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Acute Febrile Encephalopathy: An Experience from Tertiary Care Centre.

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ABSTRACT

Background: Acute febrile encephalopathy (AFE) is a very common cause of hospitalization and constitutes a medical emergency. Emergency clinicians need to diagnose accurately, timely administration of antimicrobials and adjunctive therapies to avoid complications. Aims: To study the etiological profile and outcome of patients with acute febrile encephalopathy. **Methods:** A prospective hospital based study conducted on the patients admitted in Medicine department, Dr susheela tiwari hospital during the period of August 2012 to July 2014. All patients (>18 years) with history of fever, less than 15 days duration and with altered sensorium were included in the study. **Result:** Out of total 115 studied with mean age of 40.47±17.89 yrs (range of 14 - 85 years) and male: female ratio of 1.3: 1. 48 (41.73%), 24 (20.86%) and, 20 (17.3%) patients had acute pyogenic meningitis, viral meningoencephalitis and tubercular meningitis respectively. 7 (6.08%) patients had cerebral malaria followed by 5 (4.3%) patients sepsis associated encephalopathy. 30 (62.0%), 7 (29.1%) and16 (80%) patients in acute pyogenic meningitis, acute viral meningoencephalitis and tubercular meningitis respectively survived without neurological deficit. 9 (18.7%), 8 (33.3%) and 2 (10%) patients in acute pyogenic meningitis, viral meningoencephalitis, tubercular meningitis respectively had residual neurological deficit at discharge. There were 25 deaths (21.7%) in present study. **Conclusion:** The causes of acute febrile encephalopathy varies from infectious causes to noninfectious metabolic disorders. Acute pyogenic meningitis was the leading cause of AFE followed by acute viral meningoencephalitis.

Keywords: Acute febrile encephalopathy, fever, malaria, meningitis.

INTRODUCTION

Acute febrile encephalopathy (AFE) is a clinical term used to describe patients manifesting with a short and febrile illness (less than 15 days), characterized by diffuse and nonspecific brain insult manifested by a combination of seizures and decereberation.[1] CNS infections are the most common causes of altered mental status in patients with febrile non-traumatic coma.[2] Fever with altered mental state commonly results from bacterial meningitis, Japanese B encephalitis (JE), cerebral malaria (CM), and typhoid encephalopathy.[3] In tropical countries like India, CM, JE, and bacterial meningitis are the common causes of AFE, while tubercular meningitis (TBM) can present with subacute or chronic history.

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In febrile illness, encephalopathy may result either from pathogenic mechanism directly effecting the nervous system or it may be due to systematic complications like hypoglycemia, hyperpyrexia, hypotension, hypoxia, electrolyte imbalance or release of systemic chemical mediators.[3] Bacterial meningitis has an annual incidence of 4 to 6 cases per 100, 000 adults. At present about 1.2 million sporadic cases of bacterial meningitis occur annually worldwide with approximately 135, 000 deaths being attributed to it in 20044.The burden of Hib (Haemophilus Influenza Type b) disease in India was 2.4 million cases of severe cases with ensuing 72000 deaths.[5] Bacterial meningitis has therefore proved to be an important cause of acute febrile encephalopathy in Indian perspective.

Viral Meningitis has been estimated to have an incidence of approximately 75000 cases per year worldwide.[6] Although from the data it appears that the incidence of Japanese encephalitis is much more in our country that other countries there is paucity of data in this context. In case of meningoencephalitis there are approximately 20,000 reported cases in

USA per year.[7] The majority of cases of viral acute encephalitis syndrome (~90%) have no specific treatment (AES).[8] Japanese encephalitis/Acute encephalitis syndrome was reported from 171 endemic districts in 17 states of India. A population of 375 million is at risk of developing AES in India alone. Seventy to 75% of disease burden is in Uttar Pradesh.[9] In India, fever with altered mental state commonly results from bacterial meningitis, viral encephalitis, tubercular meningitis, cerebral malaria and enteric encephalopathy along with several unrecognized entities. The profile of acute febrile encephalopathy varies across different geographical regions and in different seasons in the same area. it is very clear that understanding the burden of these diseases in our respective regions becomes much more important in addressing patients with acute febrile encephalopathy and to take proper steps in decreasing the mortality caused by it.

MATERIALS AND METHODS

A prospective hospital based study conducted on the patients admitted in Medicine department, Dr susheela tiwari hospital during the period of August 2012 to July 2014. All patients with history a of fever of less than 15 days duration and with altered sensorium who presented in Medicine OPD, Emergency or Medicine wards were included in the study. A pre-designed questionnaire was used to obtain a data which incorporated personal information such as name, age, sex, address, clinical profile, associated risk factors and investigations. This was done after explaining the purpose of this study and obtaining written informed consent.

All patients were subjected to complete routine haematological, biochemical investigations. Other special investigations which were relevant to our study such as malaria (card+smear), dengue card, widal (paired sera), ultrasound were done wherever needed. Routine Cerebrospinal fluid (CSF) analysis was done in all the subjects. In cases wherever needed, CSF was sent outside for Adenosine Deaminase (ADA) analysis and or analysis of viral serology. Plain Computed Tomography (CT scan) head was done in all patients. Magnetic resonance imaging head or contrast enhanced computed tomography head was also done in selected cases. Electroencephalography (EEG) was also done in patients wherever required. ADA analysis of CSF and viral serology of CSF was not available in our hospital laboratory and these were evaluated elsewhere.

Inclusion criteria

1. Fever of less than 15 days duration.
2. Altered mentation either at onset or following fever and lasting for at least 24 hours.

Exclusion criteria

The patients excluded were those who at the time of presentation had

Altered mentation due to

1. Deranged metabolic parameters: Hypoglycemia (Blood sugar <50mg/dl), Hypoxia (Pao_2 < 60 mmHg), Hypercarbia ($Paco_2$ >50 mmHg), Hyponatremia (serum sodium<120mEq/lt), Hypernatremia (>145meq/lt), Azotemia (S.creatinine >5 mg/dl), Diabetic ketoacidosis, Hyperosmolar coma,Hepatic encephalopathy.
2. SOL (space occupying lesion)
3. Cerebrovascular accidents followed by fever as lesions in brain could be reason for alteration in mentation.
4. Any past history of CNS disorder.

RESULTS

There was a male preponderance with 65 (56.52%) patients being male and 50 (43.47%) being females. The ratio of male: female was 1.3:1. The youngest patient was of 14 years and the oldest was 85 years of age. Patients were divided into eight age groups according to their age. Maximum number of patients were seen in 20-29 yrs and 30-39 yrs age group each having 24 (20.86%) of the patients. The mean age was 40.47±17.89 yrs. Maximum number of patients, 72 (62.6%) presented with history of fever of 5-9days.Thirty one patients (26.9%) were in the group of 10-15days and Twelve patients (10.43%) were in the group of 1-4days.

In group of very short febrile illness i.e. 1-4 days, maximum number of cases were of pyogenic meningitis (50%), followed by meningoencephalitis (33%). It was seen that as the duration of fever was increasing there was rising trend in number of case of tubercular meningitis. Also there was fall in number of cases of pyogenic meningitis and viral meningitis. Maximum no of patients (49%) were seen in the rainy season from June to September. The burden of patients in rainy season was maximum of encephalitis and cerebral malaria.

Fever and Altered sensorium was the most common symptom seen in 100% of cases. Forty seven (40.876%), thirty five (30.83%) and eighteen (15.6%) patients had headache, seizures and vomiting respectively. After fever and altered sensorium which was also inclusion criteria of present study, headache was the commonest symptom which was present in 24 (50%), 8 (33.3%) and 9 (45%) number of cases in pyogenic meningitis, viral meningoencephalitis and tubercular meningitis respectively. Cerebral malaria and sepsis associated encephalopathy had headache in 3 (42.8%) and 1 (20%) patients respectively. Incidence of seizures was commonest in viral meningoencephalitis (45.8%) followed by pyogenic meningitis (29.1%). Not a single case of dengue encephalopathy and enteric encephalopathy had seizures. Vomiting was seen most commonly in pyogenic meningitis with 10 (20.83%) patients followed by 3 (15%) patients of tubercular

meningitis and 2 (8%) patients of viral meningoencephalitis. Neck rigidity was present maximum in acute viral meningitis (83.4%) followed by tubercular meningitis (70%) whereas in viral meningoencephalitis 29.1%patients had neck rigidity.[Table 1]

Table 1: Symptoms/Signs and etiology.

Etiology	Symptoms			
	Seizures	Headache	Vomiting	Neck rigidity
APM	14 (29.1.%)	24 (50%)	10 (20.83%)	40 (83.4%)
AVM	11 (45.8%)	8 (33.3%)	2 (8%)	7 (29.1%)
TBM	4 (20%)	9 (45%)	3 (15%)	14 (70%)
CM	1 (14.3)	3 (42.8%)	1 (14.3%)	0
SAE	1 (20%)	1 (20%)	1 (20%)	1 (20%)
DE	0	2 (100%)	0	0
EE	0	0	1 (50%)	0
Cryp.M	1 (50%)	0	0	0

There were total of 45 (39.13%) patients who had associated one or more comorbid conditions. Sixteen (13.9%) patients were diabetic, 14 (12.1.0%) were hypertensive, and 3 (2.06%) patient were both diabetic and hypertensive. It was found that mortality rate was higher (37.5%) in patients with diabetes, however hypertension and tuberculosis did not affected the outcome in patients.

Forty eight (41.73%), 24 (20.86%) and, 20 (17.3%) patients had acute pyogenic meningitis, viral meningoencephalitis and tubercular meningitis respectively. Seven (6.08%) patients had cerebral malaria followed by 5 (4.3%) patients who had infection elsewhere and were diagnosed as sepsis associated encephalopathy. Two patients were dengue reactive for NS 1 antigen also presented with altered sensorium. Two patients were seropositive for HIV and had CSF positive for cryptococcal antigen. Lastly 2 (1.7%) patients had evidence of enteric encephalopathy. In 5 patients etiological diagnosis was not reached and they remained undiagnosed.[Figure 1]

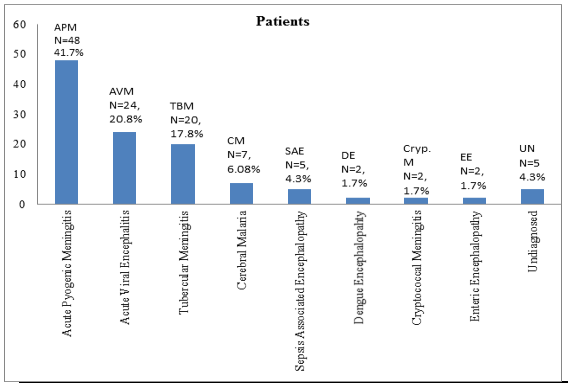

Figure 1: Distribution of cases on basis of etiology.

Out of the total patients 67 (58.27%) were completely cured without neurological deficit, twenty three (20%) patients were left with permanent neurological deficit and 25 (21.7%) patients expired. Thirty (62.0%), 7 (29.1%) and16 (80%) patients in acute pyogenic meningitis, acute viral meningoencephalitis and tubercular meningitis respectively survived without neurological deficit. Tubercular meningitis had the maximum (80%) survival without neurological deficit amongst the major etiologies followed by pyogenic meningitis (62.5%). Acute viral meningoencephalitis had the lowest (29.1%) survival without neurological deficit. Nine (18.7%), 8 (33.3%) and 2 (10%) patients in acute pyogenic meningitis, viral meningoencephalitis, tubercular meningitis respectively had residual neurological deficit at discharge. The highest (33.3) percentage of residual neurological deficit was seen in acute viral meningoencephalitis amongst the major etiologies.[Table 2]

Table 2: Etiological diagnosis and outcome.

Etiology	Survived without neurological deficit	Survived with neurological deficit	Expired
APM	30 (62.5%)	9 (18.7%)	9 (18.7%)
AVM	7 (29.1%)	8 (33.3%)	9 (37.5%)
TBM	16 (80%)	2 (10%)	2 (10%)
CM	3 (42.8%)	1 (14.2%)	3 (42.8%)
SAE	2 (40%)	2 (40%)	1 (20%)
DE	2 (100%)	0	0
EE	2 (100%)	0	0
Cryp.M	1 (50%)		1 (50%)

There were 25 deaths (21.7%) in present study. Among the various major etiologies the death rate was highest (37.5%) in acute viral meningoencephalitis followed by 18.75% in acute pyogenic meningitis. Tubercular meningitis had a relatively lower (10%) death rate. In cerebral malaria, sepsis associated encephalopathy and cryptococcal meningitis the death rate was 42.8%, 20% and 50% respectively but as the number of patients was too low an inference cannot be made.[Figure 2]

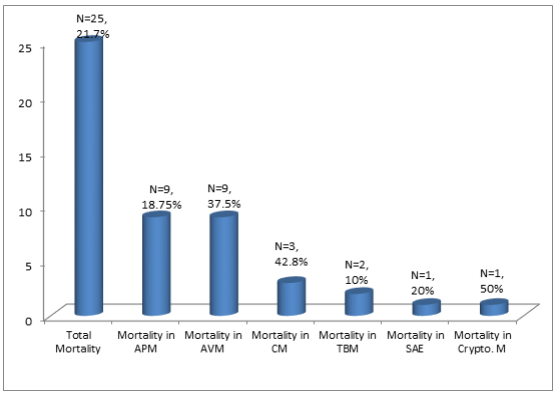

Figure 2: Etiological diagnosis and mortality.

Seventeen (30.9%) patients from hilly region died in present study. Mortality rate was only 13.35% in patients who were from plain. This high value of death rate from hill region was statistically significant. (p=.022) Those who were admitted within 7 days of onset of symptoms were regarded as early hospitalization. In contrast those who were admitted after 7 days were regarded as late hospitalization. Mortality rate was compared in both groups. Mortality was11% in those who were hospitalised early. Mortality rate was 34.6% in those who were hospitalised late. Correlation between time span in hospitalization and outcome was statistically significant. (p=0.02)

DISCUSSION

Acute febrile encephalopathy is a common condition leading to hospital admission in adults and children in India. Various studies in Children with non-traumatic coma have shown that CNS infections are the commonest cause of altered sensorium.[2] In adults there are not much studies which depicts etiological causes of acute febrile encephalopathy. During the entire study period, a total of 160 patients were admitted with complain of acute febrile encephalopathy out of which 45 patients were excluded as they did not met the inclusion criteria, Remaining 115 patients were included in the study.

There was a male preponderance with 65 patients that is 56.52% being male and 50 patients that is 43.47% being females. Similar pattern was seen in other studies. Bhalla et al in his study in the year 2010 reported 78% males and Modi et al in his study in 2012 reported 58% of cases being males.1,11 In the present study the minimum age of patient was 14 year and the maximum age was 85 year. The mean age was 40.47±17.89 years. Mean age was 30.14±14.79 years in study by Bhalla et al and 31.89±14.24 in the study by Modi et al. Mean age of pyogenic meningitis, viral meningoencephalitis, and tubercular meningitis ranged from 40 to 45years. Similarly mean age in cerebral malaria, sepsis associated encephalopathy and enteric encephalopathy ranged from 28-37years.[1,10]

Fever and altered sensorium was the most common symptom seen in 100% of patients. Forty seven patients (40.86%) had headache and 35 patients (30.43%) had seizures at time of presentation or had recent history of seizures. Eighteen patients, (15.6%) had repeated vomiting at presentation. In study done by Bhalla et al fever and headache were found to be the most common symptoms seen in 100% and 94% patients, respectively and had 26% patients with seizures.[1] In present study 30.43% of the patients had seizures which was in concordance with our study. Fever, headache and altered sensorium were also the most common presenting complaints of patients in other studies by Kashinkunti et al and Modi et al.[10,11] In our study a total of 48 (41.73%) patients had acute pyogenic/bacterial meningitis. Twenty four patients (20.86%) had viral meningoencephalitis. Twenty patients (17.4%) were found to be suffering from tubercular meningitis. Seven patients (6.08%) had cerebral malaria followed by five patients (4.3%) who had infection elsewhere and were diagnosed as sepsis associated encephalopathy.

In study done by Bhalla et al from Northwest India out of 127 patients studied a total of 42 patients had meningitis out of which 32 (25.2%) patients were having acute pyogenic meningitis and 10 (7.87%) patients were having tubercular meningitis (TBM). Thirty-eight patients (29.9%) had evidence of meningoencephalitis, which was followed by cerebral malaria, leptospirosis, and brain abscess as a cause of primary CNS infection. Sixteen patients (12.7%) had infections elsewhere and were diagnosed as sepsis-associated encephalopathy (SAE). Four patients (3.15%) were diagnosed as having cerebral malaria and 3 patients (2.36%) had leptospirosis and acute disseminated encephalomyelitis each. In the study by Modi et al of out 120 patients, pyogenic meningitis was found in 44 (36.7%) was the commonest etiology followed by acute viral encephalitis (AVE) 34 (28.33%).[1,10]

In present study as well as in study done by Bhalla et al1 and Modi et al4 the maximum burden of disease was of pyogenic meningitis and viral meningoencephalitis. But there was difference in percentage of various etiologies. Number of cases of pyogenic meningitis was high (41.73%) in present study in comparison to other study done by Bhalla et al and Modi et al (25.2% and36.7%) respectively. Similarly number of tubercular meningitis was also higher (17.4%) as compared to study done by Bhalla et al and Modi et al (7.8% and 4.2%) respectively. Both pyogenic meningitis and tubercular meningitis are more common with poor hygine, poor sanitation, low socioeconomic status and underdeveloped region. Our patients were mostly from hilly region where health services are poor as well as standard of living is also poor. Author contributes these factors as a presumptive reason for high pyogenic and tubercular meningitis cases in the present study. In acute viral meningoencephalitis the distribution was almost equal with 52% (13) patients in the plain and 48% (12) patients in the hilly region, though this finding was not in keeping with the popular belief that viral etiologies are mainly found in the plain areas but this can be attributed to the fact that firstly Uttarakhand is mainly a hilly terrain and our hospital is located in the footsteps of entire hilly range of the state therefore a substantial number of patients coming to the hospital are from the hilly areas. Secondly it could be a possibility that there might have always been a substantial number of case of meningitis in the hilly areas but due to poor health facilities most of the cases remain undiagnosed. A study done by Bhattachan et al on Japanese

encephalitis in hill and mountain districts of Nepal revealed that In 2007, a total of 360 AES cases were reported from 40 hill or mountain districts.12 Therefore the popular belief that hilly areas always has less incidence of viral etiologies may not be true.

In the present study the total number of cases of acute viral meningoencephalitis was 24 (21%) which was comparable to study done by Bhalla et al and Modi et al (29% and 28%) respectively.[1,10] Our study highlights the fact that despite of previous presumption that viral encephalitis is very low in hilly region, it is significantly present in the hills also and any patient of acute febrile encephalopathy irrespective of from hilly or plain region should be considered for diagnosis of viral encephalitis. In our study we had a total of seven (6.08%) patients of cerebral malaria. This was in concordance with the other study done in Northern part of the country such as study by Bhalla et al in Northwest India where a total four (3.15%) patients were diagnosed as cerebral malaria. In another study done by Kashinkunti et al the cases of cerebral malaria were 6%.[11]

Dengue hemorrhagic fever presents as a short febrile illness and thrombocytopenia but may rarely present with alteration in sensorium. 13 In our study we had two patients who were dengue reactive for NS 1 antigen who presented with altered sensorium. Comparing this with other studies done, done by Bhalla et al and Modi et al on acute febrile encephalopathy they had no patients of Dengue encephalopathy.[1,4] Study done by Jain et al on epidemiology and etiology of acute encephalitis syndrome in North India revealed that out of the total 1578 patients of AES, dengue virus was the causative agent in 10.8% of the cases.[14] In our study we had five patients who were diagnosed as sepsis associated encephalopathy. This was in concordance with other studies where sepsis associated encephalopathy too was an important differential diagnosis of acute febrile encephalopathy. In the study done by Modi et al there were 11 (9.17%) patients of SAE whereas in the study done by Bhalla et al there were 16 (12.7%) patients of SAE.[1,10]

Enteric encephalopathy is also one of the differential diagnosis of acute febrile encephalopathy. In our study we had two patients of fever with altered sensorium who were diagnosed as enteric encephalopathy. In a study on neurological manifestation of enteric fever by Lakhotia et al , out of the total of 232 patients of enteric fever, neurological manifestations were present in 68 (27.1%) patients.15 No clean cut segregation of cases in any specific weather was found. There was slight inclination of cases in month of June to September which is rainy season. The maximum contribution in rainy season was given by cerebral malaria and encephalitis. There were a total of 25 (21.73%) deaths of patients in present study.

Comparing the mortality with other studies, overall mortality in our study was higher (21.7%) than mortality in the study done by Modi et al where the overall mortality was 13.4%.10 The percent wise mortality in other groups in his study was 17.6%, 11.5% 11.5% and 36.7% in acute viral meningitis, acute pyogenic meningitis, cerebral malaria and sepsis associated encephalopathy respectively. In study by Bhalla et al there were total 127 patients. Twenty one (16.5%) deaths were reported. The maximum mortality (33%) was seen in patients with SAE. On comparing the mortality of other etiologies, in present study mortality rate of cerebral malaria was 42.8% which was higher in comparison to study of Bhalla et al (25%) Modi et al (11.5%). Sepsis associated encephalopathy is also associated with high mortality rates. Mortality in our study was found to be 20% which was relatively less than mortality in study by Modi et al (36.7%) and Bhalla et al (33%).[1,10]

In the classic report by Sprung et al., the mortality rate of septic patients with altered mental status was 49% compared with a rate of 26% in septic patients with no neurological symptoms.[16] Eidelman et al. reported that the severity of neurological symptoms secondary to encephalopathy in patients in the ICU, as assessed by the Glasgow Coma Scale, was correlated to prognosis, with a mortality rate of up to 63% in patients who presented with Glasgow Coma Scale scores between 3 and 8.17 In both the studies mortality was compared among those who had features of encephalopathy versus without encephalopathy in patients of sepsis. Mortality was very high 49% and 63% in those who were having sepsis with encephalopathy.

The age wise mortality distribution was also evaluated. The highest (33.4%) mortality was seen in the age group of 30-39 years followed by age group of 40-49 years (21%) followed by 20% in age group of 20-29 years. The least mortality was seen in the age group 50-59 years and 10-19 years, 1 in each group. Apparently by this percentage it appears that young patient of 20-40 years are more prone for poor outcome but on further analyzing data the author concludes that this high percentage of mortality in younger age of patient was because of more number in younger age group and also disease with high mortality i.e acute viral meningoencephalitis cerebral malaria and sepsis associated encephalopathy were more in younger age group.

Region wise (hilly vs plain) revealed 17 (68%) mortality in the hilly region as compared to 8 deaths (32%) in plain areas. This data was also found to be statistically significant with a p value of 0.22.Possible explanation of this finding is that patients from hilly region presented in advanced stage of disease, deprived of primary treatment.

Next mortality was also calculated in association with comorbid conditions such as diabetes, hypertension, tuberculosis. Mortality was 12

(30.8%) in patients with associated comorbid conditions and 13 (17.1%) in patients without associated comorbid conditions. Although high mortality in comorbid conditions was found but this observation was not statistically significant (p=0.09). Patient was grouped as early and late hospitalization on basis of time taken from onset of symptoms to time of hospitalization. Mortality was 11% in those who were hospitalized within 7 days of onset of symptoms. Mortality was 34% in those who were admitted after 7 days of onset of symptoms. Lastly mortality in patients admitted in Intensive care unit and those in ward was studied. It revealed that out of total 25 mortalities, 6 (24%) occurred in ICU and 19 (76%) occurred in the patients admitted in the wards. Our study also had several limitations, First a complete serological panel was needed to accurately reach a diagnosis which was not available in the hospital. Secondly polymerase chain reaction (PCR) was not done for diagnosis of viral encephalitis as serology may not always be positive in the initial days and third that brain MRI was also not done in all patients due to financial reasons, which could have contributed in reaching the etiological diagnosis of AFE. Despite that by simple time treated gold standard of CSF analysis, rest of the time diagnosis was made.

CONCLUSION

In our study the incidence of mosquito borne diseases (mosquito borne encephalitis and cerebral malaria) was significant. This finding was in contrast to the popular belief that there is less incidence of mosquito borne diseases is low in hilly areas. Few studies from Nepal and other hilly areas also had similar finding. Further dedicated study is required to evaluate patients from hill region separately as present study provided data where patient population was mixed. (Hill and plain). Result of that study exclusively from hill may help in further planning of better health care in remote hilly areas of the state.

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