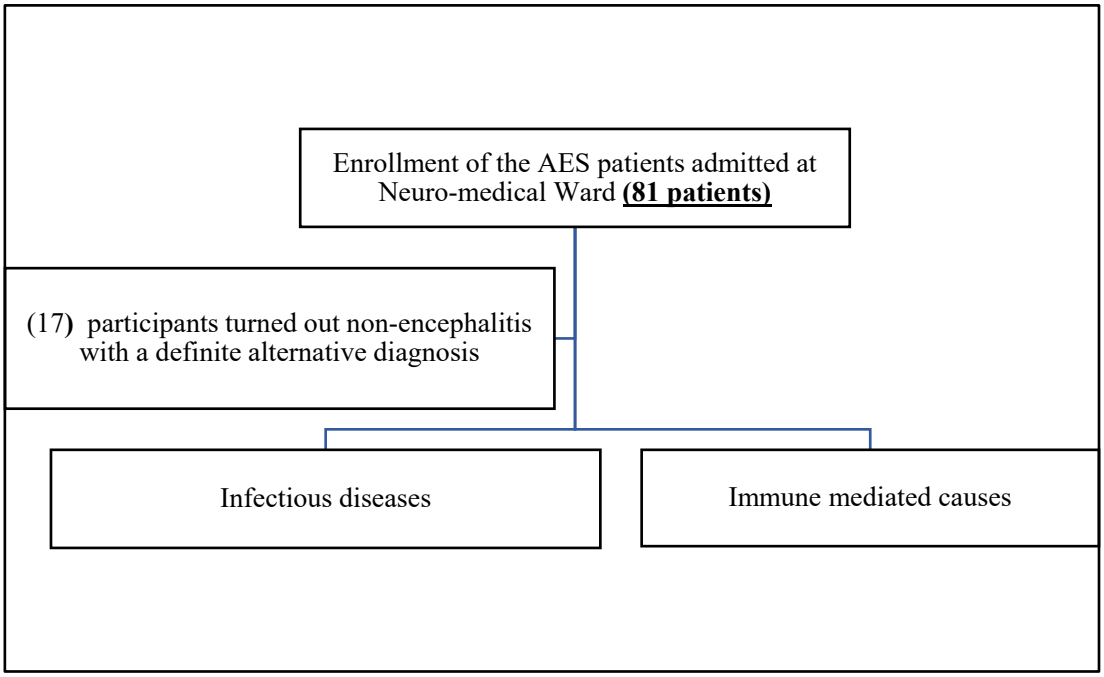

Figure 1. Flow chart of the study.

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Out of the remaining 64 encephalitis cases, viral encephalitis cases constitute 32, pyogenic meningoncephalitis 16, tuberculous meningoencephalitis 8, immune encephalitis 6, fungal 3,. Six patients were expired among 64, and the mortality rate of encephalitis in this study was 9.37%, (95% CI, 3.3, 15.8). Among these 64 encephalitis cases, only 31/64 (48.44%) cases got exact aetiological diagnosis. Of 31 aetiology identified cases, infectious encephalitis accounted for 83.87% (26/31) and immune causes accounted for 16.13% (5/31), of the latter, four were anti-NMDAR ab autoimmune encephalitis and one was systemic lupus erythematosus (SLE) cerebritis. The proportion of aetiology undiagnosed encephalitis cases was 33/64 (51.56%).

The identified bacterial causes were higher than identified viral causes in this study. Herpes simplex encephalitis (HSE) was the commonest cause among laboratory confirmed cases. Regarding tuberculous meningitis, only one bacteriologically confirmed case by nucleic acid amplification test and seven cases were probable tuberculous meningitis cases. A case of VZV infection (Ramsay Hunt syndrome) with meningoencephalitis was detected in this study. The organisms detected in this study were shown in Table 1.

Table 1. Classification and causes of acute encephalitis cases with exact aetiology identified (n=31).

Confirmed/probable cases (n=31, [48.4%, 95% CI – 36.2, 60.8])			
A. Infectious causes (n=26, [83.9%, 95% CI – 65.3, 93.5])			
	Confirmed	**Probable**	**Total (%)**
1. Viral causes (n=7, [22.6%. 95% CI – 10.7, 41.6])			
Herpes simplex Virus-1	6	-	6 (85.7)
Varicella Zoster Virus	1	-	1 (14.3)
2. Bacterial causes including *Mycobacterium tuberculosis* **(n=16, [51.6%, 95% CI – 33.6, 69.2])**			
Haemophilus Influenzae	2	-	2 (12.5)
Streptococcus pneumonia	2	-	2 (12.5)
Streptococcus pyogenes	1	-	1 (6.3)
Listeria monocytogenes	1	-	1 (6.3)
Mycobacterium tuberculosis	1	7	8 (50.0)
Sphingomonas paucimobilis	1	-	1 (6.3)
Burkholderia cepacia	1	-	1 (6.3)
3. Fungal infection (n=2, [6.5%, 95% CI – 1.5, 23.9])			
Cryptococcus neoformans	1	-	1 (50.0)
Aspergillus	1	-	1 (50.0)
4. Dual infection (n=1, [3.2%, 95% CI – 0.4, 21.6])			
H. influenzae and Cryptococcus neoformans	1	-	1 (100)
B. Immune-mediated cause (n=5, [16.1%, 95% CI – 6.5, 34.6])			
1.Anti-NMDAR immuneencephalitis	4	-	4 (75.0)
2. SLE cerebritis	1	-	1 (25.0)
Total	**24**	**7**	**31 (100)**

N= number of cases, 95% CI= 95% Confidence Interval, 95% CI = 95% Confidence Interval. Anti-NMDAR Ab = anti-N methyl-D-Aspartate Receptor Antibody. SLE = Systemic Lupus Erythematosus.

Among the aetiology identified encephalitis, seven cases were immunocompromised patients. Three probable tuberculous meningitis patients were with retroviral infection and one was end stage renal disease (ESRD) due to prolonged diabetes mellitus. In this study, a case of plasmacytoma with post autologous stem cell transplant on immunosuppressant, presented with acute meningoencephalitis and *Listeria monocytogenes* was detected. Interestingly, one dual pathogen

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infected case was immunocompetent. The causes of encephalitis cases among immunocompetent and immunosuppressed patients were shown in Table 2.

Table 2. Identified causes of encephalitis in immunocompetent and immunocompromised patients (n=31).

Aetiology	Immunocompetent	Immunocompromised
Herpes simplex Virus-1	6	-
Varicella-Zoster Virus	1	-
Haemophilus Influenzae	2	-
Streptococcus pneumoniae	1	1
Streptococcus pyogenes	1	-
Listeria monocytogenes	-	1
Mycobacterium tuberculosis	4	4
Sphingomonas paucimobillis	1	-
Burkholderia cepacia	1	-
Cryptococcus neoformans	-	1
Aspergillus	1	-
Haemophilus. influenzae and Cryptococcus neoformans	1	-
Autoimmune encephalitis	4	-
SLE cerebritis	1	
Total	**24**	**7**

SLE = Systemic Lupus Erythematosus.

Demographic profiles, clinical presentations, laboratory parameters and neuroimaging results of aetiologically identified encephalitis cases were compared among bacterial, viral, fungal and autoimmune causes and described in Table 3. Male were more affected than female among bacterial cause and female were more at viral cause ($P < 0.05$). CSF pleocytosis and abnormal CSF protein levels were significantly high at bacterial cause ($P < 0.05$).

Table 3. Demographic features, clinical findings, CSF analysis and radiological features for patients with encephalitis (n=30, dual infection was excluded in this table).

	Total	Viral Cause	Bacterial Cause	Fungal Cause	Immune cause	P value
	n (%)	n (%)	n (%)	n (%)	n (%)	
A. Demographic profiles						
1. Age (n=30)						
<35 years	13 (43.3)	2 (15.4)	6 (46.2)	0 (0)	5 (38.5)	0.088
35-59 years	11 (36.7)	3 (27.3)	6 (54.5)	2 (18.2)	0 (0)	
≥60 years	6 (20.0)	2 (33.3)	4 (66.7)	0 (0)	0 (0)	
2. Sex (n=30)						
Male	15 (50.0)	2 (13.3)	11 (73.3)	2 (13.3)	0 (0)	**0.015**
Female	15 (50.0)	5 (33.3)	5 (33.3)	0 (0)	5 (33.3)	
B. Clinical signs and symptoms						
Headache (n=30)						
Present	17 (56.7)	4 (23.5)	9 (52.9)	2 (11.8)	2 (11.8)	0.553
Absent	13 (43.3)	3 (23.1)	7 (53.8)	0 (0)	3 (23.1)	
Seizure/convulsion (n=29)						
Present	14 (48.3)	3 (21.4)	6 (42.9)	2 (14.3)	3 (21.4)	0.405
Absent	15 (51.7)	4 (26.7)	9 (60.0)	0 (0)	2 (13.3)	
Vomiting (n=30)						
Present	9 (30.0)	2 (22.2)	4 (44.4)	2 (22.2)	1 (11.1)	0.164
Absent	21 (70.0)	5 (23.8)	12 (57.1)	0 (0)	4 (19.1)	
Changes in sensorium (n=30)						
Present	25 (83.3)	4 (16.0)	15 (60.0)	2 (8.0)	4 (16.0)	0.161
Absent	5 (16.7)	3 (60.0)	1 (20.0)	0 (0)	1 (20.0)	

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Sign of meningism (n=27)						
Present	11 (40.7)	2 (18.2)	6 (54.5)	2 (18.2)	1 (9.1)	0.223
Absent	16 (59.3)	5 (31.3)	7 (43.7)	0 (0)	4 (25.0)	
Focal neurological deficit (n=30)						0.362
Present	7 (23.3)	1 (14.3)	5 (71.4)	1 (14.3)	0 (0)	
Absent	23 (76.7)	6 (26.1)	11 (47.8)	1 (4.4)	5 (21.7)	
Constitutional symptoms (n=29)						0.781
Present	15 (51.7)	2 (13.3)	9 (60.0)	1 (6.7)	3 (20.0)	
Absent	14 (48.3)	4 (28.6)	7 (50.0)	1 (7.1)	2 (14.3)	
Comorbidities (n=30)						
Present	16 (53.3)	5 (31.1)	9 (56.3)	1 (6.3)	1 (6.3)	0.359
Absent	14 (46.7)	2 (14.3)	7 (50.0)	1 (7.1)	4 (28.6)	
GCS (n=30)						
≤10	11 (36.7)	3 (27.3)	6 (54.5)	0 (0)	2 (18.2)	0.729
>10	19 (63.3)	4 (21.1)	10 (52.6)	2 (10.5)	3 (15.8)	
C. CSF analysis						
CSF protein (n=28)						
Normal	11 (39.3)	4 (36.4)	2 (18.2)	1 (9.1)	4 (36.4)	**0.043**
Abnormal	17 (60.7)	3 (17.7)	12 (70.6)	1 (5.9)	1 (5.9)	
* CSF protein level (n=28)	61 (5:246)	45 (19.3:72)	69.5 (5:246)	101.3 (37.6:165)	22 (21:68)	0.117
CSF pleocytosis (n=28)						
Normal	12 (42.9)	4 (33.3)	3 (25.0)	0 (0)	5 (41.7)	**0.010**
Abnormal	16 (57.1)	3 (18.7)	11 (68.8)	2 (12.5)	0 (0)	
CSF: Blood Glucose Ratio (n=26)						0.108
Normal (≥0.5)	15 (57.7)	5 (33.3)	6 (40.0)	0 (0)	4 (26.7)	
Abnormal (< 0.5)	11 (42.3)	1 (9.1)	7 (63.6)	2 (18.2)	1 (9.1)	
*CSF glucose level (n=28)	67 (18:136)	80 (61:136)	62 (18:109)	49.39 (32:66.78)	88 (57:100)	0.136
D. Radiological Investigations						
CT/MRI Results (n=30)						
Normal	21 (70.0)	5 (23.8)	13 (61.9)	0 (0)	3 (14.3)	0.118
Abnormal	9 (30.0)	2 (22.2)	3 (33.3)	2 (22.2)	2 (22.2)	

*The data were shown with median (Minimum, maximum). CT= Computed tomography, MRI= Magnetic Resonance Imaging. (P < 0.05) was significant cutoff point.

Among the neuroimaging results of 31 aetiology identified encephalitis cases, five cases (two HSE, one tuberculous, one anti-NMDAR encephalitis and one SLE cerebritis) showed encephalitis, two tuberculous cases showed infection related infarcts, one cryptococcal case showed meningitis one aspergillous case had venous sinus thrombosis and sinusitis, and the rest 22 cases were normal. EEG was done in 71.6% (58/81); normal in 39.7% (23/58), diffuse slowing in 24.1% (14/58), focal slowing in 17.2% (10/58), focal epileptiform discharges 13.8% (8/58), electrographic seizures/status epilepticus in 8.6% (5/58) and periodic lateralized epileptiform discharges (PLEDs) in 3.4% (2/58). Two cases of PLEDs were HSE confirmed cases.

Regarding the clinical outcomes of encephalitis, the mortality rate was 6/64, 9.4% [95%CI: 4.2, 19.7] and 2/31 (6.45%) of patients with identified causes had poor outcome. One was herpes encephalitis who could not afford the cost for the treatment and the another one was plasmacytoma case (post stem cell transplant) with *Listeria* infection. On the other hand, 4/34 (11.8%) of encephalitis without identified aetiology had bad outcome. Regression analysis was done to predict the fatal outcome, demographic factors, clinical presentations and laboratory parameters (Table 4). There was no significant variables for determining the fatal outcomes in this study.

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Table 4. Univariate analysis of variables for predicting survival of patients with encephalitis (n=64).

	Total	Fatal outcome	cOR	95% CI	P value
	n (%)	n (%)			
Age					
<35 years	25 (39.1)	2 (8.0)	Ref.		
35-59 years	26 (40.6)	3 (11.5)	1.50	0.23, 9.83	0.673
≥60 years	13 (20.3)	1 (7.7)	0.96	0.79, 11.67	0.973
Sex					
Male	33 (51.6)	4 (12.1)	2.00	0.34, 11.78	0.444
Female	31 (48.4)	2 (6.4)	Ref.		
Immune status					
Immunocompetent	56 (87.5)	5 (8.9)	Ref.		
Immunocompromised	8 (12.5)	1 (12.5)	1.46	0.15, 14.36	0.747
Seizure/convulsion					
Present	26 (41.3)	4 (15.4)	3.18	0.54, 18.85	0.202
Absent	37 (58.7)	2 (5.4)	Ref.		
Vomiting					
Present	18 (28.1)	1 (5.6)	0.48	0.52, 4.44	0.520
Absent	46 (71.9)	5 (83.3)	Ref.		
Changes in sensorium					
Present	46 (73.0)	6 (100)	-	-	-
Absent	17 (27.0)	0 (0.0)	-	-	-
Sign of meningism					
Present	27 (45.0)	3 (11.1)	1.25	0.23, 6.76	0.796
Absent	33 (55.0)	3 (9.1)	Ref.		
Focal neurological deficit					
Present	12 (18.8)	2 (16.7)	2.40	0.39, 14.95	0.348
Absent	52 (81.2)	4 (7.7)	Ref.		
Constitutional symptoms					
Present	30 (51.7)	3 (10.0)	1.44	0.22, 9.36	0.700
Absent	28 (48.3)	2 (7.1)	Ref.		
Comorbidities					
Present	31 (48.4)	2 (6.4)	0.50	0.08, 2.95	0.444
Absent	33 (51.6)	4 (12.1)	Ref.		
GCS					
≤10	19 (29.7)	3 (15.8)	2.63	0.48, 14.38	0.266
>10	45 (70.3)	3 (6.7)	Ref.		
CSF protein					
Normal	30 (49.2)	4 (13.3)	Ref.		
Abnormal	31 (50.8)	2 (6.4)	0.45	0.08, 2.65	0.376
CSF pleocytosis					
Normal	28 (45.9)	1 (3.6)	Ref.		
Abnormal	33 (54.1)	5 (15.1)	4.82	0.53, 44.00	0.163
CSF: Blood Glucose Ratio					
Normal	37 (63.8)	3 (8.1)	Ref.		
Abnormal	21 (36.2)	3 (14.3)	1.89	0.35, 10.33	0.463
CT/MRI Results					
Normal	43 (70.5)	4 (9.3)	Ref.		
Abnormal	18 (29.5)	2 (11.1)	1.22	0.20, 7.33	0.829

CT= Computed tomography, MRI= Magnetic Resonance Imaging. (P < 0.05) was significant cutoff point.

4. Discussion

Central Nervous System (CNS) infection is the second commonest among Neuro-medical ward inpatients at YGH, and morbidity and mortality are also high for these patients [12]. In this study, the mortality rate was 9.38% (6 out of 64 encephalitis cases) and it was still high mortality. If the exact aetiology is known, early diagnosis and effective treatment can be given such as anti-viral drugs for

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herpes virus, antibiotics for bacterial causes, antifungals for fungal causes. Subsequently, morbidity and mortality of the disease can be reduced. And it also avoids unnecessary antimicrobials [13]. Unlike other infections, CNS infections need parenteral and prolonged antivirals, antibiotics and antifungals (at least 10-14 days) [13]. By knowing the exact organisms, use of antimicrobials can be organism-directed therapy and this reduces cost significantly, avoids use of unnecessary expensive antimicrobials, posing lesser risk of adverse effects.

Since HSE is the commonest cause identified as in literature, in places where there is no testing facilities, empirical acyclovir should be given. However, acyclovir nephropathy can occur up to 48% [14]. In this study, HSE was also the commonest cause. A case of HSE actually presented with stroke like presentation (sudden onset left hemiparesis with extreme right gaze deviation) with fever started only on day 2, for which the diagnosis at first point was stroke. CT (Head) was normal. MRI (brain) was also reported as right temporal infarct. However, because of confusion and EEG showing PLEDs and electrographic seizures, CSF study was proceeded. At molecular test, HSV-1 was detected, completely changing the line of management saving doctors and patient from missing appropriate treatment of HSE. HSE is curable but if untreated, it has grave consequences. According to literature, empiric acyclovir therapy should be started at presentation and the dose can be increased for VZV encephalitis cases. In this study, a case with typical features of Ramsay Hunt syndrome (right lower motor neuron facial palsy with right ear ache with redness in right ear) was recruited because of subtle right sixth cranial neuropathy with mild sensorial change. CSF VZV PCR turned out positive, indicating CNS extension, which has led us to giving parenteral acyclovir instead of per oral acyclovir for just Ramsay Hurt syndrome[15]. The nucleic acid amplification testing from CSF specimens has greatly increased the ability to diagnose infections of the CNS, especially viral infections caused by the herpesviruses [16]. Thus, it is essential to establish the HSV PCR testing or ME panel testing in public sector laboratories.

Tubercular meningitis (TBM) is one of the predominant causes of acute febrile encephalopathy in developing countries including Myanmar [17]. In this study, one lab confirmed cases and seven probable cases of TB meningoencephalitis were included, and TB was one of the commonest causes of encephalitis in this study. Based on the fourth national tuberculosis survey in 2017-2018, the estimated adult pulmonary TB cases was 468/100,000 populations [18]. Thus, TB should be considered at the first differential diagnosis of encephalitis and meningitis cases. Among our 8 tuberculous meningoencephalitis patients, 50% were immunocompromised but all 8 patients had good outcome. This might be because of our AES criteria which has recruited only early cases of CNS tuberculosis patients, and early diagnosis and immediate treatment improves outcome of TBM [19].

Although a small sample size in this study, *Sphingomonas paucimobillis* meningitis, *Listeria monocytogenes* and *Burkholderia cepacia* and *Aspergillus* meningitis/encephalitis cases were identified. Although *Sphingomonas paucimobillis* infection mostly occurred among immunocompromised patients, few studies reported that *Sphingomonas paucimobillis* can also infect in immunocompetent individuals [20] and even about coinfection of *Sphingomonas paucimobillis and Listeria monocytogenes was also noted* in an immunocompetent individual [21]. *Burkholderia cepacia* is a rare cause worldwide but now becoming emerging cause as a bacterial meningitis [22,23].

Burkhodelria cepacia and *Aspergillus* were isolated from serum samples and *Sphingomonas paucimobilis* was isolated from CSF samples of routine culture and antibiotic sensitivity assays. Two patients got positive CSF culture results *(Staphylococcus hominis and Staphylococcus epidemidis).* But their CSF biochemical and microscopic assay results and clinical features were not compatible with pyogenic meningitis and those cases were determined as contaminated result in this study. Therefore, only routine CSF culture was not enough to get the diagnosis of encephalitis cases.

During the study period, a case of cryptococcal meningoencephalitis (CM) was totally unexpected since the case is immunocompetent. Previous researches described that CM cases in immunocompetent patients is underestimation and it is not as rare as previously estimated. Many studies showed that up to 43.5 % of cases occur in immunocompetent young individuals, non-HIV/non-organ transplant patients [24–26] Furthermore, among immunocompetent patients, 67% of whom presented with CM had auto-antibodies [27]In this study, we came across two cases of

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Haemophilus influenzae encephalitis, which we did not have any experience before, since it was nearly never tested before in our country. This case has alerted the clinicians to have a high index of suspicion since it might be one of the commonest identifiable organisms of encephalitis in Myanmar. Myanmar is an endemic country for many arboviruses such as DENV, JEV, ZKV and CHIKV[9,10]. Unfortunately, no cases were identified as the causes in this study.

Immune encephalitis accounted for 16.13% of aetiology identified encephalitis cases (5/31) and only 9.38% (6/64) among all presumed encephalitis cases. Four were anti-NMDAR ab positive, one was SLE case and one was presumed autoimmune encephalitis [28]. 26 % of paediatric encephalitis cases were diagnosed as presumed autoimmune encephalitis in a study conducted in Myanmar during 2017-2018 [29]. In our study, because of limited resources and sample size, only anti-NMDAR Ab was tested and this would have underestimated the actual number of autoimmune encephalitis.

In this study only 31/64 encephalitis cases could have the definite aetiology confirmed. Even in developed countries, the proportion of undiagnosed encephalitis cases were still high[30]. However, many advanced diagnostic tests are available nowadays and both infectious and non-infectious causes can be identified and the mortality rate of the patients will be reduced.

5. Conclusions

Herpes and tuberculous was the commonest causes and followed by the autoimmune encephalitis and the proportion of patients who did not get accurate diagnosis was high. Not only molecular testing but also routine laboratory tests together with clinical and radiological findings should be used to get the early diagnosis of encephalitis cases. Furthermore, many emerging and reemerging pathogens are found to cause encephalitis and annual surveillance should be conducted.

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Informed Consent Statement: Due to vulnerability and incapacity to give an informed consent, immediate family members or caretakers were well informed to give a surrogate informed consent on behalf of the eligible patients.

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