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Incidence of Encephalitis in the Intensive Care Unit, a Tertiary Care Hospital, Pakistan: A 5-Year Retrospective Study

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Abstract

Objective: Encephalitis is a disease that has a major impact on health systems worldwide in terms of mortality, morbidity and costs. Furthermore, it is a challenging disease for the treating physician, as the patient presentation varies, and not all patients present with typical complaints. In addition, if left untreated or if there is a delay in the treatment, the mortality rate due to encephalitis can increase. The incidence of encephalitis in Pakistan is scarce in the literature because, in most of cases, the specific cause is not evaluated due to lack of resources and also because the majority of cases are not reported. The aim of this study was to determine the incidence and outcomes of encephalitis in patients admitted to a tertiary care hospital intensive care unit in Pakistan.

Methods: This retrospective study was conducted in the intensive care unit of the Aziz Fatimah Medical College and Hospital, Faisalabad. After obtaining the ethical approval, a total of 75 patients were found in the medical records with a confirmed diagnosis of encephalitis out of total 3,921 patients admitted to the intensive care unit in the 5-year period from 1st January 2013 to 31st December 2018.

Results: The most common clinical presentation were seizures (64%) followed by headache (53%), irritability (29.3%) and hemiparesis (26.7%). Among all patients, 44 needed invasive ventilation, and 7 required non-invasive ventilation. In addition, the outcomes were variable.

Conclusion: The incidence of encephalitis was 1.9% in the 5-year period, and the mortality rate was 37.3%. Also, 6.7% patients improved without any complications.

Keywords: Encephalitis, incidence, outcome

Introduction

Encephalitis is a brain disease that causes the inflammation of the parenchymal tissue, thus leading to clinical features of the cerebrum dysfunction (1).

It is one of the diseases with an impact on the public health, and it is also fatal if left untreated. Encephalitis is a challenging disease because it is difficult to investigate and treat it as its sign and symptoms mimic clinically other neurological diseases, it has a multifactorial aetiology, and there is a lack of resources to diagnose it. Globally, the most important cause of encephalitis is viral. Nowadays, there is an advancement in knowing the aetiologies behind encephalitis, but many cases remain undiagnosed because of the introduction of new viruses every day. To decrease encephalitis mortality and morbidity rates, the key step is an early diagnosis and quick treatment plan.

We could not find any studies in the literature that reported the incidence of encephalitis in an intensive care unit in Pakistan, and to improve the estimate of the encephalitis incidence in Pakistan, this study was conducted.

The primary objective of this study was to determine the incidence of encephalitis in patients admitted to the intensive care unit, tertiary care hospital, Pakistan, and the secondary objective was to determine the outcome of patients with encephalitis in terms of mortality and morbidity.

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Methods

After an approval from the Ethical Review Committee of the hospital (Ref: No: DME/448-19), we collected the list of medical record numbers of all patients admitted to the intensive care unit with the confirmed diagnosis of encephalitis from 1st January 2013 to 31st December 2018 in Aziz Fatima Medical College and Hospital, Faisalabad, Pakistan, and the total number of admissions during this period in the intensive care unit was also documented. A retrospective review of the charts of all patients was done. As this was a retrospective study, informed consent was not required. The demographic data, clinical characteristics at the time of presentation, and outcomes in terms of mortality, morbidity and need of invasive/non-invasive ventilation were documented and analysed. Patient's first vitals (either in the emergency room, ward or intensive care unit) and the first findings sent were recorded on the data collection form. A code was assigned to all patients at the time of data collection by the investigator, and to maintain confidentiality, data entry was performed using the code.

Statistical analysis

A statistical analysis was performed using the Statistical Packages for Social Science version 19 (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were computed for quantitative variables.

Results

In the present study, there were a total of 75 patients with a confirmed diagnosis of encephalitis out of 3,921 patients admitted to the intensive care unit in a 5-year period from 2013 to 2018 with the 1.9% (75/3,921) incidence of encephalitis.

Table 1. Demographic of patients with encephalitis admitted to the intensive care unit (n=75)

Variables	Point estimates
Age (Years)	29.77±12.45
Gender	
Male	41 (54.7%)
Female	34 (45.3%)
Chronic Illness	
Hypertension	12 (16%)
Diabetes	11 (14.7%)
Ischaemic heart disease	2 (2.7%)
Thyroid disease	5 (6.7%)
Asthma/ COPD	17 (22.7%)
Kidney disease	1 (1.3%)
Neurologic illness	3 (4%)
HCV	10
Epilepsy	3

COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus

All the patients included in this study with a confirmed diagnosis of encephalitis were admitted under the neuro-medicine service.

The mean age was 29.77±12.45 years (Table 1), the mean duration of ICU stay was 5.45±2.62 days, and the mean length of hospital stay was 9.33±5.06 days (Table 3).

Overall, there were 54.7% male patients and 45.3% female patients (Table 1). The main reasons for the intensive care unit admission were encephalitis-associated signs and symptoms. The estimated GCS at the time of presentation was 8.35±3.49 (Table 2).

Among all the patients, 53% (n=40) presented with headache, 64% (n=48) with seizures, 29.3% (n=22) with irritability and 26.7% (n=20) with hemiparesis (Table 2).

Table 2. Clinical characteristics of patients with encephalitis admitted to intensive care unit (n=75)

Variables	Point Estimates
Vital	
Heart rate (beats min^{-1})	101.21±23.86
Systolic BP (mmHg)	112±19.63
Respiratory rate (breaths min^{-1})	27.71±7.18
Temperature (Fahrenheit)	99.66±10.68
Duration of fever (days)	2±0.98
SpO_2 (%)	91.88±11.94
Signs/Symptoms	
CNS	
GCS	8.35±3.49
Headache	40(53.3%)
Seizure	48(64%)
Irritability	22(29.3%)
Hemiparesis	20(26.7%)
CBC	
Hb (g dL^{-1})	10.88±2.17
HCT (%)	32.52±6.79
TLC	1542.53±17.811
PLT	272,440.01±4,622.27
Creatinine (mg dL^{-1})	1.10±0.353
LFTs	
SGPT (U L^{-1})	32.4±17.02
PT (sec)	11.49±2.03
APTT (sec)	25.45±4.73
INR (sec)	1.06±0.26

B.P: blood pressure; CNS: central nervous system; GCS: Glasgow Coma Scale; CBC: complete blood count; HCT: haematocrit; TLC: total leukocytes; PLT: platelets; LFTs: liver function tests; SGPT: serum glutamic pyruvic transaminase; PT: prothrombin time; APTT: activated partial thromboplastin time; INR: international normalized ratio

Table 3. Outcomes in patients with encephalitis admitted to the intensive care unit (n=75)

Variables	Point estimates
Mortality in ICU	28 (37.3%)
Respiratory failure	
Invasive ventilation	44 (58.7%)
Non-invasive ventilation	7 (9.3%)
Neurologic status	
Altered GCS	11 (14.7%)
Hemiparesis	15 (20%)
Brain death	23 (30.7%)
Elevated ICP	21 (28%)
None	5 (6.7%)
Renal failure	5 (6.7%)
Septic shock	11 (14.7%)
Length of stay in ICU	5.45±2.62
Length of stay in hospital	9.33±5.06

ICU: intensive care unit; GCS: Glasgow Coma Scale; ICP: intracranial pressure

Out of 75 patients, 44 patients (58.7%) needed invasive ventilation, and 7 patients (9.3%) required non-invasive ventilation (Table 3).

In addition, the outcomes were variable (Table 3), that is, the altered GCS in 14.7%, hemiparesis in 20%, elevated ICP in 28%, renal failure in 6.7%, septic shock in 14.7% and brain death in 30.7% of patients. Furthermore, 6.7% of patients improved without any complications.

The mortality rate of encephalitis in our study was 37.3% (n=28) (Table 3), and the death occurred in the intensive care unit.

Discussion

Encephalitis is a fatal disease if left untreated, and its main clinical characteristics features include altered mental status (decreased level of consciousness, lethargy, personality changes and unusual behaviour), seizures, and/or focal neurologic sign, often accompanied by fever, headache, nausea and vomiting (2).

The relationship between the febrile state and alteration in the consciousness level of patients may have been known for decades, but Sydenham was the first one in the 17th century who reported this relationship, which we call encephalitis today (3). Although with the advancement of technology encephalitis continues to be a highly catastrophic medical illness with an increasing rate of mortality between 6% and18% and morbidity up to 56% (4). As mortality and morbidity due to encephalitis are very high, this brain disorder is a major health concern (5). It is also one of the diseases that have an impact on health-related costs due to an increased number of hospitalisations and also due to residual neurological deficit in one-half of the patients who survived after being infected with encephalitis (1). According to a study conducted by Vincet et al in 2010, globally, the number of admissions of patients due to encephalitis have increased and it exceeds 20,000 and because of this the health related cost has also been increased in vice versa (1, 6).

In 2017, the World Health Organization (WHO) published its data on the reporting of deaths due to encephalitis, and the encephalitis-related death rate was 0.21% considering the total number of deaths in Pakistan, while the overall number of deaths due to encephalitis has increased to 2,514 (7). The annual estimated incidence of encephalitis ranges between 3.5 and 7.5 cases per 100,000 patients (5).

The aetiology behind encephalitis is multifactorial. According to the literature, its cause is not identifiable in most of the patients, even with the advancement of technologies, and less than half of cases are idiopathic (1, 8). In 2013, a retrospective study was conducted by Thakur et al. (9) in the United States, and it was reported that viruses are the most common cause of encephalitis at 27.2%, as compared to bacteria/fungi and autoimmune factors at 9.7% and 16.5%, respectively. Also, in the same study, the cause was unknown in 46.6% of infected patients, and herpes was the most common cause of viral encephalitis as 17 out of 28 patients with viral encephalitis were diagnosed with herpes simplex encephalitis (9). The most common cause of encephalitis in Japan, China, India and South-East Africa is Japanese viral encephalitis (10). The reported incidence is almost 50,000, and the number of deaths due to this virus is 15,000 annually (11). Otherwise, herpes simplex virus is the most common virus causing encephalitis, and also, it is the only virus that is treatable (12, 13). There is scarcity of data about encephalitis in Asia. In India, encephalitis was diagnosed for the very first time in 1955 in Tamil Nandu, and now this disease has spread to involve 19 states and almost 171 districts.

Among the many causes of encephalitis, encephalitis caused by herpes simplex virus is fatal and can lead to mortality in up to 70% of patients without treatment (12, 13). The incidence of encephalitis varies in different studies in the literature. The exact incidence of herpes simplex encephalitis is not documented, but in the literature the estimated incidence is 1 case per million per year (12). Although, in developed countries, the annual incidence of herpes encephalitis is 1/250,000 to 1/500,000 (14), the documented worldwide annual incidence of encephalitis ranges between 0.07 and 12.6 cases per 100,000 people (1).

There are few data available about encephalitis and its outcomes in Asian countries. According to the available data in India, in 6 years (2008-2014), almost 6,000 patients died, and over 44,000 patients were infected with encephalitis. In recent years, this number has increased, and more than 125 patients died in a single hospital in 2016 in India (15).

The pathogenesis of encephalitis has been described in many studies, but still, there are mechanisms that are unexplainable due to the multifactorial aetiology of encephalitis (16). In viral encephalitis, there is a neural cells infection associated with the perivascular region inflammation. Viral encephalitis mainly affects the grey brain matter. In post-infective causes of encephalitis, there is no direct involvement of brain cells but generalised perivascular inflammation and demyelination, and this type of encephalitis only involves the white brain matter (17), although the basic mechanism is that the immunological interaction develops between the brain cells and the immune response of the body. The blood-brain barrier is crossed by the T-lymphocytes activated in response to the immune system stimulation, and ultimately, the specific T-cells enter the brain and generate encephalitis (18). Magnetic resonance imaging is most sensitive in the early diagnosis of encephalitis, and it is also the imaging of choice (12).

Currently, the available drug of choice to treat encephalitis is acyclovir (8), an antiviral medicine, but this is only the definitive treatment of herpes virus encephalitis. For varicella-zoster virus, the role of acyclovir has not been documented in the literature, but it speeds up the recovery of a varicella-zoster-virus-associated infection. Furthermore, there is no available medicine to treat encephalitis due to enterovirus, although in the United Kingdom, a medicine named pleconaril has been mentioned to manage enterovirus-associated infections of severe intensity. Again in the literature, for West Nile virus, a particular medication has not been not reported. In infections due to human herpesvirus-6, foscarnet is the drug of choice, and in cytomegalovirus-associated encephalitis, the preferred drugs are foscarnet and ganciclovir. In addition, for other types of encephalitis, a specific treatment has yet to be evaluated (8).

In the literature, data related to the incidence of encephalitis in Pakistan are very limited. This may be because of lack of resources to diagnose the disease and underestimation of the severity of problems due to encephalitis. According to the WHO report published in December 2015, Japanese encephalitis virus is the most common virus in Asia with approximately 68,000 infected patients per year. The reported mortality due to Japanese encephalitis is 30%, and the incidence of complication in survivors is 30%-50%. Japanese encephalitis virus can transmit endemically in almost 24 countries of WHO South-East Asia and Western Pacific Areas, and thus the risk of the infection transmission increases, affecting over 3 million of people. Treatment of Japanese viral encephalitis is only supportive, and there is no definitive treatment. Therefore, the WHO recommendations are to merge Japanese viral encephalitis vaccines in the National Immunization Schedules in those regions where Japanese viral encephalitis is endemic and a major health hazard. According to the available literature on Japanese viral encephalitis, there are 13,600-20,400 deaths each year due to Japanese viral encephalitis and almost 68,000 infected cases every year (19).

The patients diagnosed with encephalitis may need intensive care admission for management. An altered GCS that compromises the airway and seizures that effect the conscious level of the patient & needs deep sedation and respiratory distress due to aspiration pneumonia or muscular weakness are the main reasons of the intensive care unit admissions (8). According to the study conducted by Sonneville et al. (4), 42 % patients with encephalitis need mechanical ventilation at the time of admission, and 13% of patients needs mechanical ventilation thereafter. In another study conducted on children with encephalitis, 44.8% patients required mechanical ventilation (20). In 2017, a study was conducted in India which concluded that 42% patients with encephalitis need invasive ventilation (21). In comparison to the above studies, our study also increased an increased number (58.7%) of encephalitis patients on invasive ventilation and only 9.3% patients on non-invasive ventilation. However, another study concluded that the overall rate of endotracheal intubation and mechanical ventilation was 6.3% in patients with encephalitis admitted to the intensive care unit (22). In our study, the high incidence of mechanical ventilation may be due to the alteration in the consciousness level of patients as we found an estimated GCS of 8.35±3.49 at the time of presentation.

Among the various factors related to the poor prognosis of the patients with encephalitis, age is one of them. Individuals aged <12 months and >55 years are at high risk for poor prognosis (23). Furthermore, in the literature, it has been documented that age groups at the extreme (children and elderly) are vulnerable with regard to encephalitis, but all age groups can be affected by encephalitis (5, 8). In our study, all adult patients were recruited with the diagnosis of encephalitis as our intensive care unit deals only with adult patients, and therefore, we have not found this differences of age-related incidence in our study. In line with our study, the previous studies that included adult patients have also not found the same age-related high incidence (4, 9). Again, in comparison to our study, another study conducted by Sonneville et al. (4) showed that there was no any relationship found between the age and prognosis of patients with encephalitis as the inclusion criteria only included adult patients.

In the literature, there is a predominance of male patients infected with encephalitis (5). Also, in another study conducted in 2014, the incidence of male patients having encephalitis was 62% (4). In line with these findings, the male-to-female ratio of encephalitis in our study was 54.7%/45.3%. However, Bradshaw et al. (24) have found that both the gender showed the same risk with regard to encephalitis.

The clinical presentation of the patients with encephalitis is variable. Kramer et al. (8) described that all patients with encephalitis usually do not present with the normal level of consciousness and that 10% to 25% present with coma. Furthermore, in the same study by Kramer et al. (8), the incidence of seizures was different, and it depends on the type of organism that is 10% with West Nile virus and 85% infected with Japanese encephalitis virus. In comparison to this study, our study showed the estimated GCS of 8.35±3.49, and all patients presented with an altered level of consciousness and seizures, which were the most common symptoms (64%) at the time of presentation in the critical care unit. In line with our study, Harutyunyan et al. (22) also reported that the altered conscious level and seizures were the most common reason for critical care unit admission. Furthermore, in recent studies, the reported incidence of seizures at the time of presentation was 42%-50% (25-27). In addition, according to the study published in 2017, the documented incidence of seizures in patients with encephalitis was almost 50% (21).

The outcome of patients with encephalitis varies, from complete recovery to death in 4% to 30% cases (1). Among all the viruses causing encephalitis, HSV is extremely fatal with a high mortality rate up to 70% reported in the literature if treatment is not applied in a timely manner (10, 12), and even after treatment, a patient may die in 20% of the cases (9). In most of the treated cases, complications can develop (28). According to the previous study, there is variability in the outcome of patients after viral encephalitis, and it depends on the type of the organism, for example, 41% of the patients have good recovery with autoimmune encephalitis, and 54.2 % of patients have a better outcome with unknown cause (22). Again in 2015, Singh et al. (29) described that the type of microorganism plays a very important role in the overall outcome, as they found an outcome to be favourable at the time of discharge in viral, autoimmune and encephalitis of the unknown aetiology, and the incidence of good outcome was 50.55%, 40.5% and 54.2%, respectively. In our study, we were unable to find the aetiologies behind encephalitis as we do not have facilities available to evaluate the cause of encephalitis. Contrary to the previous studies, we have found complete recovery in only 6.5% patients without any complications. Although we have found complete recovery in a small number of patients, we cannot correlate the outcome with the type of microorganism because of lack of resources in our setup to identify the type of organism. In line with our study, only 2.5% patients showed full recovery in a study conducted by Whitley et al. (28). In addition, in the same study (28), he has showed that the outcome is directly proportional to the patient GCS. Contrary to this, in our study, the estimated GCS was 8±3, and also, we have found the outcome to be independent of GCS.

In our study, an estimated length of stay of patients with encephalitis in the intensive care unit was 5.45±2.62 days. In comparison to our study, Sonneville et al. (20) in 2015 also concluded that the duration of stay in the intensive care unit was estimated to be 9 days (5-22 days).

Furthermore, more studies and various technologies are required to investigate the aetiology of the disease and its pathogenesis. In the literature, there is no standard algorithm to follow when investigating encephalitis that is unexplained, but general guidelines are available (30).

There are few limitations to our study. First, this is a retrospective study, so a serial follow-up was not done systematically during their intensive care unit stay. Second, this study only focused on those patients with encephalitis admitted to the intensive care unit, and therefore, it does not represent all the patients admitted to hospital with the diagnosis of encephalitis. Third, this study was conducted in an only-adult intensive care unit, so the findings of this study are not applicable to population of all age groups. Fourth, the type of organism was not identifiable in our study because of lack of resources in our setup and sometimes non-affordability of the patient attendants as these investigations are expensive if done from some other setup. Fifth, the results of our study may not be applicable to all ICUs as they were obtained from a single hospital. Finally, prospective studies are needed in future to further elaborate the incidence of encephalitis and its outcomes in developing countries such as Pakistan.

Conclusion

Although there are advancements in technology, and physicians are very much aware of the disease process, the incidence of mortality and morbidity is still increased, meaning that health care facilities should pay special attention on monitoring, plans and programmes to properly allocate the resources.

Our study concluded that the overall incidence of encephalitis in patients admitted to the intensive care unit, tertiary care hospital in Pakistan in the period from 2013 to 2018 was 1.9% (75/3,921). In patients with encephalitis, seizures were the most common symptom at the time of presentation, and only 6.7% patients showed complete recovery without any complications. Overall, the mortality rate was 37.3% in patients with encephalitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Aziz Fatimah Medical College & Hospital (Ref: No: DME/448-19).

Informed Consent: Written informed consent was not obtained because of the retrospective nature of the study and we have gathered the data from the medical records of the patients.

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