The Profile of Acute Encephalitis Cases Admitted at the Philippine Children's Medical Center from 2008-2012: A 5 Year Retrospective Study

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ABSTRACT

BACKGROUND: The common etiologies of encephalitis are Japanese B encephalitis and Herpes simplex virus encephalitis and also autoimmune mediated causes like the anti-N-Methyl D-Aspartate receptor (NMDAR) encephalitis. These are known for their propensity to cause severe neurologic complications.

OBJECTIVES: 1.To determine the incidence of acute encephalitis among pediatric patients admitted in a tertiary hospital from 2008-2012 based on: demographic, socio-economic and clinical profile; 2. To determine other variables related with the incidence of encephalitis such as presence of non-specific signs and symptoms, presence of Neurologic signs and symptoms and the diagnostics used like Cerebrospinal fluid, Electroencephalogram and neuroimaging; 3.To determine the different hospital epidemiological indices of encephalitis among pediatric patients.

METHODOLOGY: We reviewed the medical records of all encephalitis cases admitted in a tertiary hospital from January 2008 to December 2012. Viral studies on the serum and CSF were obtained from the Philippine Research Institute of Tropical Medicine while specimen for Anti-NMDAR were sent to Dalmau Laboratory in Barcelona, Spain and to Oxford Radcliffe Hospitals, Pathology Laboratory in UK.

RESULTS: Among the 109 cases reviewed, only 19 (18%) cases were subsequently verified as to etiology. Most of the cases were Japanese B encephalitis (68%). Majority belongs to 5-9 age group with male preponderance.

CONCLUSION: Most of the cases (66%) had no neurologic deficit upon discharge with only 4.5% mortality rate

KEY WORDS: Viral Encephalitis; Anti N-Methyl D Aspartate receptor encephalitis; Japanese B encephalitis; Herpes Simplex virus encephalitis; choreoathetoid; orofacial dyskinesias

INTRODUCTION

The clinical involvement of the central nervous system (CNS) is an unusual manifestation of human viral infection. The spectrum of brain involvement and the outcome of the disease are dependent on the specific pathogen, the immunological state of the host and a range of environmental factors. Although specific therapy is limited to only several viral agents, correct diagnosis, and supportive and symptomatic treatment (when no specific therapy is available) are mandatory to ensure the best prognosis.

Acute encephalitis syndrome (AES) is a constellation of clinical signs and/or symptoms, i.e. acute fever, with an acute change in mental status and/or new onset of seizures. These clinical signs suggest the patient has acute inflammation of the brain and are used by clinicians to identify patients with acute encephalitis. Viruses are regarded as the most important cause of the acute encephalitis syndrome worldwide. However, the syndrome can be associated with a range of pathogens, including acute bacterial, parasitic infections or can be autoimmune. Where population based studies have been undertaken, the incidence ranges between 3.5 and 7.4 cases per 100,000 patient-years.[1]

Acute encephalitis can be associated with severe complications, including impaired consciousness, seizures, limb paresis or death. In Asia, the major identified cause of acute encephalitis is Japanese B encephalitis (JE) virus. It affects over 50,000 people annually, leading to 8-30% mortality and 50-60% disability, with the children bearing the brunt of the disease burden.[1]

A severe form of encephalitis associated with antibodies against NR1-NR2 heteromeres of the NMDA receptor was recently identified. NMDA receptors are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. The receptors are heteromeres of NR1 subunits that bind glycine and NR2 subunits that bind glutamate. This test is a cell based indirect immunofluorescence antibody (IFA) assay for anti-NR1, which is strongly associated with treatment-responsive limbic encephalitis. Anti-N-methyl-D- aspartate receptor (NMDAR) encephalitis is an inflammatory encephalopathic autoimmune disease frequently affecting young women with teratomas of the ovary. It is also observed in men, children and females without tumors. [2]

Clinical distinction between viral encephalitis and nonviral infective meningoencephalitis is difficult, often impossible. Epidemiological and demographic features, such as prevalent or emergent infections in the community, occupation, a history of travel and animal contacts may provide helpful clues. In acute bacterialmeningitis, meningeal symptoms of intense headache, photophobia and vomiting appear early and are usually more severe than the encephalopathic features. Presence of multiple cranial neuropathies is also suggestive of a primary meningeal process. History of continued fever and a subacute onset of symptoms with progressive obtundation and/or features of raised intracranial pressure are more typical of suppurative intracranial infections such as brain abscess. Tuberculous meningitis (TBM) also presents similarly, and in children, symptoms of TBM are often subacute in onset. In a nonepidemic setting, the most common cause of focalencephalopathic findings is HSE; however, among cases with biopsy-proven herpes encephalitis, there were no distinguishing clinical characteristics between patientspositive for HSV and those who were negative (Whitley and Gnann, 2002).

Locally, there is still no available data regarding the incidence and burden of all the causes of encephalitis syndrome in the Philippines whether it be infectious or autoimmune in origin.

REVIEW OF RELATED LITERATURE

Encephalitis is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be due to a non infective condition such as in acute disseminated encephalomyelitis (ADEM) or to an infective process, which is diffuse and usually viral. Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), mumps, measles and enteroviruses are responsible for most cases of viral encephalitis in immune-competent individual (Koskiniemi et al.,2001).

In the most robust, prospective studies conducted in Western industrialised countries, a minimum incidence of 10.5 per 100,000 acute encephalitic syndrome cases were reported for children and 2.2 per 100,000 for adults. The minimum incidence for all ages was 6.34 per 100,000 from a tropical setting. On this basis, for ease of use in protocols and for future WHO surveillance standards, a minimum incidence of 10 per 100,000 AES cases is suggested as an appropriate target for studies of children alone and 2 per 100,000 for adults and 6 per 100,000 for all age groups.

Japanese encephalitis (JE) has been documented to be endemic in the Philippines but only few studies document the incidence by using laboratory diagnostics.The Philippine Department of Health (DOH) is particularly concerned with Region 3 since several encephalitis cases were noted to occur but still remained insufficiently characterized. JE cases were reported from Region 3 provinces such as Tarlac, Bulacan, Nueva Ecija and Pampanga as well as in other areas such as Laguna, Quezon Province and Cavite. Nationwide syndromic surveillance for meningitis and encephalitis, complemented by sentinel sites with case-based surveillance and collection of specimens for laboratory confirmation is the model used in other countries (e.g. Thailand) and recommended by WHO for estimating the disease burden due to different pathogens causing meningoencephalitis. The assumption here is that children with JE and bacterial meningitis are typically very sick and would normally be treated in a hospital; therefore, sentinel surveillance focuses on tertiary level hospitals rather than lower-level health facilities.[4]

Encephalitis with antibodies against N-methyl -D-aspartate (NMDA)-type glutamate receptors was recently recognized as a defined clinical entity. The initial reports concerned exclusively young women with ovarian germinal tumor and encephalitis. All had a number of clinical signs in common: cognitive deterioration and abnormal movements of the orofacial region and limbs. The outcome after tumor resection was favorable and the patients displayed slow clinical recovery. These patients also had antibodies against NMDA receptors, consistent with a paraneoplastic syndrome. However, the spectrum of the disease is probably wider. The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction (acute memory disturbances), behavioural changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis, hemianopia etc.) and seizures. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination.

SIGNIFICANCE OF THE STUDY

Thus, the result of this descriptive type of study would increase the index of suspicion for encephalitis cases in the absence of readily available diagnostic tests. This study can also be utilized to generate evidence which can be presented to health policy makers in the National Capital Region and in the Philippines in general. This study can also be used by a future researcher as a basis for another research that will verify some important findings from this study.

SCOPE AND DELIMITATION OF THE STUDY

This study involves a review and analysis of case records of all acute pediatric encephalitis patients from 2008 to 2012. In as much as this is a hospital based study, it is limited to the use of secondary data which is vulnerable to selection bias arising from the selective factors that guide affected individuals to a particular medical facility. Furthermore, hospital records are sometimes incomplete and inaccurate.

OPERATIONAL DEFINITION OF TERMS

1. **Encephalitis**- is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. It can be due to a non-infective condition such as in acute disseminated encephalomyelitis (ADEM) and Anti N-methyl-

D- aspartate receptor encephalitis or to an infective process, which is diffuse and usually viral like Japanese B encephalitis and Herpes Simplex Virus encephalitis.

2. **Encephalopathy-** is defined as a disruption of brain function that is not because of a direct structural or inflammatory process. It is mediated via metabolic processes and can be caused by intoxications, drugs, systemic organ dysfunction (e.g. liver, pancreas) or systemic infection that spares the brain.

3. **Japanese B encephalitis** - is among the most important viral encephalitides in Asia, especially in rural and suburban areas where rice culture and pig farming coexist. It has also occurred rarely and sporadically in northern Australia and parts of the Western Pacific. JE is due to infection with the JE virus (JEV), a mosquito-borne flavivirus. The main JEV transmission cycle involves *Culex tritaeniorhynchus* mosquitoes and similar species that lay eggs in rice paddies and other open water sources, with pigs and aquatic birds as principal vertebrate amplifying hosts. Humans are generally thought to be dead-end JEV hosts, i.e. they seldom develop enough viremia to infect feeding mosquitoes. Fewer than 1% of human JEV infections result in JE. Approximately 20–30% of JE cases are fatal and 30–50% of survivors have significant neurologic sequelae.

4. **Herpes Simplex Virus encephalitis** - Herpes simplex encephalitis (HSE) is an acute or subacute illness that causes both general and focal signs of cerebral dysfunction. Brain infection is thought to occur by means of direct neuronal transmission of the virus from a peripheral site to the brain via the trigeminal or olfactory nerve. The exact pathogenesis is unclear, and factors that precipitate HSE are unknown.

5. **Anti-N-Methyl-D-aspartate receptor encephalitis** - is an inflammatory encephalopathic autoimmune disease frequently affecting young women with teratomas of the ovary. It is also observed in men, children, and females without tumors. The N-methyl-D-aspartate receptor (NMDAR) is an ion channel located in the post-synaptic membrane that plays a key role in synaptic transmission and plasticity. The receptor is made up of two subunits, NR1 and NR2, that contain extracellular epitopes. Anti-NMDAR antibodies are directed against the extracellularepitope of the NR1 subunit. This test is a cell-based indirect immunofluorescence antibody (IFA) assay for anti-NR1, which is strongly associated with treatment-responsive limbic encephalitis.

6. **Probable cases** - is a suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case, in the context of an outbreak.

7. **Confirmed cases** - is a suspected case that has been laboratory-confirmed.

8. **Annual Hospital Incidence Rate** - this refers to the computed total number of encephalitis cases admitted in the hospital in a year divided by the total number of Pediatric Admissions in the same year multiplied by a factor (ie. I000 or 10,000 or 100,000 population).

9. **Annual Hospital Encephalitis Case Fatality Rate** - this refers to the computed total number of encephalitis cases admitted but died in the hospital in a year divided by the total number of encephalitis cases admitted in that hospital in the same year multiplied by 100.

10. **Annual Pediatric Encephalitis Survival Rate** - this refers to the computed total number of encephalitis cases admitted and survived in the ward of the hospital in a year divided by the total number of encephalitis cases admitted in the same year multiplied by 100.

OBJECTIVES

General Objective:

To determine the incidence of acute encephalitis among pediatric patients admitted in a tertiary hospital from 2008-2012 based on:

1. demographic
2. socio-economic and
3. clinical profile

Specific Objective:

1. To determine the incidence of encephalitis based on the following variables.
   - 1.1 Age Groups
   - 1.2 Sex
   - 1.3 Etiology
     - 1.3.1 Probable
     - 1.3.2 Confirmed
       - 1.3.2.1 Japanese B
       - 1.3.2.2 Anti NMDAR
       - 1.3.2.3 Herpes Simplex Virus
   - 1.4 Place of Residence
2. To determine other variables related with the incidence of encephalitis such as:
   - 2.1 Presence of non-specific signs and symptoms
   - 2.2 Presence of Neurologic signs and symptoms
   - 2.3 Diagnostics
     - 2.2.1 Cerebrospinal fluid CSF)
     - 2.2.2 Electroencephalogram (EEG)
     - 2.2.3 Neuroimaging (Cranial Ultrasound, Cranial Computed Tomography scan, Cranial Magnetic Resonance Imaging)
   - 2.4 Outcome upon discharge
3. To determine the following hospital epidemiological indices of encephalitis among Pediatric patients from 2008 to 2012:
   - 3.1 Annual Hospital Incidence Rates
   - 3.2 Annual Hospital Case Fatality Rates
   - 3.3 Annual Hospital Survival Rates

METHODOLOGY

This study utilized a descriptive type of study in which a retrospective analysis of medical records of pediatric encephalitis cases admitted in a tertiary hospital from 2008 to 2012 was done.

Sample size consisted of one hundred nine (109) pediatric patients diagnosed with encephalitis. No sample size estimation was done since total enumeration of cases within the five year period was adopted.

The variables being considered in this profile of encephalitis cases are age groups, sex, place of residence, etiology, nutritional status, presenting signs and symptoms, diagnostics used, response to treatment and outcome upon discharge.

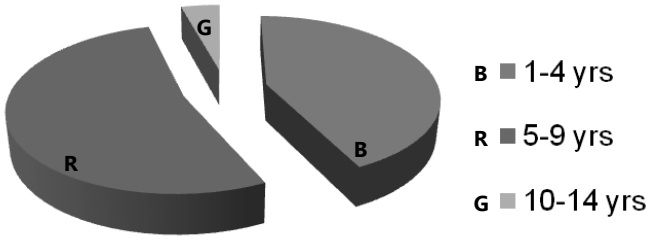
Descriptive statistics was used in this study. Graphical and tabular presentations were utilized as tools in presenting the demographic, clinical and socio-economic profile of the subjects.

PRESENTATION OF RESULTS

I. DEMOGRAPHIC PROFILE

A. Age Groups

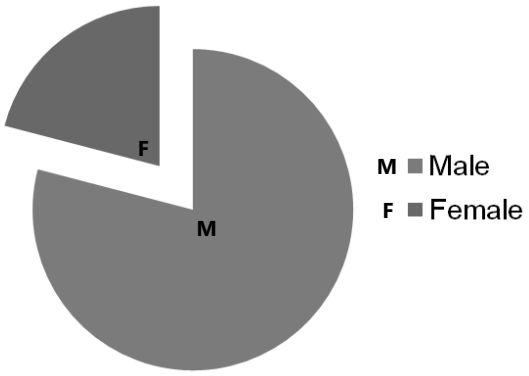
Figure. 1. Percentage Distribution of Encephalitis Cases According to Age, n = 109, 2008-2012



The highest percentage of encephalitis cases belong to age groups 5-9 years old (37%) followed by the 1-4 years old (30%) and lastly by the age group 10-14 years old (3%).

B. Gender

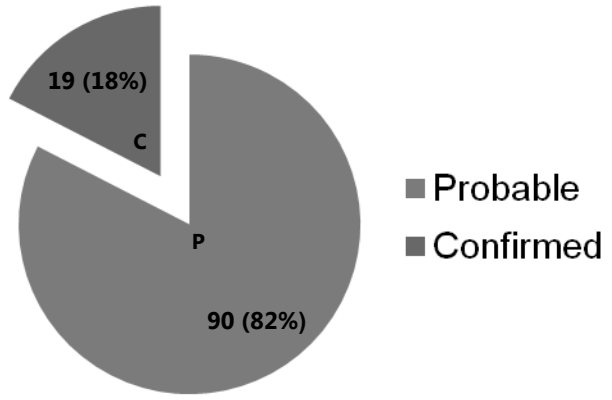
Figure. 2. Percentage Distribution of Encephalitis Cases According to Gender, n = 109, 2008-2012



The proportion of male subjects (80%) is higher than the female subjects (20%).

C. Etiology

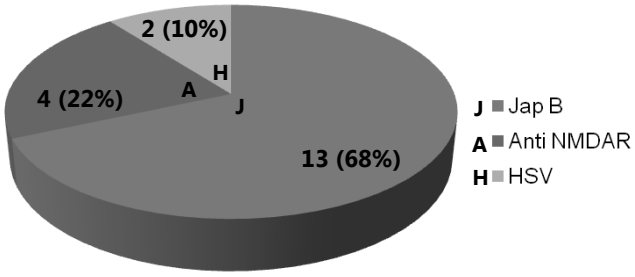
Figure. 3. Percentage Distribution of Encephalitis Cases According to Etiology, n=109, 2008-2012



Among the 109 encephalitis cases that were reviewed, only 19 (18%) were subsequently verified as to their etiology. The 90 (82%) cases manifested signs and symptoms of encephalitis but tested negative in the diagnostic tests.

D. Etiology

Figure. 4. Percentage Distribution of Confirmed encephalitis cases according to Etiology, n=19, 2008-2012



Among the 19 confirmed cases, majority were Japanese B encephaltis (68%) followed by Anti-NMDAR encephalitis (22%).

E. Place of Residence

Table 1. Percentage Distribution of encephalitis cases according to Place of Residence, n=109, 2008-2012

Region	N=109
NCR	61 (55%)
III	16 (15%)
IV	13 (12%)
II	11 (10%)
V	8 (8%)

Most of the encephalitis cases came from the National Capital Region (55%) followed by Region III (15%) and Region IV (12%).

F. Place of Residence

Table 2.1 Percentage Distribution of confirmed Japanese B encephalitis cases according to Place of Residence, n=13, 2008-2012

Region	N=13
IV	6 (46%)
III	3 (23%)
V	2 (15%)
NCR	1 (8%)
II	1 (8%)

Majority of the Japanese B encephalitis cases came from Region IV (46%) followed by Region III (23%) and Region V (15%).

Table 2.2 Percentage Distribution of confirmed Anti- NMDAR encephalitis cases according to Place of Residence, n=4, 2008-2012

Region	N=4
II	1 (25%)
III	1 (25%)
NCR	1 (25%)
IV	1 (25%)

The 4 cases of Anti NMDAR encephalitis came from Region II (25%), Region III (25%), National Capital Region (25%) and Region IV (25%).

Table 2.3 Percentage Distribution of confirmed Herpes Simplex Virus encephalitis cases according to Place of Residence n=2, 2008-2012

Region	N=2
III	1 (50%)
NCR	1 (50%)

The 2 cases of Herpes Simplex virus encephalitis came from Region III and National Capital Region.

II.CLINICAL FINDINGS

G. Presenting Signs and Symptoms

Table 3. Non specific Signs and Symptoms elicited from the history of encephalitis, N=109, 2008-2012

Symptoms	No. of Cases	Percent (%)
Fever	109	100%
Headache	88	80%
Vomiting	82	75%
Chills	30	28%
Nausea	25	23%
Decrease appetite	25	23%
Dizziness	24	22%

All (100%) of the patients had fever during the first 4-5 days of their illness. Almost 75-80% of cases experienced headache and vomiting. Thirty (28%) of patients had chills. Only 22% 23% of cases had nausea, decreased appetite and dizziness.

III. NEUROLOGIC FINDINGS

A. Presence of Neurologic Findings

Table 4. Presence of Neurologic findings elicited from the history of encephalitis, N= 109, 2008-2012

Neurologic	No. of Cases	Percent (%)
Altered sensorium	93	85%
Neck Rigidity	89	82%
Seizures	72	66%
Involuntary movements	70	64%
choreoathetoid	21	19%
catatonia	15	14%
Rigidity	13	12%
Orofacial dyskinesia	12	11%
Dystonic posturing	9	8%
Abulia	65	60%
Abnormal muscle tone	56	51%
Abnormal motor function	50	45%
Abnormal reflexes	50	45%

Majority of the patients manifested encephalopathic symptoms such as altered sensorium (85%), neck rigidity (82%), seizures (72%) and abulia (60%). Involuntary movements were also noted in 64% of cases. The 5 movement disorders noted were choreoathetoid (19%), catatonia (14%), rigidity (12%), orofacial dyskinesias (11%) and dystonic posturing (8%).

B. Neurologic Findings of Japanese B encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 4. Neurologic findings of Japanese B encephalitis, N= 13, 2008-2012

	< 7days	days	>14days
Altered sensorium	8	5	-
Abulia/Masked like facies	8	5	-
Involuntary movements	3	9	1
Catatonia	1	4	-
Choreoathetoid	-	1	1
Orofacial dyskinesia	2	4	-
Hypertonia	7	6	-
Hyperreflexia	7	6	-
Presence of Babinski	7	6	-
Seizures	9	4	-
Behavioral changes	1	1	-
Neck Rigidity	3	10	-

Most of the neurological signs and symptoms occurred within 3-5 days from the onset offever except for the involuntary movements which were noted mostly during the second week of illness.Abulia or mutism which were seen mostly during the first week of illness were described with an expressionless face even when the patient cried or grimaced. Seizures also appeared more frequent during first week of illness.

C. Neurologic Findings of Anti-NMDA receptor encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 5. Neurologic findings of Anti-NMDAR encephalitis, N= 4,2008-2012

	< 7days	7-14days	>14days
Altered sensorium	1	3	-
Involuntary movements			
Catatonia	1	3	-
	1	-	-
Choreoathetoid	-	1	-
Orofacial dyskinesia	-	1	-
Dystonic posturing	-	1	-
Behavioral Changes	3	1	-
Seizures	2	2	-
Hypertonia	2	2	-
Hyperreflexia	1	3	-
Presence of Babinski	-	4	-

Most of the Anti-NMDAR cases manifested behavioral changes, seizures and hypertonia during the first week of illness whereas the altered sensorium, involuntary movements, hyperreflexia and presence of Babinski sign were observed during the second week of illness.

D. Neurologic Findings of Herpes simplex virus encephalitis cases on the time they were first seen. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days).

Table 6. Neurologic findings of Herpes Simplex virus encephalitis, N= 2, 2008-2012

	< 7days	7-14days	>14days
Altered sensorium	-	1	1
Involuntary movements			
Orofacial dyskinesia	-	1	-
Hyperreflexia	-	2	-
Neck rigidity	-	2	-
Presence of Babinski	-	2	-

Of the only 2 cases of Herpes Simplex virus encephalitis, the neurologic signs and symptoms were mostly noted during the second week of illness.

IV. BLOOD AND CEREBROSPINAL FLUID (CSF) FINDINGS

Viral studies on the serum and CSF were obtained and sent to Philippine Research Institute of Tropical Medicine, Manila while specimen for Anti-NMDAR were sent to Dalmau Laboratory in Barcelona, and to Dr. Angela Davis in Oxford Radcliffe Hospitals, Pathology Laboratory in United Kingdom.

Opening pressure on lumbar tap were taken in all patients. The highest pressure was 28mm water. Among the confirmed cases, the succeeding tables will show the results of the cerebrospinal fluid based on the time of extraction.

Table 7. Peripheral Count of Japanese B encephalitis cases, N=13, 2008-2012

WBC (/cu L)	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
<5	-	-	-
5-10,000	-	2	-
10,001-15,000	1	3	-
15,001-20,000	2	-	-
20,001-25,000	2	-	-
25,001-30,000	2	-	-
30,001-35,000	-	-	-

Table 7 shows that mild leukocytosis was seen in 54% of cases during the first week of illness. The highest was 32,000/cu L initially. By the second week, most counts were already within the normal limits.

Table 8. Cerebrospinal fluid result of Japanese B encephalitis cases, N=13, 2008-2012

A.WBC (10^6/cu mm)	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
<10	-	-	-
11-100	-	-	-
101-200	2	3	-
201-300	3	2	-
301-400	1	-	1
401-500	1	-	-
>500	-	-	-

Table 9. Cerebrospinal fluid result of Japanese B encephalitis cases, N=13, 2008-2012

A. WBC Differential count	< 7days (N=7)	7-14days (N=5)	>14days (N=1)
L>N	5	2	1
N>L	2	3	-
B. Sugar (mg%)			
>45%	4	4	1
<45%	3	1	-
C. Protein (gm/L)			
15-45	5	2	-
46-100	1	3	1
101-150	1	-	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

Table 8 showed pleocytosis in the first week ranged from 101-470cells/cu mm. The counts gradually reversed so that by the third week, almost 90% were normal. Lymphocytosis was predominant in the first week of the disease, Table 9-A. Occasionally polymorphonuclear cells predominated in the first week. The sugar levels were mostly normal (58%) except in three, Table 9-B. The protein levels were commonly normal (71%), and when elevated, mild increased levels were seen even in the late period, Table 9-C. However, levels higher than 100 mg% were not seen after the first week.

Table 10. Peripheral Count of Anti-NMDAR encephalitis cases, N=4, 2008-2012

WBC (/cu L)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
<5	-	-	-
5-10,000	-	2	-
10,001-15,000	1	1	-
15,001-20,000	-	-	-
20,001-25,000	-	-	-
25,001-30,000	-	-	-
30,001-35,000	-	-	-

Table 10 showed that mild leukocytosis was seen in only 25% during the first two weeks of illness.

Table 11. Cerebrospinal fluid result of Anti NMDAR encephalitis cases, N=4, 2008-2012

WBC (10^6/cu mm)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
<10	-	-	-
11-100	-	1	-
101-200	1	2	-
201-300	-	-	-
301-400	-	-	-
401-500	-	-	-
>500	-	-	-

Table 12. Cerebrospinal fluid result of Anti NMDAR encephalitis cases, N=4, 2008-2012

A. WBC Differential count	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
L>N			-
N>L	1	1	-
	-	2	
B. Sugar (mg%)			
>45%	1	4	-
<45%	-	1	-
C. Protein (gm/L)			
15-45	-	2	-
46-100	1	1	-
101-150	-	1	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

Tables 11 and 12 showed that mild pleocytosis ranged from 11-200 cells/cu mm during the first and second week of illness. Differential count was noted with equal proportion. Sugar and protein levels were within normal limits.

Table 13. Peripheral Count of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

WBC (/cu L)	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
<5	-	-	-
5-10,000	-	1	1
10,001-15,000	-	-	-
15,001-20,000	-	-	-
20,001-25,000	-	-	-
25,001-30,000	-	-	-
30,001-35,000	-	-	-

Tables 13 showed that the two cases had normal peripheral counts by the second and third week.

Table 14. Cerebrospinal fluid result of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

WBC (10^6/cu mm)	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
<10	-	-	-
11-100	-	-	-
101-200	-	1	-
201-300	-	-	1

Table 15. Cerebrospinal fluid result of Herpes Simplex virus encephalitis cases, N=2, 2008-2012

	< 7days (N=0)	7-14days (N=1)	>14days (N=1)
A. WBC Differential count			
L>N	-	1	1
N>L	-	-	-
B. Sugar (mg%)			
>45%	-	1	1
<45%	-	-	-
C. Protein (gm/L)			
15-45	-	-	-
46-100	-	-	1
101-150	-	1	-
151-200	-	-	-

L- lymphocytic; N- Neutrophilic

The CSF leukocyte count, different count, sugar and protein levels of the two HSV encephalitis cases were within normal limits when they were examined by the second and third week of illness.

V. ELECTROENCEPHALOGRAM(EEG) FINDINGS

All encephalitis cases underwent electroencephalogramupon admission. They were arbitrarily grouped as acute (< 7 days), subacute (7-12 days), and chronic (>14 days) based on the days of their illness when they were admitted.

Table 16. EEG findings of all the confirmed encephalitis cases, N=19, 2008-2012

I. Japanese B (N=13)	< 7days (N=5)	7-14days (N=6)	>14days (N=2)
Abnormal			
Generalized slowing	5	4	-
Focal slowing	-	2	-
Normal	-	-	2
II. Anti-NMDAR (N=4)	< 7days (N=1)	7-14days (N=3)	>14days (N=0)
Abnormal			
Generalized slowing	1	2	-
Focal slowing	-	1	-
Normal	-	-	-
III. HSV (N=2)	< 7days (N=0)	7-14days (N=2)	>14days (N=0)
Abnormal			
Generalized slowing	-	1	-
Focal slowing with Left temporal discharges	-	1	-
Normal	-	-	-

Most of the Japanese B encephalitis cases (38%) showed generalized slowing of the background activity during the first week of illness and decreased to 30% by the second week of illness. 15% of the cases also showed focal slowing on the fronto-temporal regions by the second week. During the third week, 15% of the Japanese B encephalitis cases had normal EEG results.

Of the four Anti-NMDAR encephalitis cases, 3 (75%) showed generalized slowing of the background activity during their first two weeks of illness while only 1 (25%) showed intermittent slowing over the left fronto-temporal regions during the second week of illness.

Of the two cases of HSV, 1 (50%) showed generalized slowing of the background activity and the other case showed focal slowing with epileptiform discharges over the left temporal region. Both cases however were seen during their second week of illness.

VI. NEUROIMAGING FINDINGS

Table 14. Neuroimaging findings of all the confirmed cases (Japanese B (N=13), Anti-NMDAR (N=4), Herpes simplex virus (N=2)) encephalitis cases, N=19, 2008-2012

I. Japanese B (N=13)	< 7days (n=2)	7-14days (N=7)	>14days (N=4)
Abnormal	2	7	-
Normal	-	-	4
II. Anti-NMDAR (N=4)	< 7days (N=1)	7-14days (N=4)	>14days (N=0)
Abnormal	1	3	-
Normal	-	-	-
III.HSV (N=2)	< 7days (N=0)	7-14days (N=2)	>14days (N=0)
Abnormal	-	2	-
Normal	-	-	-

Abnormal findings in the neuroimaging of most of the Japanese B encephalitis cases (54%) were seen during their second week of illness while 15% were seen during the first week of illness. Cranial magnetic resonance imaging, computed topography and ultrasound were done. All showed cerebral edema with hyperintense signal abnormalities over the basal ganglia, brainstem and bilateral thalamic regions. Four (30%) of the Japanese B encephalitis cases showed normal results taken during their 3rd to 4th week of illness.

Of the four Anti-NMDAR cases, 3 (75%) showed cerebral edema and areas of hyperintensity in the medial temporal lobes and hippocampus taken during the second week of illness. One case (25%) showed meningeal enhancement on cranial CT done during the first week of illness.

Cerebral edema and hemorrhage seen as hypointense and hyperintense in the Left fronto-temporal areas on T2 and T1 weighted images respectively were seen in the two HSV patients during the 10th-12th week of illness.

VII. OUTCOME

Table 15. Outcome of all the encephalitis cases upon discharge (Japanese B (N=13), Anti-NMDAR (N=4), Herpes simplex virus (N=2)) encephalitis cases, N=109, 2008-2012.

Category	**N=109**
No deficit	61 (66%)
Mild deficit	25 (23%)
Moderate to severe deficit	18 (16.5%)
Died	5 (4.5%)

Majority of the encephalitis cases (66%) did not show any neurologic deficit upon discharge. Mild deficit was seen in 23% while 16.5% manifested moderate to severe deficit. Five cases (4.5%) died during their confinement. Two of the mortalities had severe pneumonia and 3 patients had disseminated intravascular coagulopathy.

Table 16. Outcome of the Japanese B encephalitis cases upon discharge, N=13, 2008-2012.

Category	**N=13**
No deficit	1
Mild deficit	8
Moderate to severe deficit	2
Died	2

Majority of the Japanese B encephalitis (62%) showed mild neurologic deficit, 2 (15%) had moderate to severe deficit and two patients died. Only 1 (8%) patient was discharged with no neurologic deficit.

Table 17. Outcome of the Anti-NMDAR encephalitis cases upon discharge, N=4, 2008-2012.

Category	**N=4**
No deficit	-
Mild deficit	3
Moderate to severe deficit	1
Died	-

Most of the Anti-NMDAR encephalitis (75%) showed mild deficit upon discharge while 1 (25%) had moderate to severe neurologic deficit.

Table 18. Outcome of the Herpes Simplex virus encephalitis cases upon discharge, N=2, 2008-2012.

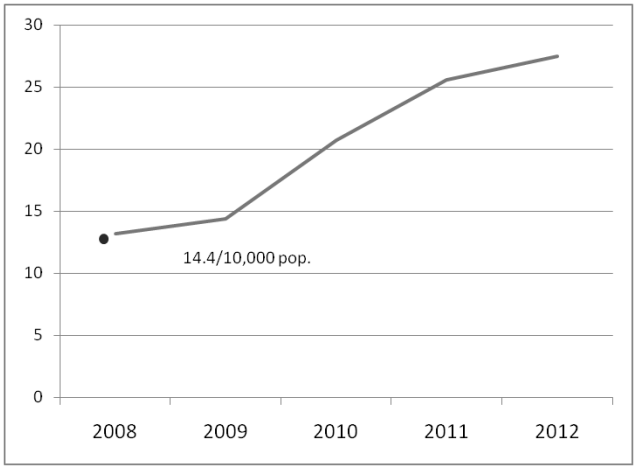
Category	N=2
I-No deficit	-
II-Mild deficit	1
III-Moderate to severe deficit	-
IV-Died	1

Mild deficit was manifested by one (50%) of the two HSV patients while the other died of severe systemic infection.

VIII. HOSPITAL EPIDEMIOLOGIC INDICES

A. Annual Hospital Incidence Rates of Encephalitis

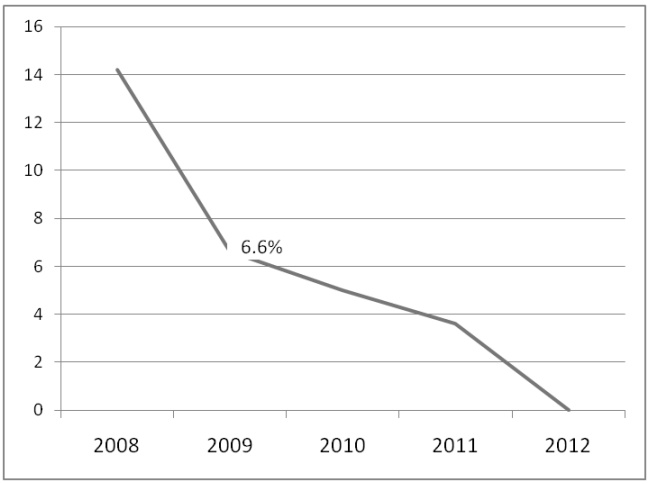
Figure 5. Annual Hospital Incidence Rates of Encephalitis from 2008 to 2012



The line graph above shows an increasing trend of Annual Hospital Incidence Rates of Encephalitis from 2008 to 2012 in a tertiary hospital. Most encephalitis cases occurred in 2012.

B. Annual Hospital Case Fatality Rates of Encephalitis

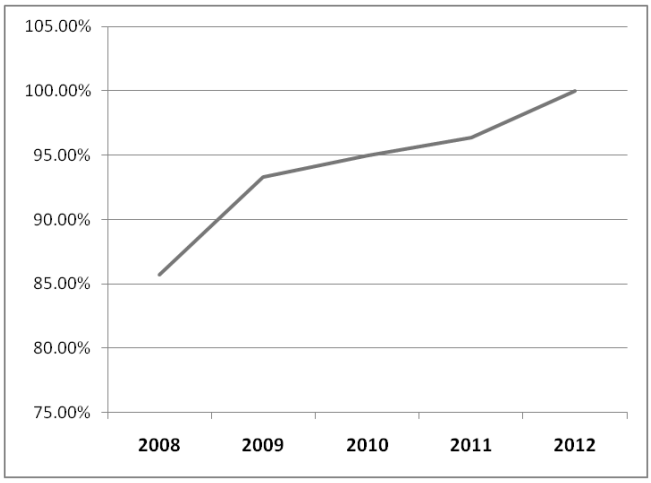
Figure 6. Annual Hospital Case Fatality Rates of Encephalitis from 2008 to 2012



The line graph above shows a decreasing trend of Annual Hospital Case Fatality Rates of Encephalitis from 2008 to 2012in a tertiary hospital

C. Annual Pediatric Encephalitis Survival Rate

Figure 7. Annual PediatricEncephalitisSurvival Rate from 2008 to 2012



The line graph above shows an increasing trend of Annual Hospital Survival Rates of Encephalitis from 2008 to 2012in a tertiary hospital.

DISCUSSION

The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction (acute memory disturbances), behavioural changes (disorientation, hallucinations, psychosis, personality changes, agitation), focal neurological abnormalities (such as anomia, dysphasia, hemiparesis, hemianopia etc.) and seizures. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination. The neurological manifestations gathered from the history of our patients were generally similar to the observations of other authors. In Japanese B encephalitis cases, abulia or mutism accompanied by masked facies were more common and prominent in our study and presented as the initial neurological deficit in 8 cases. Previous studies have described masked facial expressions to be a characteristic feature of JEV encephalitis although other viral or nonspecific encephalitis can produce a similar feature. Seizures have been observed to be more common in younger age group. Most of the Anti -NMDAR cases manifested behavioral changes, seizures and hypertonia.

Demographic Profile

The history is mandatory in the assessment of the patient with suspected viral encephalitis.The geographical location as well as the recent travel history could be of relevance to identify causative pathogens that are endemic or prevalent in certain geographical regions. The mode of disease course up to the appearance of the neurological signs may provide clues to the aetiology. Likewise, the evolution of the clinical signs and their severity depend on host and other factors such as immune state and age and cannot serve as guidelines to identify the pathogen. In general, the very young and the very old have the most extensive and serious signs of encephalitis.

Clinical Profile

Clinical distinction between viral encephalitis and non viral infective meningoencephalitis is difficult, often impossible. The neck rigidity in the subacute and chronic periods was mostly due to increased muscular tone rather than meningeal irritation. The choreoathetosis seen in the 2nd week of illness probably surface when the level of consciousness improved because choreic patients are known to lose these abnormal movements during sleep. Choreoathetosis may also be chronic sequelae of the disease. These involuntary movements can be attributed to thalamic -subthalamic lesions and basal ganglia. The pathological reflexes correlate well with motor or tone abnormalities.

Laboratory Profile

Peripheral blood count and cellular morphology, arehelpful in separating viral from non-viral infections. Lymphocytosis in the peripheral blood is common in viral encephalitis. The auxiliary studies that examine viral infections of the nervous system include studies that characterize the extent and nature of CNS involvement (EEG and neuroimaging), microbiological attempts to identify the pathogen and histopathology. EEG is generally regarded as a non-specific investigation, although it is still sometimes a useful tool in certain situations. Thus, leucoencephalitides shows more diffuse slow activity in the EEG. Likewise, the EEG findings in post-infectious encephalitides differ from infectious encephalitis only in the time schedule of the abnormalities. The main benefit of EEG is to demonstrate cerebral involvement during the early state of the disease.

CONCLUSION

The geographical location of encephalitis cases were observed mostly in the rural areas and were correlated on the different practices of the people. The characteristic neurological features in our cases that could be considered as Japanese B encephalitis are abulia with masked facies, variable changes in mentation, and asymmetric and irregular distributionof motor and tone abnormality. For the anti-NMDAR cases, they manifested behavioural

changes, seizures and hypertonia during the first week of illness whereas the altered sensorium, involuntary movements, hyperreflexia and presence of Babinski sign during the second week of illness. The first week of the disease prominently showed neutrophilic pleocytosis in theperipheral smear while the cerebrospinal fluid showed leucocytic lymphocytosis, mild to normalprotein level and normal sugar values. Most of the Japanese B encephalitis cases and anti-NMDAR encephalitis showed generalized slowing of the background activity during the 10^{th}-14^{th} day of illness while herpes simplex virus encephalitis showed focal background slowing and there is a temporal focus showing lateralized epileptiform discharges. However, this is usually temporary.

Magnetic resonance imaging (MRI) is more sensitiveand specific than CT for the evaluation of encephalitis. Neuroimaging findings in Japanese B encephalitis showed cerebral edema with hyperintense signal abnormalities over the basal ganglia, brainstem and bilateral thalamic regions. Cranial MRI findings for anti-NMDAR encephalitis cases are cerebral edema and areas of hyperintensity in the medial temporal lobes and hippocampus while areas of hemorrhage were seen as hypointense and hyperintense in the Left fronto-temporal areas on T2 and T1 weighted images respectively in HSV patients. Most of the encephalitis cases only manifested mild deficit upon discharge.

Based on the hospital data for the past 5 years, there is an increasing trend of incidence and survival rates and a decreasing case fatality rates.

REFERENCES

1. Ajit Rayamajhi, Imran Ansani, et al. Clinical and Prognostic features among children with acute encephalitis syndrome in Nepal: a retrospective study. BMC Infectious Diseases 2011.
2. Anti-NMDA Receptor (NR1) IgG antibodies for diagnosis of Limbic Encephalitis. November 2010.
3. Lebas Axel, MD et al., Expanding Spectrum of Encephalitis with NMDA Receptor Antibodies in young Chlidren, Journal of Child Neurology. June 13, 2009.
4. Dalmau J, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurology* 2008;7(12):1091–8.
5. Granerod J, Crowcroft NS: The epidemiology of acute encephalitis.Neuropsychol Rehabil 2007, 17(4-5):406-428.
6. San Luis, Amado, Curtis G. Hayes, et al. The Neurologic features of Japanese Encephalitis in the Philippines. Philippine Journal of Microbiology Infectious Disease, 1990.
7. WHO- Recommended standards for Surveillance of Selected vaccines- preventable diseases WHO/V & B/03.01, January 2006. Available from: http:// www.who.int/vaccines-documents/ DocsPDF06/843.pdf
8. Grant L. Campbell, Susan L. Hills, et al. Estimated Global incidence of Japanese encephalitis: A systemic review. Bulletin World Health Organization, 2011; 89:766-774E doi:10.2471.
9. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neurophil antibodies: MRI and PET correlates. Brain. 2005;128 (pt 8):1764-1777.