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Loque BCT, Butler CA. Clinico-epidemiologic Features and Outcome of Infectious and Immune-mediated Pediatric Encephalitis
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ORIGINAL ARTICLE

CLINICO-EPIDEMIOLOGIC FEATURES AND OUTCOME OF INFECTIOUS AND IMMUNE-MEDIATED PEDIATRIC ENCEPHALITIS

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ABSTRACT

Introduction: The etiology of encephalitis involves an enormous range and can be classified as infectious or immune-mediated. There are several factors influencing its prognosis and has been associated with significant morbidity and mortality. This study aims to evaluate the clinico-epidemiologic characteristics and outcomes of infectious and immune-mediated encephalitis among pediatric patients.

Methodology: Retrospective descriptive cross-sectional study that included patients aged 6 months to 17 years old with encephalitis in a tertiary hospital between January 2010 to December 2020.

Results: A total of 23 cases were reviewed and 60.87% were infectious while that of immune-mediated was 39.13%. Among those with identified infectious cause, *Mycoplasma pneumonia* was the most common (28.57%). Infectious encephalitis was more common among younger males (35.71%) while immune-mediated affected female adolescents more (55.56%). The most common neurologic manifestation was altered mental status and/or behavioral changes. Treatment such as antibiotics (78.26%), anticonvulsant therapy (78.26%), and steroids (43.48%) were given. All immune-mediated cases received steroids. More than half of patients had complete recovery (56.52%).

Conclusion: Pediatric encephalitis should be considered among patients with neurologic dysfunction with or without systemic involvement. Behavioral changes in an apparently well child should prompt clinicians to consider anti-NMDAR encephalitis, especially if viral studies are negative and with no other known cause. Viruses remain to be the most common etiology, but other possible causes should be highly considered such as anti-NMDAR and Mycoplasma. A normal CSF analysis, imaging and/or encephalography (EEG) may not totally exclude encephalitis. Prognosis is relatively good hence an early diagnosis and initiation of appropriate management is important.

KEYWORDS: *Encephalitis, Infectious Encephalitis, Viral Encephalitis, Mycoplasma, Immune-mediated Encephalitis*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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INTRODUCTION

Acute encephalitis is the acute inflammatory process which involves the brain parenchyma associated with symptoms of neurologic dysfunction along with systemic symptoms.[1] In the year 2008, Acute Encephalitis Syndrome (AES) was coined by the World Health Organization (WHO), which referred to the acute-onset of fever and presence of change in mental status (including signs and symptoms such as confusion, disorientation, delirium or coma) and/or new-onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year.[2,3] The reported worldwide incidence varies, relatively ranging from 3.5 to 7.4 cases per 100,000 patient-years. It affects all ages but compared to adults, incidence tends to be higher in the pediatric population, with more than 16 cases per 100,000 patient-years.[4,5] In the Philippines, the Epidemiologic Bureau of the Department of Health under the Philippine Integrated Disease Surveillance and Response (PIDSR) system established the Acute Meningitis-Encephalitis Syndrome (AMES) Surveillance, which officially started in 2015. Based on its latest data, a total of 1664 AMES cases were reported from January 1 to May 25, 2019, wherein majority were males (58%) and mostly were children less than 5 years of age (49%).[6,7]

Etiology of encephalitis involves an enormous range and can be classified as infectious, para-infectious, autoimmune, and/or of unknown cause. Among all the possible infectious causes, viruses remained to be the most common.[8] Cases of primarily immune mediated or autoimmune in nature have been recognized as well, which manifests with a broad clinical spectrum. Acute encephalitis has been associated with significant morbidity and mortality, with outcomes ranging from full recovery to death. Several studies on pediatric encephalitis reported mortality rate of less than 10%, but over 50% of these patients have significant neurologic and behavioral sequelae.[1] The accurate determination of its prognosis remains elusive.

Currently, majority of published studies on pediatric encephalitis were focused mainly on acute viral encephalitis, being it the most common. There is minimal availability of studies that covers the clinical profile and outcomes of both infectious and immune mediated cases, especially in the local setting. It is important to take into consideration other possible etiologies, the different factors associated to its occurrence, as well as their presentation depending on the cause. This will then help in early detection and diagnosis, leading to a more directed approach in management and prevention of development of complications. Hence, additional data will be of significant help.

This study aimed to evaluate the clinico-epidemiologic characteristics of pediatric encephalitis patients admitted in an urban tertiary hospital from January 2010 to December 2020. The specific objectives were: 1) to determine the proportion of acute encephalitis attributed as infectious and immune-mediated; 2) to characterize the cases of acute encephalitis in terms of etiology, age, sex, nutritional status, presenting systemic and neurologic manifestations, duration of symptoms prior to admission, diagnostic work-ups, length of hospital stay, and medical management; and 3) to classify the outcomes of these patients at the time of discharge as to complete or partial recovery, and mortality.

METHODOLOGY

This was a retrospective descriptive cross-sectional study of subjects aged 6 months to 17 years old admitted in an urban tertiary hospital between January 1, 2010 to December 31, 2020, with a final diagnosis of acute encephalitis regardless of its etiology, and/or with the following ICD 10 codes:

- A83 (mosquito-borne viral encephalitis)
- A84 (tick-borne encephalitis)
- A85 (other viral encephalitis, not elsewhere classified)
- A86 (unspecified viral encephalitis)
- B00.4 (herpes viral encephalitis)

- B01.1 (varicella encephalitis, myelitis and encephalomyelitis)
- B10.01 (human herpes virus 6 encephalitis)
- B02.0 (zoster encephalitis)
- G04.0 (acute disseminated encephalitis and encephalomyelitis)
- G04.81 (other encephalitis and encephalomyelitis)
- G04.9 (encephalitis and encephalomyelitis, unspecified)

Patients with final diagnoses of acute meningoencephalitis and those with other known neurologic conditions were excluded. A total enumeration of cases was done.

Upon the approval of the Makati Medical Center Institutional Review Board (IRB), a list of eligible patients was obtained from the medical records, admission census of the department of Pediatrics during the stated years, as well as from the records of pediatric infectious disease specialists and neurologists. A full medical chart review of eligible subjects was done and retrieved via the ArchiveOne database and electronic medical records (EMR) system. A patient data sheet was used for each eligible subject in acquiring the required information.

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Continuous data which follows the normal distribution were summarized using mean and standard deviation while non-Gaussian variables were reported as median and range. Categorical variables were reported as frequency and proportion. Missing values were not imputed. STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

Operational Definition of Terms

1. Acute Encephalitis – acute onset of any changes in mental status (such as confusion, disorientation, coma, inability to talk, increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness), and/or new onset of seizures (excluding simple febrile seizures), with or without acute onset or a recent history of fever.
2. Etiology – primary cause identified, based on ancillaries done, and classified as either infectious or immune-mediated
   2a. Infectious – includes all viral, bacterial, fungal, and parasitic causes
   2b. Immune mediated – may be autoimmune in nature, e.g., anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, acute disseminated encephalomyelitis
      2b.1 Laboratory confirmed anti-NMDAR encephalitis – patients with anti-NMDAR antibody detected on CSF
      2b.2 Possible anti-NMDAR encephalitis – patients who were still diagnosed with anti-NMDAR encephalitis, with no detection of CSF anti-NMDAR antibody done or with negative results but still presented with either or combination of the following: rapid onset of abnormal behavior, psychiatric symptoms, cognitive or speech dysfunction, seizures, dyskinesias or movement disorders, autonomic dysfunction or with ovarian tumors detected
3. Nutritional status – based on subject's body mass index (weight in kilograms divided by height in meters squared) on admission
4. Hospital stay – length of the patient's stay in the hospital in terms of number of days from the date of admission until the date of discharge
5. Outcome – clinical state of the patient at the time of discharge
   5a. Complete recovery – complete resolution of presenting symptoms
   5b. Partial recovery – partial resolution of presenting symptoms or those still with neurologic deficits or neurologic sequelae
   5c. Mortality

Ethical Considerations

This study was conducted upon the approval of the Makati Medical Center Institutional Review Board (IRB).

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Patient confidentiality and anonymity was strictly observed throughout the entire duration of the study in compliance with the Data Privacy Act of 2012 (Republic Act 10173). A waiver of informed consent was requested and granted by the IRB as the study was done via chart review only. There was no direct contact involved with eligible subjects. No disclosure was done by the authors, nor any potential conflict of interest identified.

RESULTS

A total of 23 patients admitted in an urban tertiary hospital from January 2010 to December 2020 were diagnosed with encephalitis. All etiologies were included and further classified as infectious or immune-mediated.

Table 1. Infectious Etiology of Pediatric Encephalitis

Identified Infectious Etiology	Frequency (n=14)	%	
		All (23)	Infectious (14)
Unspecified viral	4	17.39	28.57
Mycoplasma	4	17.39	28.57
Dengue	2	8.70	14.29
Varicella	1	4.35	7.14
Herpes Simplex Virus (HSV)	1	4.35	7.14
Measles	1	4.35	7.14
Enterovirus	1	4.35	7.14

Table 2. Immune-mediated Pediatric Encephalitis

Identified Immune-mediated Etiology	Frequency (n=9)	%	
		All (23)	Immune mediated (9)
Anti-NMDA receptor encephalitis	8	34.78	88.89
• Possible	5	21.74	55.56
• Laboratory confirmed	3	13.04	33.33
Autoimmune (Unspecified)	1	4.35	11.11

Fourteen patients were classified as infectious (60.87%) and nine were of immune-mediated etiology (39.13%). Encephalitis with a viral etiology occurred in the majority (10 in 14) of the cases reviewed and four of which had no specific cause identified but with CSF findings suggestive of viral encephalitis (e.g., normal to elevated WBC count, normal to elevated protein, normal CSF/serum glucose ratio) and bacterial cultures were negative. However, among all infectious cases with an identified causative agent, *M. pneumoniae* was the determined cause in 4 of the 14 cases (28.57%). Table 2 shows the cases of immune-mediated encephalitis and eight out of nine were managed as anti-N-methyl D aspartate receptor (anti-NMDAR) encephalitis – five of which were considered as possible cases while three cases were laboratory confirmed with anti-NMDAR antibody detected on their CSF.

Table 3. Age and Sex Distribution of Pediatric Encephalitis Patients

Parameter	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Median (Range); Frequency (%)		
Age (years)	12 (1–17)	9.5 (1–17)	13 (4–15)
1-5	8 (34.78)	5 (35.71)	3 (33.33)
6-10	3 (13.04)	2 (14.29)	1 (11.11)
11-15	9 (39.13)	4 (28.57)	5 (55.56)
16-17	3 (13.04)	3 (21.43)	0 (0)
Sex			
Male	14 (60.87)	10 (71.43)	4 (44.44)
Female	9 (39.13)	4 (28.57)	5 (55.56)

Overall, affected patients were from 1 to 17 years old, with the median age of 12 years old. Majority belongs to the 11-15 age group (39.13%) and followed by the 1-5 years age group (34.78%). Sixty-one percent were males, and they were mostly of the infectious type (71.43%). Infectious encephalitis was distributed among children aged 1-5 years old (35.71%) followed by the 11-15 years old age group (28.57%). On the other hand, immune-mediated encephalitis was observed to be more common among adolescents (11-15 years old) at 56% with slight female preponderance (55.56%).

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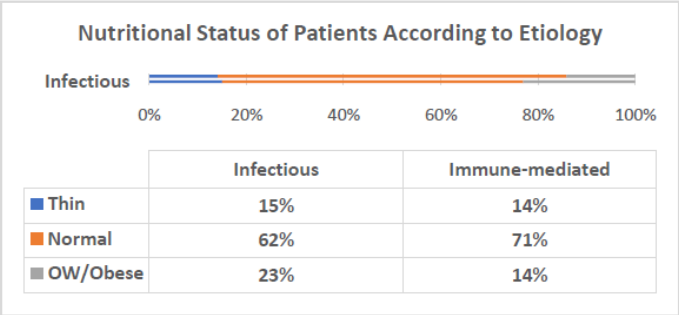
Table 4. Nutritional Status of Pediatric Encephalitis Patients



	Infectious	Immune-mediated
Thin	15%	14%
Normal	62%	71%
OW/Obese	23%	14%

The nutritional status of the patients was based on their body mass index (BMI) and interpreted in correlation with age. Normal BMI was observed in 62% and 71% of children with infectious and immune-mediated encephalitis, respectively. Twenty-three percent of children with infectious encephalitis were classified as either overweight or obese.

Table 5. Neurologic and Systemic Manifestations of Pediatric Encephalitis Patients

Manifestations	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Frequency (%)		
Neurologic manifestations	**23 (100)**	**14 (100)**	**9 (100)**
Altered mental status/ behavioral changes	17 (73.91)	8 (57.14)	9 (100)
Seizures	16 (69.57)	10 (71.43)	6 (66.67)
Headache	9 (39.13)	5 (35.71)	4 (44.44)
Dyskinesia (orofacial, limb)	3 (13.04)	0 (0)	3 (33.33)
Insomnia	2 (8.69)	0 (0)	2 (22.22)
Gen. body weakness	2 (8.69)	1 (7.14)	1 (11.11)
Systemic manifestations	**20 (86.96)**	**14 (100)**	**6 (66.67)**
Fever	18 (78.26)	13 (92.86)	5 (55.56)
Vomiting	10 (43.48)	8 (57.14)	2 (22.22)
Respiratory symptoms	9 (39.13)	6 (42.86)	3 (33.33)
Rashes	4 (17.39)	4 (28.57)	0 (0)
Abdominal pain	2 (8.7)	2 (14.29)	0 (0)
Loose stools	2 (8.7)	2 (14.29)	0 (0)

Table 5 shows the frequency of the neurologic, as well as systemic manifestations of pediatric encephalitis observed in this study. The most common neurologic manifestation was altered mental status and/or behavioral changes (73.91%). All patients with immune-mediated encephalitis presented with behavioral changes. Seizures were seen in almost 70% of patients, and this was noted in majority of the infectious cases (71.43%).

Common systemic manifestations were fever (78.26%), vomiting (43.48%), and respiratory symptoms (39.13%). All patients with the infectious type and more than half of the immune-mediated cases (6 out of 9) presented with systemic symptoms. Fever remained to be the most common on both groups. Two anti-NMDAR encephalitis patients had adnexal tumors detected upon further work up during admission.

The duration of symptoms prior to admission ranges from less than a day (18 hours) to 270 days, with a median duration of symptoms prior to admission was eight days. Patients of the infectious type had a median duration of six days of symptoms prior to admission while those of the immune-mediated type had thirty days.

Table 6. CSF Analysis of Pediatric Encephalitis Patients

Parameter	All	Classification of etiology	
		Infectious	Immune-mediated
	Frequency (%)		
WBC count	[n=21]	[n=12]	[n=9]
Normal	12 (57.14)	8 (66.67)	4 (44.44)
High	9 (42.86)	4 (33.33)	5 (55.56)
Lymphocyte predominance	4 (44.44)	2 (50)	2 (40)
Segmenter predominance	2 (22.22)	1 (25)	1 (20)
Unspecified	3 (33.33)	1 (25)	2 (40)
Glucose	[n=20]	[n=11]	[n=9]
Normal	15 (75)	9 (81.82)	6 (66.67)
Low	4 (20)	1 (9.09)	3 (33.33)
Slightly low	1 (5)	1 (9.09)	0 (0)
Protein	[n=20]	[n=11]	[n=9]
Normal	13 (65)	7 (63.64)	6 (66.67)
High	4 (20)	3 (27.27)	1 (11.11)
Low	3 (15)	1 (9.09)	2 (22.22)
Culture/Viral Studies			
HSV 1&2 Positive	1 (6.67)	1 (12.50)	0 (0)
Enterovirus Positive	1 (14.29)	1 (20)	0 (0)
Antibodies (PCR)			
Anti NMDA (+)	3 (13.04)	0 (0)	3 (33.33)
Dengue IgG (+), IgM (-)	1 (4.35)	1 (7.14)	0 (0)

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Out of the twenty-three subjects, only twenty-one had CSF analysis done. Those two patients who did not have lumbar tap had contraindications such as disseminated cutaneous lesions even on puncture site (Varicella) and hemodynamic instability with high risk for bleeding and coagulopathy (Dengue shock syndrome). As seen in Table 6, WBC count was normal in more than half of the patients (57.14%). Among the infectious group, pleocytosis was only observed in four patients who had Herpes simplex virus (HSV), enterovirus, dengue and one unidentified viral etiology. Fifty-six percent of the immune-mediated encephalitis had elevated WBC count. There was no significant shift in the levels of CSF glucose and protein for both groups and were normal at 75% and 65%, respectively.

Among those with specified causes, three infectious cases were determined via CSF viral studies, particularly HSV, Enterovirus (viral DNA/RNA PCR) and Dengue (antibody) while three subjects were confirmed to be anti-NMDA receptor encephalitis by the presence of anti-NMDAR antibodies in their CSF samples. Infectious causes and metabolic disturbances were ruled out among those with immune-mediated cases prior to diagnosis.

Table 7. Serology, Neuroimaging and Electroencephalography of Pediatric Encephalitis Patients

Diagnostics	All	Classification of etiology	
		Infectious	Immune-mediated
	Frequency (%)		
Serology			
Dengue NS1 Antigen (+)	1 (4.35)	1 (7.14)	0 (0)
Dengue IgM & IgG Antibody (+)	1 (4.35)	1 (7.14)	0 (0)
Mycoplasma IgM Antibody (+)	4 (17.39)	4 (28.57)	0 (0)
Neuroimaging			
CT scan	[n=6]	[n=4]	[n=2]
Normal	5 (83.33)	3 (75)	2 (100)
Pertinent findings	1 (16.67)	1 (25)	0 (0)
MRI	[n=19]	[n=11]	[n=8]
Normal	5 (26.32)	3 (27.27)	2 (25)
Pertinent findings	14 (73.68)	8 (72.73)	6 (75)
Electroencephalography	[n=17]	[n=9]	[n=8]
Normal	4 (23.53)	3 (33.33)	1 (12.50)
Abnormal	13 (76.47)	6 (66.67)	7 (87.50)

The remaining identified cases tested positive for serum Mycoplasma IgM (17.39%) and Dengue NS1 antigen (4.35%). The patient who had Dengue antibody detected on CSF was also positive with serum Dengue antibodies (IgM and IgG).

In terms of neuroimaging done, 83.33% had normal plain cranial CT scan while among those who had MRI of the brain, 73.68% had intracranial changes such as diffuse leptomeningeal enhancement of the cerebral hemispheres, diffuse cortical thickening, ill-defined diffuse symmetric abnormal signals in the bilateral cerebral white matter on T2W and FLAIR sequence, nonspecific non-enhancing punctate FLAIR hyperintensities in the right frontal white matter, bilateral ventricular dilatation, etc. Among those seventeen patients who had electroencephalography (EEG) done, abnormal results were observed in 13 patients (76.47%). Among those with immune-mediated encephalitis, 87.5% of them showed diffuse slowing of background activity, specifically in the theta-delta range.

Table 8. Medical Management of Pediatric Encephalitis Patients

Medical Management	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Frequency (%)		
Antibiotics	18 (78.26)	14 (100)	4 (44.44)
Anticonvulsant therapy	18 (78.26)	11 (78.57)	7 (77.78)
Steroids	10 (43.48)	1 (7.14)	9 (100)
Antiviral therapy	5 (21.74)	5 (35.71)	0 (0)
IVIG	5 (21.74)	0 (0)	5 (55.56)
Immunosuppressant	2 (8.7)	0 (0)	2 (22.22)
Monoclonal antibodies	1 (4.35)	0 (0)	1 (11.11)
Others (anti-psychotics, tranquilizers)	8 (34.78)	4 (28.57)	4 (44.44)

The most common medical treatments given for pediatric encephalitis were antibiotics (78.26%), anticonvulsant therapy (78.26%), and steroids (43.48%). Acyclovir was given in five patients (21.74%) upon the establishment of the diagnosis of a viral etiology. All of the patients with immune-mediated encephalitis were managed with steroids (high dose methylprednisolone for 3-5 days) and 55.56% also received intravenous immunoglobulin (IVIG).

Table 9. Length of hospital stay and Outcome of Pediatric Encephalitis Patients

Parameter	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Median (Range); Frequency (%)		
Length of hospital stay (days)	13 (4 – 79)	12 (4 – 79)	17 (6 – 41)
Outcome at time of discharge			
Complete recovery	13 (56.52)	11 (78.57)	2 (22.22)
Partial recovery	9 (39.13)	3 (21.43)	6 (66.67)
Mortality	1 (4.35)	0 (0)	1 (11.11)

The overall median duration of hospital stay was 13 days (4 to 79 days), 12 days (4 to 79 days) in infectious type and 17 days (6 to 41 days) in immune-mediated type. Complete recovery was seen in more than half of all patients (56.52%). Among those with the infectious etiology, complete recovery was seen in 78.57%. Partial recovery, defined as those with partial resolution of presenting symptoms or those still with neurologic deficits or neurologic sequelae (such as improving motor strength of extremities, minimal orofacial and/or limb dyskinesia) at the time of discharge, was noted in nine patients overall (39.13%) and six (66.67%) of which were of the immune-mediated type. However, two of these patients were transferred to another institution in the middle of their treatment. There was one mortality, who was diagnosed with an immune-mediated acute encephalitis.

DISCUSSION

This retrospective study determined the clinico-epidemiologic profile of pediatric encephalitis patients in an urban tertiary hospital. More than half of the patients had an infectious etiology, and among which, 28.57% still remained to be of unknown specific viral cause.

Identified etiologies included *Mycoplasma pneumoniae* (n=4, 28.57%), Dengue virus (n=2, 14.29%), and one case each of HSV, varicella, measles and enterovirus. On the other hand, 39.13% were classified as immune-mediated encephalitis, and eight out of these nine subjects (88.89%) were managed as anti-NMDAR encephalitis. Although the majority of the immune-mediated encephalitis patients were not confirmed cases with the presence of CSF anti-NMDA receptor antibody, (test was not available in earlier years), three cases were found to have anti- NMDA receptor antibody in the CSF.

In general, the patients affected in this study ranged from 1 to 17 years old, with a median age of 12 years, and mainly involved two age groups: 1-5 years old (34.78%) and 11-15 years old (39.13%). A plurality of them were males (60.87%). Similar to a local study on acute viral encephalitis among pediatric patients in a tertiary government hospital by Alcaraz, et. al in 2016, wherein bulk of the cases were noted in the 1-4 years age group with male predominance, the infectious encephalitis subjects in this study were mostly males (71.43%) aged 1-5 years old (35.71%) and 11-15 years old (28.57%).[9] On the contrary, immune-mediated encephalitis were observed more commonly among adolescents aged 11-15 years old (55.56%), with a slight female preponderance (55.56%). In a study done in Texas in 2020, male children were noted to more likely have infectious encephalitis, whereas female children present with an autoimmune etiology (58% vs. 34%). Also, the proportion of autoimmune cases relative to the infectious type increases with age.[10]

Infectious encephalitis patients had a relatively shorter median duration of symptoms prior to admission (6 days) as compared to the immune-mediated group (30 days). This may be due to the finding that patients with the infectious type usually presented with both systemic and neurologic symptoms almost always simultaneously prompting a more immediate consult.

On the other hand, the immune-mediated cases also presented with nonspecific but mostly mild systemic manifestations such as fever, vomiting and respiratory symptoms, described to be the prodromal phase in cases of anti-NMDAR encephalitis by Peery, et. al.[11]

The most prominent neurologic manifestation among these patients was the acute or subacute onset of behavioral changes in an apparently well child such as aggressiveness, violent behaviors, restlessness, hallucinations and insomnia. Due to the psychotic symptoms, three of these patients had psychiatric consult initially prior to the work up for encephalitis. This could have been one of the reasons for the delay in the admission and diagnosis. Hence, it is important to rule out organic pathology first prior to considering psychiatric disorders.

Several mechanisms of injury of the central nervous system were proposed to explain the onset of these neurologic symptoms, depending on its etiology. Parenchymal destruction, including direct neuronal and glial invasion with apoptosis, as well as mechanical and vascular injuries, such as vascular occlusion leading to infarction and secondary effects of cerebral edema, were associated with cases of direct infections to the central nervous system (CNS) as well as para-infectious processes. On the other hand, immune-mediated mechanisms, such as cytotoxic antibodies causing apoptosis and impaired neuronal function and cytokine effects, are observed in autoimmune encephalitis.[8]

Clinically, infectious and immune-mediated encephalitis have a substantial overlap in presentation. As based on the International Encephalitis Consortium's diagnostic criteria for encephalitis of presumed infectious or autoimmune etiology, all the subjects included in this study presented with neurologic dysfunction, such as altered mental status, new onset of seizures and/or focal neurologic symptoms, for at least 24 hours, with no alternative cause identified.[12] Altered mental status and/or behavioral changes was the most common CNS manifestation (73.91%). All immune-mediated encephalitis patients presented with behavioral changes.

Majority of the infectious cases (71.43%) manifested with seizures – mostly were characterized as generalized tonic-clonic, but focal seizures were also noted. One patient with dengue encephalitis also presented as status epilepticus.

Fever was still the most common systemic symptom observed overall, as well as for either group. Some physical findings could help in providing clues in the identification of the specific etiology. The characteristics of the generalized cutaneous lesions present in four patients were distinctive to their respective infectious cause – papulovesicular lesions seen on the subject who had fulminant varicella with encephalitis, petechial rashes in one case of dengue encephalitis, maculopapular rashes with cephalocaudal distribution in the case of measles encephalitis, and macular rashes on the patient who had enteroviral encephalitis. There were no other lesions observed for the remaining infectious causes or for those who had the immune-mediated type.

CSF analysis was nonspecific in this study in terms of presence of pleocytosis and alterations in the levels of glucose and protein, hence, a normal CSF WBC count, glucose and protein levels may not totally rule out encephalitis. In a study on viral encephalitis by Chaudhuri, it was pointed that although CSF abnormalities may support the diagnosis, some changes may be nonspecific and may seem to be not helpful in determining the specific etiology. Also, it is important to emphasize the importance of observing proper handling, transport and storage of the CSF samples to be used, as well as the timing of the lumbar puncture, as these may affect the results as well.[13]

Serologic testing for serum antigen and antibodies, in correlation with the clinical presentation, has been very helpful in the etiologic identification among the subjects in this study. All the cases of Mycoplasma encephalitis were diagnosed with the evidence of a positive serum IgM (enzyme immunoassay) during the course of the illness.

Due to the low yield of positive CSF PCR results for *Mycoplasma pneumoniae,* Christie, et al. defined *M. pneumoniae*-associated encephalitis as any patient with the presence of acute *M. pneumoniae* infection by a positive IgM, a significant rise in IgG titers between acute and convalescent specimens, or a positive respiratory or CSF PCR.[14]

Neuroimaging can be a helpful tool in the diagnosis of pediatric encephalitis and to exclude other possible neurologic conditions. MRI is more sensitive and provides more details. Six out of twenty-three patients had CT scan done and five of which (83.33%) were normal. MRI was done in 19 patients and 14 (73.68%) had pertinent findings, however, mostly were non-specific. There were no specific imaging findings identified that were correlated to their respective etiology. Three subjects had both neuroimaging done and their CT scans were all normal but had significant findings on MRI – one case of autoimmune encephalitis had abnormal enhancements along both cerebral sulci, sylvian fissures, suprasellar cistern and prepontine cistern; second case is a confirmed case of anti-NMDAR encephalitis with focal encephalitis on the right posterior temporal and adjacent parieto-occipital area; and the last case was a case of Mycoplasma associated encephalitis which showed some spectroscopic signs of slight neuronal loss in both medial temporal lobes. In cases wherein intracranial infections such as encephalitis are highly suspected, cranial MRI with or without contrast would be a reasonable first-line imaging since it will provide more detailed findings. However, Fraley, et al. pointed out that CT scan without contrast is recommended as a first line study among pediatric patients presenting with acute change in mental status and suspected intracranial infections since this can promptly exclude other acute neurosurgical emergencies.[16] If further evaluation is needed and neurologic deficits seems to be unexplained by CT scan, MRI would be a useful tool.

Certain patterns in neuroimaging may also be helpful in differentiating etiologies of encephalitis, although these may not be specific and exclusive, hence, it is still important that interpretation should always be done in correlation with each patient's history and clinical presentation.[16]

Among those patients wherein an electroencephalogram (EEG) was done, abnormal results were seen in 66.67% of infectious cases and 87.5% of the immune-mediated type. Majority showed diffuse slowing of background activity, specifically in the theta-delta range among the immune-mediated cases as well as involvement of multiple lobes. This was also comparable with the EEG findings of anti-NMDAR encephalitis as described by Peery, et al.[11] Although EEG is a sensitive and an accessible diagnostic tool for the evaluation of CNS function, most patients with encephalitis will have abnormal results and most of the abnormalities noted are non-specific. Therefore, it would be reasonable to seek advice from pediatric neurology specialists regarding the use of EEG for a particular patient.[16]

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is an autoimmune disease mediated by antibodies against the GluN1 subunit of the NMDA receptor, characterized by a complex neuropsychiatric syndrome.[17] Eight out of nine subjects with immune-mediated encephalitis in this study were managed as anti-NMDAR encephalitis, with three cases confirmed with the detection of anti-NMDAR antibodies in their CSF. Graus, et al. emphasizes that the absence of auto-antibodies does not totally rule out an immune-mediated process and a positive test may not always imply an accurate diagnosis.[15] Behavioral changes were the most prominent presentation observed among all classified as immune-mediated during the time of admission.

Almost all showed psychotic symptoms, such as auditory and visual hallucinations, aggressive episodes, violent behaviors, flighty speech, and either excessive nonsense talking or decreased verbal output. Majority of these patients initially presented with inability to focus and concentrate, e.g., in school activities, confusion, restlessness and insomnia prior to the psychotic symptoms. One confirmed anti-NMDAR encephalitis subject from the younger age group (4-year-old female) was described to have behavioral regression to a 1-year old, with no verbal output and regard, as well as bladder and bowel incontinence, with slight central "atrophic" changes in the brain and spectroscopic findings of minimal "neuronal loss" in medial temporal lobes seen on the cranial MRI. Orofacial and limb dyskinesia were also observed in three patients, and two of which were confirmed cases. Facial dyskinesias and abnormal limb movements are frequently seen in cases of anti-NMDAR encephalitis and may also serve as vital clues in the recognition of the disease, particularly if associated with other symptoms such as behavioral changes.[17] Peery, et al. elaborated that anti-NMDAR encephalitis, in its fulminant form, manifests with a prodromal phase which was characterized by nonspecific systemic symptoms. This is then followed by other phases – psychotic (emotional and behavioral disturbances, psychosis, delusions, hallucinations, decreased cognitive skills, difficulty speaking, and agitation) and/or seizure phase (commonly generalized tonic-clonic in character), unresponsive phase (may seem to be mute or akinetic), and hyperkinetic phase.[11] In all of these cases, infectious causes and metabolic disturbances were all ruled out before the diagnosis that is immune-mediated in nature was made.

Previous studies emphasized the association of an underlying ovarian tumor among female patients with anti-NMDAR encephalitis.

In this study, two anti-NMDAR cases, one of which was laboratory confirmed, also had adnexal tumors – a right ovarian hemangioma on biopsy after exploratory laparotomy and oophorectomy in a 13-year old subject, while the other was considered to be an ovarian teratoma in nature in a 14-year old patient, based on its characteristics on whole abdominal CT scan, however biopsy for confirmation was not done since she was transferred to another institution for continuation of management.

Dalmau, et al. pointed out that even though the presence of tumors, specifically those expressing NMDA receptors, precipitates the breaking of immune tolerance, there still seem to be other immunologic triggers that are involved.[18] The presence of an underlying tumor is not a requirement in the clinical presentation especially in the pediatric age group. Furthermore, tumor association appears to be inversely related to age and tends to be more common among adult cases.[11] However, screening for adnexal masses in suspected cases of anti-NMDAR encephalitis particularly in older children and adolescents may assist in establishing the diagnosis.

***Mycoplasma pneumoniae* encephalitis**

Mycoplasma pneumoniae is a known respiratory pathogen, however extrapulmonary complications are not that rare as well, occurring between 5-10% of hospitalized patients. The incidence of *Mycoplasma pneumoniae*-associated encephalitis is predominantly in the pediatric age group.[14] The age of the affected patients in this study ranged from 1 to 13 years old, with no gender predominance. Among those with identified infectious etiology in this study, *Mycoplasma pneumoniae* was the most common at 28.57%, whom all tested positive for serum Mycoplasma IgM. All these four patients presented with seizures responsive to anti-convulsant medications, such as diazepam, levetiracetam and phenobarbital.

Although respiratory symptoms are the most common presentation of typical *M. pneumoniae* infections and that the respiratory tract seems to be the most common entry site, systemic symptoms observed among these patients were non-specific – with fever and gastrointestinal symptoms seen in three patients, and respiratory symptoms noted only in two cases. Interestingly, this finding was consistent with other studies, in that respiratory symptoms tend to be less common in neuro-invasive cases of Mycoplasma infections.[14] There was also no other extrapulmonary (e.g., mucocutaneous) manifestations observed among these patients.

There were no specific changes found on neuroimaging and EEG that were common among all the cases. Cranial MRI showed diffuse cortical thickening with increased signal intensity on multiple lobes, intense gyri form restricted diffusion signals and cortical swelling with T2W/FLAIR hyperintense signals, and slight neuronal loss.

EEG changes include poorly organized bilateral theta-delta slowing of background activity and slowing with sharp epileptiform activities. One patient had normal MRI and EEG. The most common medical treatment given to the subjects were broad spectrum antibiotics (78.26%), such as third generation cephalosporins (ceftriaxone), which was given empirically mainly because of the overlap clinically of encephalitis with bacterial meningitis. Macrolides, like azithromycin and clarithromycin, were given to all the patients diagnosed with *Mycoplasma pneumoniae*-associated encephalitis. Anticonvulsant therapy (78.26%) was given to all patients who presented with seizures and majority were well-controlled. The therapeutic goal is the modulation of the body's immune response.[16] All patients with immune-mediated encephalitis were managed with steroids, specifically high dose methylprednisolone and 55.56% also received intravenous immunoglobulin (IVIG). Due to the behavioral disturbances such as agitation and aggressive episodes seen in some patients, they were also given anti-psychotics and tranquilizers (35%).

The overall median duration of hospital stay was 13 days (4 to 79 days) and was observed to be shorter (12 days) among the infectious type compared to the immune-mediated cases (17 days). Prognosis was relatively good as observed in this study with more than half of the subjects had complete recovery prior to discharge (56.52%). In terms of outcomes, majority of the infectious cases in this study had complete recovery. There were nine patients (39.13%) who had partial resolution of neurologic symptoms and six of them were classified as immune-mediated.

Fraley, et al. emphasized that in autoimmune cases, the recovery time may be prolonged and may take weeks from the time of clinical presentation to signs of improvement.[16] The case of HSV encephalitis developed central respiratory failure as a complication, with tracheostomy done eventually. The patient was on rehabilitation therapy upon discharge. The patient with acute enteroviral encephalitis had upper and lower motor deficits, who was improving with physical and occupational therapy, however was transferred to another institution. There was one mortality noted in this study who had an immune-mediated type of encephalitis. The said patient expired due to nosocomial complications.

CONCLUSION

Encephalitis should be considered among patients who present with acute onset of neurologic symptoms such as seizures, alteration in mental status, with or without systemic symptoms. Behavioral changes in an apparently well child, such as clinical symptoms of aggressiveness, violent behaviors, restlessness, hallucinations, and insomnia, should prompt clinicians to consider encephalitis, specifically anti-NMDAR encephalitis. This is particularly important if the viral studies are negative and there is no other determined cause to explain the behaviors. It is also imperative to rule out organic pathology first prior to considering psychiatric disorders.

Although viral etiologic agents remain to be the most common cause of encephalitis, other possible etiologies should be highly considered, such as *Mycoplasma pneumoniae* and immune-mediated causes, with anti-NMDAR encephalitis being the most common. Infectious encephalitis was observed to be more common among males in the younger age group. Immune-mediated encephalitis was noted to affect female adolescents more.

A complete work-up such as CSF analysis, culture/viral studies, serologic testing, neuroimaging and electroencephalogram are of significant help in establishing the diagnosis of encephalitis and more importantly, in the determination of its etiology. However, a normal CSF analysis, imaging and/or EEG may not totally exclude encephalitis. Cranial MRI is more helpful in the detection of changes in the brain. Prognosis is relatively good, however, full recovery among immune-mediated encephalitis patients may take time. A prompt diagnosis and early initiation of appropriate management leads to a good outcome and further complications and permanent neurologic sequelae may be avoided.

RECOMMENDATIONS

A larger population of pediatric encephalitis, covering both infectious and immune-mediated type, or a multi-center study are recommended for future studies to further describe its clinical and epidemiologic profile. Geographic location, travel history, ethnicity, as well as immunization history may be included as factors to be reviewed among these patients and evaluate if these may contribute to etiology identification.

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