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Compliance with international guidelines in adults with encephalitis

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ABSTRACT

Background: Encephalitis is associated with significant neurological disability and mortality. Many guidelines are published for encephalitis management but compliance with them is unknown.

Objectives: To evaluate the appropriate management and compliance to the current guidelines in adults with encephalitis.

Study design: A retrospective multicenter study at 17 hospitals in the Greater Houston area from August 1, 2008 through September 30, 2017. All cases met the definition for possible or probable encephalitis as per the international encephalitis consortium guidelines.

Results: A total of 241 adults (age >17 years) with encephalitis were enrolled. The most common etiologies were unknown (41.9%), viral (27.8%) and autoimmune (21.2%). An adverse clinical outcome was seen in 49% with 12.4% in hospital mortality. A high compliance with guidelines (>90%) was only seen in obtaining a brain computerized tomography (CT) scan, blood cultures and cerebrospinal fluid (CSF) gram stain and culture. An HSV polymerase chain reaction (PCR) was done in 84% and only repeated in 14.2% of patients with an initial negative result. Furthermore, only two-thirds of patients were started empirically on intravenous acyclovir and antibiotics. Evaluation for other etiologies were not uniformly performed: arboviral serologies (57.3%), CSF anti-N-Methyl-D-Aspartate Receptor (NMDA) receptor antibody (35.7%), and CSF varicella zoster virus (VZV) PCR (32%). The highest yield for the tests were arboviral serologies (42%), anti-NMDA antibodies (41.2%) and VZV PCR (16.4%).

Conclusion: The management of encephalitis as per current guidelines is suboptimal leading to underutilization of currently available diagnostic tests and empirical therapy.

1. Introduction

1.1. Background

Encephalitis is an inflammatory process of the brain associated with mortality ranging between 4–36% of patients depending on the etiological agent, country of the study, immunosuppression, and inclusion of adults or children or both [1,2]. Furthermore, up to two-thirds of survivors from viral encephalitis (Herpes simplex virus, Japanese encephalitis, West Nile virus) have neurological and/or neurocognitive sequelae [3–5]. The incidence of encephalitis varies by country between 0.4–16 cases per 100,000 persons [2]. Infections and autoimmune etiologies are considered to be the most important causes of encephalitis representing approximately 40% and 20%, respectively when systematically evaluated [1]. However, between 37–80% of encephalitis cases remain with unknown etiologies [2,6–8]. In the past, brain biopsy was the gold standard for diagnostic method for encephalitis but currently it is infrequently done as less invasive and highly sensitive diagnostic tools such as polymerase chain reaction (PCR) for viruses in the cerebrospinal fluid (CSF) was introduced [9]. The variability in the proportion of unknown etiologies between studies is most likely driven by the availability and use of molecular diagnostic techniques, and testing for arboviral serologies and autoimmune etiologies [10].

In this study, we are evaluating the work up, management and outcome of 241 adults with encephalitis based on the majority of current guidelines recommendations in literature [11–14]. To our knowledge, this is the first study evaluating the compliance to the current guidelines in adults with encephalitis.

2. Methods

2.1. Ethical consideration

The study was approved by the UT Health Committee for the
Protection of Human Subjects, by the Memorial Hermann Hospital Research Review Committee and the Harris Health Research Committee.

2.2. Study design

We conducted a retrospective study of 241 adults with a diagnosis of encephalitis. The study was collected from 17 hospitals from the Memorial Hermann Health (MHH) System and Harris Health System (HHS) in the Greater Houston area between August of 2008 and September of 2017. Primary outcome of the study was assessing encephalitis management and compliance to current guidelines in our population. As summarized in (Supplemental Digital Content – Table 1), all guidelines of encephalitis management have major parts in evaluating and managing patients with encephalitis; exposure evaluation, appropriate utilization of diagnostic and neurodiagnostic studies, and proportion and timing of empirical antibiotic and antiviral therapy [11–15]. In our study, we followed these major parts and compared them with our population.

2.3. Case definition and diagnostic criteria

As per IEC guidelines, an encephalitis case was determined by the presence of the major criterion (presentation of altered mental status without alternative cause lasting more than 24 h) and at least 2 minor criteria: a. fever 72 h before or after presentation, b. new onset seizures, c. new onset focal neurological findings, d. white blood cell count >5 mm³ in the cerebrospinal fluid (CSF), e. new neuroimaging findings, f. abnormal electroencephalogram consistent with encephalitis. Case outcomes were defined using the Glasgow Outcome Scale (GOS), where, 5 is considered a good recovery, 4 being consistent with moderate disability, 3 with severe disability, 2 with a vegetative state, and 1 with death. Anything that was scored as a 4 or less was defined as an adverse clinical outcome (ACO) [16].

Herpes viral infections (HSV, VZV, CMV and EBV) were identified by CSF polymerase chain reaction (PCR). Arboviral diseases were diagnosed via a panel of testing that included immunoglobulin M (IgM) for St. Louis encephalitis virus, Eastern equine encephalitis virus, Venezuelan equine encephalitis virus, La Crosse virus, and West Nile virus. Bacterial diseases were identified either through CSF culture or via relevant serological testing (IgM) for Rickettsia, Brucella and Mycoplasma. Fungal infections were identified by CSF culture or CSF antigen. Parasitic infections were identified by microscopic examination of brain tissues or CSF antigen. Patients were considered positive for autoimmune encephalitis if the CSF antibody test was present in an abnormal range in the absence of any other identified cause of encephalitis and presence of current autoimmune disease such as Hashimoto thyroiditis. Also positive CSF antibodies for N-methyl-D-aspartate (NMDA) or voltage - gated potassium channel (VGKC) defined as autoimmune encephalitis.

2.4. Data collection

Medical records were reviewed independently by two physicians and all cases met the definition for possible or probable encephalitis as per the international encephalitis consortium (IEC) guidelines [14]. Data extraction from the medical record was done utilizing a standardized form. Extracted data included information on demographics, clinical presentation, diagnostic testing, and treatment. All patients were assigned as infectious, autoimmune or idiopathic.
2.5. Sample size

A total of 1,241 patients were identified with an International classification of disease (ICD)-9 discharge diagnosis code of encephalitis. After review of the medical records, we excluded the following patients: did not have a central nervous system infection (n = 580), healthcare-associated ventriculitis or meningitis (n = 148), community-acquired bacterial meningitis (n = 101), aseptic meningitis (n = 72), fungal meningitis (n = 68), tuberculous meningitis (n = 25), parasitic infection (n = 3), and incomplete medical records (n = 3). Only 241 (19 %) met the definition of encephalitis.

2.6. Statistical analysis

Statistical analysis was performed with SPPS version 25 (IBM, Austin, TX, USA). Univariate analysis was performed using Fisher’s exact test, Chi square, and Student’s t-test as appropriate.

3. Results

3.1. Demographics and clinical presentation

The demographic and clinical characteristics are shown in (Table 2).

A total of 241 adults with encephalitis were enrolled. The median age was 49 years of age with the majority of patients being male (54 %), non-Caucasian (55.6 %), and with private insurance (61.4 %). During our study period, average Houston population was about 6,000,000 and the majority of Houston population were Hispanic (~41 %) followed by African American (~30.3 %) as reported by Texas Department of State Health Services. However, our study showed that African Americans (30.3 %) were disproportionately affected. A total of 68 patients (28 %) were immunocompromised with ~50 % of them being Human immunodeficiency virus (HIV) positive (n = 36), recent chemotherapy due to malignancy (n = 17), chronic immunosuppressive therapy due to autoimmune diseases (n = 13) and solid organ transplantation (n = 2). The median duration of symptoms prior to admission was 5 days. The most common presenting symptoms included fever, headache, photophobia, respiratory symptoms and nausea/vomiting. A high opening pressure (>20 cm H2O) was documented in 74 % of the patients with the most common clinical signs being focal neurological deficits (45.4 %), seizures (43.5 %), and obtundation (33 %). Coma (GCS < 8) and status epilepticus was seen in 20 % and 10 %, respectively.

3.2. Laboratory findings and etiologies

Laboratory findings and etiologies are summarized in (Table 3). The CSF profile consisted of a mild pleocytosis (median CSF serum WBC was 30 cells/mm3) with a lymphocytic predominance, a normal glucose and mildly elevated protein. The serum WBC count was 6,500 cells/mL with leukopenia and thrombocytopenia being documented in 7.5 % and 14.1 %, respectively.

In terms of etiology, the most common cause of encephalitis was idiopathic (41.9 %) followed by viral (27.8 %) and autoimmune (21.2 %). The most common causes of viral encephalitis were West Nile Virus (WNV) and Herpes Simplex Virus (HSV) were (42 %, 33 % respectively) followed by Varicella Zoster Virus (VZV) (16.4 %). The most common cause of autoimmune encephalitis was due to Anti-N-Methyl-D-Aspartate Receptor (41.2 %). Regarding bacterial etiologies, streptococci (Group A streptococcus, S. pneumoniae) and staphylococci (S. aureus) were the most common etiologies. Mycobacterium tuberculosis was seen in 4 patients. Toxoplasma gondii was the only parasite isolated in our population. Fungal etiology was not common in our study with total of three cases.

### Table 2

Baseline demographic and clinical presentation of 241 adult patients with encephalitis.

| Baseline demographic data | N (%) |
|---------------------------|-------|
| Age, median (IQR)         | 49 (33−63) |
| Male                      | 130/241 (54) |
| Race                      |         |
|   African American        | 73/241 (30.3) |
|   White                    | 58/241 (24.1) |
|   Hispanic                 | 52/241 (21.6) |
|   Unknown                  | 49/241 (20.3) |
|   Asian                    | 9/241 (3.7) |
| Insurance                  |         |
|   Private                  | 148/241 (61.4) |
|   Medicare                 | 52/241 (21.6) |
|   Uninsured                | 27/241 (11.2) |
|   Medicaid                 | 14/241 (5.8) |
| Immunocompromised          | 68/240 (28.3) |
| Days of illness prior to admission, median (IQR) | 5 (2−14) |
| IVDU                       | 5/194 (2.6) |
| Charlson scale, median (IQR) | 1 (0.4) |
| Clinical symptoms          |         |
|   Fever (>38.5 C)          | 143/236 (60.6) |
|   Photophobia              | 129/137 (94.2) |
|   Seizure                  | 104/239 (43.5) |
|   Headache                 | 86/170 (50.6) |
|   Respiratory symptoms     | 83/236 (35.2) |
|   Nausea/Vomiting          | 53/167 (31.7) |
|   Neck stiffness            | 18/137 (13.1) |
|   Skin rash                | 16/123 (13) |

**Clinical signs**
- Systolic blood pressure, median (IQR): 130 (109−145)
- Opening pressure > 20: 118/159 (74.2)
- Focal neurological deficit: 108/238 (45.4)
- GCS, median (IQR): 14 (10−15)
- GCS ≤ 13: 79/239 (33)
- Status epilepticus: 50/239 (21)
- Nuchal rigidity: 15/150 (10)

**Abbreviations:** IQR, interquartile range; IVDU, intravenous drug user; GCS, Glasgow Coma Scale.

### Table 3

| Clinical symptoms          | N (%) |
|---------------------------|-------|
| Fever (>38.5 C)           | 143/236 (60.6) |
| Photophobia               | 129/137 (94.2) |
| Seizure                   | 104/239 (43.5) |
| Headache                  | 86/170 (50.6) |
| Respiratory symptoms      | 83/236 (35.2) |
| Nausea/Vomiting           | 53/167 (31.7) |
| Neck stiffness             | 18/137 (13.1) |
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### Table 4

**Comparisons using Fisher’s exact test, Chi square, and Student’s t-test as appropriate.**

| Variable | p-value |
|----------|---------|
| Human immunodeficiency virus (HIV) positive (n=36), recent chemotherapy due to malignancy (n=17), chronic immunosuppressive therapy due to autoimmune diseases (n=13) and solid organ transplantation (n=2). |     |
| Seizure within one week of the presentation. |     |
| Respiratory symptoms such as dyspnea, cough, rhinorrhea or sore throat. |     |
| Vesicular or petechial rash. |     |
| It includes dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift. |     |

### 3.3. Exposure evaluation and diagnostic studies

The Infectious Disease Society of America (IDSA), British, Australian, International consortium, and French guidelines recommend that clinicians evaluate for potential exposures and risk factors and to perform appropriate utilization of diagnostic studies in patients with suspected encephalitis. As shown in (Table 4), we found poor documents of exposure risk factors in patients' medical charts. For example, high-risk sexual activity, recent travel history and occupational history was documented in about 30 %, 15 %, and 12.4 % of patients, respectively. All other exposure risk factors (e.g., insect, animal or, ill contact, fresh water exposure or recent vaccination history) were infrequently documented. Although exposure and risk factors were poorly documented, most of them were had high yield results.

As shown in (Table 4), the utilization of diagnostic studies was variable. Most of patients had chest X-ray and blood culture (95 %, 92.9 % respectively). Other diagnostic tests were variable such as testing for HIV (77.2 %), arbovirus (57.3 %), syphilis (49.4 %), and for mycobacterial (sputum AFB culture) or fungal etiologies (Histoplasma
Lab evaluations and etiologies of encephalitis in 241 adult patients with encephalitis.

| Laboratory findings                                      | N (%)         |
|-----------------------------------------------------------|---------------|
| Serum WBC, median, (range)a                               | 6500 (1300–43500) |
| Serum glucose, median, mg/dl, (range)                     | 110 (59–609)  |
| CSF WBC, median, cells/mm³, (range)                       | 30 (0–2500)   |
| CSF lymphocyte percent (range)                            | 83 (0–100)    |
| CSF protein, median, mg/dl, (range)                       | 76 (19–939)   |
| CSF glucose, median, mg/dl, (range)                       | 60 (1–253)    |
| Leukopeniaa                                              | 18 (7.5)      |
| Thrombocytopeniaa                                         | 34 (14.1)     |

Etiologies

- Idiopathic: 101 (41.9)
- Virala: 67 (27.8)
- Autimmuneb: 51 (21.2)
- Bacterialc: 15 (6.2)
- Parasitid: 4 (1.7)
- Fungal: 3 (1.2)

Abbreviations: WBC, white blood cells; mg/dl, milligram per deciliter; mm³, per cubic millimeter; WNV, west nile virus; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus; NMMDA, N-methyl-D-aspartate; VGKC, voltage - gated potassium channel; TB, tuberculosis.

- a Number of white blood count per microliter.
- b White blood count less than 4000 per microliter.
- c Platelets count less than 150 per microliter.
- d The distribution of causative viruses was as it follows: WNV (28), HSV (22), VZV (11), CMV (4) and Enterovirus (2).
- e They were due to anti-NMDA (21), anti-VGKC (2) and the rest were due to other autoimmune diseases: Systemic lupus erythematosus (n = 18), Sarcoidosis (n = 7), Hashimoto's disease (n = 2) and Rheumatoid arthritis (n = 1).
- f Bacterial causes were due to Mycobacterium tuberculosis (4), Group A streptococcus (3), Streptococcus pneumoniae (2), Mycoplasma (2), Rickettsia spp (1), Brucella (1), Staphylococcus aureus (2).
- g Toxoplasma gondii (n = 4).
- h Fungal etiologies include Cryptococcus neoformans (n = 2) and Coccidioides immitis (n = 1).

urinary antigen, serum cryptococcal antigens) (<20%). Testing for mycoplasma and rickettsial antibodies (IgM) was done in a minority of patients. We found that when done many of the diagnostic studies have high yield results. The highest yield and the most significant test was serum arboviral antibodies (42%).

3.4. Evaluation of neurodiagnostic studies

Neurodiagnostic studies are summarized in (Table 5). Brain CT and MRI were performed in 89.6% and 79.3% respectively. Electroencephalograph was underutilized in our study with a compliance rate of 66%. CSF gram stain and bacterial culture were done in the majority of patients. CSF HSV PCR was obtained in about 84% of patients reflecting that clinicians understand the importance of HSV in encephalitis. CSF Enterovirus PCR was obtained in about half of patients only. The tests with the highest yield were CSF anti-NMDA antibodies (41.2%) and CSF VZV PCR (16.4%). CSF infectious process was identified in 25% of all immunocompromised patient (n = 17).

3.5. Therapeutic evaluation and outcome

All reviewed guidelines of encephalitis management recommend starting empiric antibiotics and acyclovir as soon as possible, pending results of diagnostic studies [11–14]. As demonstrated in (Table 6), the compliance to empiric intravenous antibiotics and acyclovir was not favorable. Additionally, there was significant delay in initiation of empiric intravenous antibiotics and acyclovir. About 12% of our population developed acute kidney injury, which can be attributed to antimicrobials in addition to other causes. Also, most of the guidelines recommends to repeat CSF HSV PCR in 3–7 days in undiagnosed cases of encephalitis in which patients have clinical features or neuroimaging findings of HSV encephalitis [11–14]. We found 148 undiagnosed cases with suspected features of HSV encephalitis, only 14.2% had repeat CSF HSV PCR and all were negative. In terms of outcome, approximately half of the patients had an adverse clinical outcome with a mortality rate of 12.4%.

4. Discussion

All reviewed guidelines recommend a thorough exposure evaluation...
Exposures and risk factors yielded important information in a sub-
compliance to exposure evaluation was the lowest. However, most of
patients with encephalitis [11–15]. As shown in (Table 4), the
therapeutic evaluation and outcome in 241 adult patients with encephalitis.

**Table 5**

| Neuroimaging evaluation | Tests performed, n (%) | Positive results, n (%) | Immunocompetent, n = 173 | Positive results, n (%) | Immunocompromised, n = 68 |
|-------------------------|------------------------|------------------------|---------------------------|------------------------|---------------------------|
| Brain CT                 | 216 (89.6)             | 56/173 (32.4)          |                           | 24/68 (35.3)           |                           |
| Brain MRI                | 191 (79.3)             | 93/173 (53.8)          |                           | 53/68 (77.9)           |                           |
| Electroencephalography   | 159 (66)               | 82/173 (47.4)          |                           | 37/68 (54.4)           |                           |

**Table 6**

| Therapeutic evaluation | N (%) | Empiric intravenous antibiotics a | 154 (63.9) |
|------------------------|-------|----------------------------------|------------|
| Timing of antibiotics initiation (hours), median (range) b | 3 (0−71) |
| Empiric intravenous acyclovir c | 147 (61) |
| Timing of antiviral initiation (hours), median (range) d | 12 (0−264) |
| Intensive care unit admission | 124 (51.5) |
| Repeat CSF HSV PCR in 3−7 days e | 21/148 (14.2) |

**Outcome**

| Glasgow outcome score ≤ 4, n (%) | 118 (49) |
|---------------------------------|---------|
| Death, n (%) | 30 (12.4) |
| Worsening creatinine (1.5 folds) f | 28 (11.6) |

**Abbreviations:** CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; HSV, herpes simplex virus; AFB, acid fast bacilli; VDRL, venereal disease research laboratory; PCR, polymerase chain reaction; NMDA, N-methyl-D-aspartate; VZV, varicella zoster virus; CMV, cytomegalovirus; VGKC, voltage - gated potassium channel; EBV, Epstein-Barr virus.

The most common cause of encephalitis was idiopathic which is consistent with most studies [1,2,7,8]. The most common infectious cause of encephalitis in our study was WNV. In the encephalitis study done in England, HSV was the most common cause of infectious encephalitis with no cases of WNV reported [7]. In contrast, WNV is endemic in the US. Furthermore, 27 patients (96.4 %) with WNV encephalitis were diagnosed during the endemic season (between June and October) [10]. Regarding diagnostic tests, most guidelines recommend obtaining HIV test and blood culture in all patients with encephalitis and other diagnostic tests can be done based on clinical clues or epidemiological risk factors [11–15]. The compliance rate was favorable in ordering blood culture (92.9 %) but suboptimal in HIV (77.2 %). In terms of neurodiagnostic evaluations, it is recommended by all guidelines to obtain CSF analysis, CSF gram stain and culture, CSF HSV PCR, CSF VZV PCR, CSF Enterovirus PCR, brain imaging which MRI is preferable, and Electroencephalography (EEG). Further neurodiagnostic testing will be based on clinical necessity [11–15]. Most of our patients had CSF analysis, CSF gram stain and culture, and brain imaging. EEG was underutilized in our study and was only performed in two third of patients. HSV is the most common treatable cause of encephalitis and the guidelines recommend that all patients should be tested. In our study, a CSF HSV PCR was done in 84.2 %. Additionally, the guidelines advocate to repeat a CSF HSV PCR in undiagnosed cases of encephalitis in which patients have clinical features or radiological findings of HSV encephalitis [11–15]. In our study, a repeat CSF HSV PCR was only done in 14.2 % of 148 undiagnosed patients with suspected features of HSV encephalitis. This raises the concern of underdiagnosing the most common treatable etiology. A CSF VZV PCR were not uniformly done but had the highest yield in our study. Additionally, VZV encephalitis can possibly occur in absence of the typical rash as reported by Halling G. et al. in 2014 and all guidelines recommended to check CSF VZV in all patients with encephalitis regardless of the presence or absence of a rash [17].

In 2009, Gable M.S. et al., recommended to consider autoimmune
etologies including anti-NMDA antibodies in all patient with suspected encephalitis especially if the diagnosis remains unclear [18]. Although anti-NMDA antibodies were checked only in about 35 % of our population, anti-NMDA antibodies was the most common cause of auto-immune encephalitis in our study. All guidelines in agreement that empiric antibiotics and acyclovir should be started as soon as possible in patients with suspected encephalitis. In our study, empiric intravenous antibiotics and acyclovir were not started in about one third of the patients; this is worrisome as delays in therapy are associated with an increase adverse outcomes in both bacterial meningitis and herpetic encephalitis [4,13,19–21]. Furthermore, the median time to initiate intravenous acyclovir was 12 h from arriving to the emergency room. A recent study of 438 patients with herpetic encephalitis documented unfavorable outcomes in 52.9 % of patients with age and Glasgow coma scales as independent prognostic factors [4]. The authors were also able to correlate a delay in the initiation of acyclovir with a linear increase in adverse clinical outcomes and recommended to start antiviral therapy urgently in all patient with suspected encephalitis. The mortality rate in our study was 12.6 %; similar to the 5–15 % rates reported in the literature [1,14,22].

Overall, the management of encephalitis in our population was suboptimal. The reason behind this fact was not fully clear. A possible reason could be due to the lack of awareness of the encephalitis diagnosis or guidelines and/or due to the relative lack of experience on the treating clinicians in this relative rare disease.

Our study had several strengths. It is the first study to evaluate the compliance with multiple encephalitis guidelines. Second, it was a multicenter study done in 17 hospitals that included a wide variety of community hospitals and academic medical centers. Third, we only included cases that met the IEC definition of encephalitis and provided a comprehensive review of all the diagnostic and treatment modalities as recommended by guidelines. Despite the strengths, our study had some limitations. First, due to the retrospective nature of the study, some missing data could limit the conclusion of the study. Furthermore, the study was conducted in Houston and the findings needs validation in other centers.

Finally, diagnosis of encephalitis still challenging and sometimes we proceed with invasive diagnostic measures such as brain biopsy to find the causative factor [9]. Despite our currently available diagnostic tools, a large proportion of patients still have unknown etiologies. Metagenomic sequencing of CSF has recently been shown to aid in the further identifying infectious etiologies in patients with menigitis and encephalitis and could be a promising clinical tool in the near future [23].

5. Conclusion

Adults with encephalitis continue to have high rates of unknown etiologies and adverse clinical outcomes. Encephalitis management and compliance with the guidelines were suboptimal accounting for the underutilization of currently available diagnostic tests and empirical therapy in a significant proportion of patients. We hope that this study will increase awareness of encephalitis guidelines among clinicians with goals to improve the care and outcomes of this devastating disease.

Author contributions

MS contributed to conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript. MH contributed to conception and design of the study, and acquisition and analysis of data. AA contributed to acquisition and analysis of data. RH contributed to conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript.

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Declaration of Competing Interest

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