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SHORT TERM OUTCOME OF VIRAL ENCEPHALITIS CASES SEEN AT A TERTIARY CARE CENTER IN BANGLADESH: FOCUS ON HERPES SIMPLEX ENCEPHALITIS

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Abstract

Background: Acute infective encephalitis is usually viral. Herpes Simplex Encephalitis (HSE) is the commonest sporadic acute viral encephalitis in the Western world. Management of HSE has been considerably improved by the availability of acyclovir therapy and rapid Polymerase Chain Reaction (PCR) based diagnostic assays. There is paucity of data regarding recent hospital incidence, acute mortality and morbidity of patients admitted with suspected viral encephalitis. The aim of this study was to determine the frequency of HSE confirmed by PCR assay in a sample of clinically diagnosed patients of viral encephalitis admitted in a tertiary care hospital of Bangladesh and to evaluate the short term outcome of these patients with a focus on HSE.

Methods and materials: This hospital-based prospective observational study was carried out in Department of Neurology, Medicine and Pediatric Medicine of Chittagong Medical College Hospital from February 2017 to January 2018. Thirty eight clinically diagnosed patients of viral encephalitis, verified on Cerebrospinal Fluid (CSF) examination and necessary laboratory investigations were included as per inclusion and exclusion criteria. CSF was examined for HSV by PCR assays. The global outcome was determined in all patients with Glasgow Outcome Scale (GOS) at three months interval.GOS Score 1-3 were considered as poor outcome.

Results: Median age of the included patients was 30 years (Range 1-70 years) with a male to female ratio 1.1:1 Besides fever (100%) confusion (92.1%) seizure (73.7%) and abnormal behavior (52.6%) were the prominent presenting features. Mean Glasgow coma scale score at admission was 10.37 (±3.17). Mean interval of CSF collection from the symptoms onset was 6.16 (±2.59) days. Out of 38 Patients 4 (10.5%) were positive for HSV type 1 and other 34 (89.5%) had negative PCR for HSV. Four patients were lost in follow-up so, 3 months mortality data were available for 34 patients. The mortality rate was 25% (1/4) in patients with HSV encephalitis compared to 16.7% (5/30) in non-HSV encephalitis. Twenty two patients (64.8%) had favorable outcome and 12 (35.2%) had poor outcome at 3 months. A multivariate analysis identified GCS score at presentation, presence of focal neurological deficit and delay in CSF collection to be independently associated with poor outcome. There was no significant difference in clinical feature, CSF findings and outcome between HSE and non-HSE patients.

Conclusion: In the current study, 10.5% of cases encephalitis was diagnosed as having HSV. Disability persisted in 23.5% of total patients till 3 months.

Key words: Encephalitis; Herpes Simplex Virus (HSV); Bangladesh; Outcome.

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Introduction

The spectrum of clinically relevant infections of Central Nervous System (CNS) is broad and encompassing bacterial/aseptic meningitis and encephalitis.[1] Viral infections of the CNS are uncommon but potentially life threatening for the patients if these infections are not diagnosed and treated early. The initial clinical presentations of many CNS infections are nonspecific, making a definitive etiologic diagnosis challenging.[2,3]

Among different viral agents the Nipah virus, Rabies, Herpes simplex, Japanese encephalitis, Dengue and Enteroviruses are the most common viruses identified in Bangladesh. Rubella virus, Varicella zoster, Mumps and Cytomegalovirus are also frequently reported in the laboratory.[4] Herpes simplex type 1 is the most common, potentially fatal cause of sporadic encephalitis in adults and is the only viral cause that has a specific treatment. Therefore, Herpes Simplex Encephalitis (HSE) should be considered in any patient with suspected

encephalitis, and empirical antiviral acyclovir therapy should be initiated.[5,6,7] Nevertheless empirical treatment with acyclovir in all cases of suspected patients of acute viral encephalitis not only exposed the patients to adverse affect of antiviral drugs but also create an enormous financial burden on the family of the patients.

The epidemiology and etiology of encephalitis, particularly viral encephalitis remains largely unknown in our setting. Moreover, studies about the sequelae in patients with viral encephalitis of various causative agents are rare. Paucity of data about the regional epidemiology and etiology of viral encephalitis make it difficult to manage a patients with suspected viral encephalitis in a low resource setting hospital like ours are.[8] Contemplating this background this study was designed to demonstrate the initial clinical presentation, short term outcome in the patients with suspected viral encephalitis admitted in a tertiary care hospital of Bangladesh. The study also determined the frequency of HSE and compared the short term outcome of HSE and non-herpes simplex viral encephalitis.

Materials and methods

This prospective observational study was performed at Chittagong Medical College Hospital (CMCH) from February 2017 to January 2018. Consecutive admitted patients of suspected viral encephalitis (Based on symptoms, sign, CSF features and radiological findings) from Department of Neurology, Department of Medicine and Department of Pediatric Medicine were included in this study. Patients with suspected bacterial meningo-encephalitis including tuberculous meningitis, metabolic encephalopathy and severe malaria (Based on clinical and laboratory parameters including Complete Blood Count (CBC) Chest X-ray, CSF study, Blood urea, S Creatinine, Liver enzyme, Prothombin time, Serum electrolytes and Blood for malarial parasite count) were excluded from the study.

Data were collected with a predesigned case record form containing questionnaire and checklist. Data including demographic (Age & sex) clinical features at presentation (Fever, headache, seizure, focal neurological deficit, etc) laboratory findings (CSF findings, neuroimaging findings, frequency and type of positive PCR for HSV) and outcomes were recorded.

To determine the viral etiology collected CSF from the patients was analyzed in the Department of Biochemistry, CMCH for HSV screening by using Gene Proof Herpes Simplex virus (HSV-1/2) PCR kit to detect HSV-DNA. The kit was manufactured according to EC Directive 98/79/EC as an in vitro diagnostic medical device and it was designed for professional use specialized clinical and research laboratories. Real time PCR was done by ABI 7500 Fast Dx real time PCR instrument, Life Technology, USA.

HSE was defined as the suspected cases of viral encephalitis that had positive CSF PCR result for HSV. Suspected cases of viral encephalitis that had negative CSF PCR result for HSV were labeled as Non-HSE. Short term outcome included both in-hospital outcome (Duration of hospital stay, requirement of ICU facilities, complete or partial recovery and mortality) and outcome after 3 months of the onset of encephalitis evaluated by Glasgow Outcome Scale (GOS) score. GOS Score 4 and 5 were labeled as Favorable outcome and score 1-3 were labeled as poor outcome.

Statistical analyses were performed by the SPSS version 23.0. Continuous variables were expressed as mean ± Standard Deviation (SD) and median (Interquartile range) while categorical variables were expressed as count and percentage. The statistical significance of intergroup (HSE and non-herpes simplex viral encephalitis group) differences was compared through Independent samplet-test (For normally distributed data) and Mann Whitney U test (For non-parametric data) for continuous data, Chi-square (or Fisher's exact test where expected court was <5 in any cell) done for categorical data. p value < 0.05 was considered to represent a statistically significant difference.

Informed written consent was obtained from competent patients before enrollment. In patients who were unable to give fully informed consent or aged below 18 years, consent was obtained from legal relatives. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College (Memo number: CMC/PG/2017/347) on September 12, 2017.

Results

A total of 38 patients of suspected viral encephalitis were enrolled in the study. With PCR test 4

(10.5%) of them were diagnosed as HSE and PCR test were negative in other 34 cases. All of the HSE were caused by HSV-1. The median age was 30 years with almost equal representation from male and female (52.6% versus 47.4%). All of the patients had fever. Other common symptoms at presentation were decreased level of consciousness (92.1%) seizure (73.7%) abnormal behavior (52.6%) headache (36.8%) speech difficulty (31.6%) and vomiting (28.9%). On examination 47.4% patients had sign of motor deficit (In the form of hemiparesis, paraparesis and quadriparesis) 36.9% had signs of meningeal irritation and 7.9% had cranial nerve palsy. Mean GCS score at admission was 10 (±3) with a range of 3-15. The interval from the symptom onset to CSF collection ranged from 3 and 12 days with a mean value of 6.2 days (Table I). Out of 38 patients brain imaging finding was available in 15 (39.5%) patients. Among them 6 (40%) patient had normal imaging findings. Fronto-temporal site was the most common site of involvement (26.7%) (Not shown in the table). Table I shows that, there was no significant difference in demographic features, clinical and CSF features between the PCR-confirmed HSE and PCR-negative possible viral encephalitis groups.

Table I: Characteristics of the patients at admission stratified by PCR-confirmed herpes encephalitis and PCR-negative possible viral encephalitis.

Characteristics	Total (n=38)	HSV negative (n=34)	HSV positive (n=4)	p value
Demographic				
Age, years	30 (1-70)	30 (1-70)	31 (14-55)	0.817‡
Male	20 (52.6)	18 (52.9)	2 (50.0)	0.911*
Clinical presentation				
Fever	38 (100)	34 (100)	4 (100)	
Confusion	35 (92.1)	32 (94.1)	3 (75.0)	0.291*
Seizure	28 (73.7)	26 (76.5)	2 (50.0)	0.244*
Abnormal behavior	20 (52.6)	19 (55.9)	1 (25.0)	0.328*
Headache	14 (36.8)	11 (32.4)	3 (75.0)	0.132*
Speech difficulty	12 (31.6)	11 (32.4)	1 (25.0)	1.000*
Vomiting	11 (28.9)	10 (29.4)	1 (25.0)	0.568*
Malaise	2 (5.3)	2 (5.9)	0 (0)	1.000*
Motor deficit	18 (47.4)	18 (52.9)	0 (0)	0.178*
Meningeal irritation	14 (36.9)	10 (29.4)	4 (100)	0.098*
Cranial nerve palsy	3 (7.9)	3 (8.0)	0 (0)	1.000*
CSF features				
GCS	10 ±3	10 ±3	10 ±3	0.930†
Interval in days[a]	6.2±2.6	6.2±2.7	6.0±2.3	0.921†
Glucose, mg/dl	67.8±14.6	67.8±14.8	67.5±14.4	0.962†
Protein, mg/dl	66.9±15.1	66.6±15.4	70.0±13.5	0.672†
WBC, 10^3/ml	33.2±67.3	33.6±62.3	32.2±57.3	0.484†
RBC, 10^3/ml	1837±3822	1670±3760	3125±4661	0.124†

Data are presented as median (Range) frequency (Percentage) or mean ± SD as appropriate, p values were obtained from ‡Mann-Whitney U test, *Chi-square test, or †independent sample t test, [a]The interval from the symptom onset to CSF collection.

Average length of hospital stay for the patients was 14.63 (±4.49) days. Out of 38 patients 1 (2.6%) need ICU support and 4 (10.5%) expired. However, there was no significant difference between HSE and non-HSE patients with respect to these variables (Table II).

Table II : In-hospital outcomes of the study population.

Variables	Total (n=38)	HSE (n=4)	Non-HSE (n=34)	p value
Need ICU support	1 (2.6%)	1 (2.9%)	0 (0%)	1.000*
LOS (Days)	14.6 ±4.5	14.9 ±4.2	12.3±6.9	0.891†
In-hospital mortality	4 (10.5%)	1 (25%)	3 (8.8%)	0.854*

Data are presented as frequency (Percentage) or mean±SD as appropriate, p values were obtained from * Fisher Exact test, †independent sample t test, LOS: Length of Hospital Stay.

Neurological outcome and patient's quality of life were assessed at 3 months by GOS. Out of 38 patients all the relevant data were available for 34 patients up to the study endpoint. Out of 34 completed patients, 22 (64.7%) patients had favorable outcomes (GOS score 4 and 5). Figure 1 shows that, most of the patients in both HSE and non-HSE had GOS score 5 (50% and 60% respectively. There was no significant difference in outcome between the PCR-confirmed HSE and PCR-negative possible viral encephalitis groups (p=0.282).

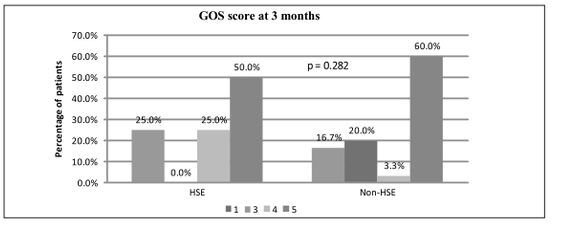

Fig 1 : GOS score at 3 months in patients stratified by PCR-confirmed HSE and PCR-negative possible viral encephalitis (Non-HSE).

Bivariate analysis with different variables and outcome shows that, GCS at admission, focal motor deficit, interval between symptom onset and CSF collection and start of antiviral therapy were significantly associated with 3 months outcome (Table III).

Table III: Factors associated with outcome in patients with suspected viral encephalitis (n=34).

Characteristics	Favorable outcome (n=22)	Poor outcome (n=12)	p value
Age, years	31.4 (±20.2)	38.7 (±23.4)	0.357†
Sex			
Female	11 (50.0%)	3 (25.0%)	0.257*
Male	11 (50.0%)	9 (75.0%)	
GCS score	11.2 (±3.5)	8.5(±2.2)	0.019†
Seizure	18 (81.8%)	8 (63.6%)	0.393*
Focal deficit	8 (36.2%)	9 (75.5%)	0.031*
CSF parameters			
Day of collection[a]	5.4 (±2.68)	7.4 (±2.11)	0.032†
Protein level, mg/dl	65.0 (±13.36)	70.9 (±18.1)	0.324†
Leucucyte count, cells/ml×10^3	38.8 (±82.01)	28.9 (±35.1)	0.732†
Treatment interval in days[b]	5.5 (±2.6)	7.3 (±3.6)	0.037†
Need ICU support	0 (0.0%)	1 (10.0%)	0.311*
Causative agents			
HSE	3 (13.6%)	1 (8.3%)	0.646*
Non-HSE	19 (86.4%)	11 (91.7%)	

[a] Interval from symptom onset to CSF collection, [b]: Interval from symptom onset to start of Antiviral therapy with acyclovir, P-value derived from *Fisher Exact test or †independent sample t test .

On multivariate analysis, 4 factors were found to be independently associated with poor outcome at 3 months, a lower GCS at admission, longer interval from symptom onset to CSF collection, and presence of focal neurological deficit at admission (Table IV). However, there was no significant difference between HSE and non-HSE patients in their outcome. Moreover, longer interval from symptom onset to start of antiviral therapy which was significant in bivariate analysis was not an independent factor for poor outcome after adjustment of other factors.

Table IV : Independent factors associated with poor outcome at 3 months in suspected viral encephalitis cases.

Parameters	Odds ratio	95% CI	p value
GCS at admission	0.651	0.439-0.967	0.033
Days interval of CSF Collection	1.71	1.08-2.69	0.021
Presence of focal neurological deficit	11.14	1.09-20.72	0.047
Interval of starting treatment, in days	1.18	0.83-1.68	0.356
HSE versus non-HSE	4.34	0.15-12.65	0.389
CI: Confidence Interval.			

Discussion

This study was the first, to our knowledge, to report the etiology and short-term follow-up results for patients with suspected viral encephalitis patients in our hospital. Out of 38 patients included in the current study, 4 (10.5%) cases were diagnosed as having HSV by PCR test. This is in agreement with a report from Ghannadet al which showed 15% positive HSV case and from ÇiftçiKavakl o lu et al which reported 10.3% HSE ina cohort of suspected viral encephalitis.[9,10] In a prospective, hospital-based study from our country reported that HSV were associated with only 2% of cases of encephalitis.[11] Positive detection rate of HSV in epidemiological studies varies from 8.2% to 92% in different studies.[12-19] The high rate of HSV infection in different studies might be due to high quality of sampling and laboratory diagnosis methods

In the current study, median age of the patients was 30 years with male to female ratio 1.1 This demographic finding was similar with a study carried out in Asian countries but significantly lower than that was reported in developed country.[9,20,21] The patients in the present study was not representative of classical adult HSE as described in western studies with respect to age, because in our study we included all patients irrespective of age. Age was a non significant factor in our cohort in the patients with HSV encephalitis and non HSV encephalitis. Our finding was in agreement with other studies.[9,10]

The average interval from symptom onset and CSF collection was 6.16 days with a range from 3-12 days. Delays for hospitalization and diagnosis, unavailability of antivirals, inappropriate sampling for PCR test may be some factors which interfere with on time treatment of the patients and thereby influence the overall outcome. Mononuclear pleocytosis and mildly elevated protein level were common findings of analysis of CSF samples, although several CSF samples were acellular or pleocytic, with polymorphonuclear predominance at the onset of the disease in the present study. However, no correlation was found between CSF abnormalities and outcome in the present study, as reported elsewhere.[10,19]

We found that, fever was invariably present at the time of hospitalization in all patients. Other prominent features were headache, decreased level of

consciousness, seizure, vomiting, abnormal behavior, and speech difficulty. These are in agreement with other studies.[9,10,22,23]

In our study, outcome of a relatively short period was evaluated. In total, 22 of 34 patients had a favorable outcome, 21 having fully recovered in our study which was comparable to the neuropsychological outcome in 45 Finnish patients presenting with encephalitis of various causes.[24] The comparison with other studies was difficult owing to different methods (Especially length of follow-up, assessment) and study periods. The long-term outcome of HSE has been studied, demonstrating a full recovery in 14%, in 17%, and 48% of patients.[25,20,22] Our results are comparable to those of the first two studies.[25,21] The results of the third study are difficult to interpret because patients were enrolled during a 12-year period and evaluated 6 months to 11 years after onset.[22]

A delay of >2 days between admission to the hospital and initiation of acyclovir therapy was found to be independently associated with poor out come in different studies.[25] In the present study interval between symptom onset and initiation of acyclovir therapy was significantly higher among the patients with poor outcome, but this difference was not persist after adjustment of other prognostic factors. In our study, mortality rate was 25% in HSE (1out of 4). But our data emphasized poor functional outcome in viral encephalitis patients (35% poor outcome) and the need for further research to improve the long-term medical condition and quality of life in surviving patients. However, these results should be carefully interpreted considering the low number of patients HSE.

Limitations

Though our research provides a new insight into the nature of the clinical and etiologic patterns of viral encephalitis in this geographic region due to lack of funding, PCR assays of an expanded spectrum of viral agents of encephalitis other than herpes simplex type 1 and 2 were lacking. Another limitation was the outcome scale used in the study. Though GOS is a validated tool to evaluate outcome after neurological insult, it has some limitations, and notably, mild neuropsychological impairment might be underestimated. Finally, sample size was small and purposively collected from a single tertiary care hospital which makes it difficult to generalize with viral encephalitis population.

Conclusions

Tthis study found the frequency of HSE confirmed by PCR to be 10.5% in our sample population. Low GCS at presentation, presence of focal neurological deficit and delay of CSF collection from symptom onset was found as independent predictive factors for poor outcome.

Recommendations

The unknown suspected non-HSV encephalitis remains to be investigated in Chittagong Medical College Hospital. Early hospitalization, high quality of CSF sampling and laboratory diagnostic methods and early administration of antiviral therapy should be provided to all patients of suspected viral encephalitis to reduce unfavorable outcome. Nevertheless, a longitudinal study with adequate cohort of representative sample with a long follow up schedule is desirable.

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Contribution of authors

MHK: Conception, data collection, analysis, drafting & final approval.
MRA: Data collection interpretation of data & final approval.
AKP:Data analysis, drafting & final approval.
MKU: Data collection, critical revision & final approval.
MMK: Interpretation of data, critical revision & final approval.
AA: Data collection, data analysis & final approval.
MAK: Design, drafting & final approval.
MH: Conception, critical revision & final approval.

Disclosure

All the authors declared no competing interest.

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