Original Article

Acute symptomatic seizures in adults: a study on etiological profile

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ABSTRACT

Background: *Acute symptomatic seizures are clinical seizures occurring in close temporal relationship with an acute central nervous system (CNS) insult, which may be metabolic, toxic, structural, infectious or inflammatory. Currently there is dearth of information on the epidemiology of acute symptomatic seizures among adult medical admissions in Bangladesh. This study was designed to determine the frequency of presentation and etiology of acute symptomatic seizures among adults.*

Methods: *This was a cross-sectional study of adult patients admitted with new onset seizure under Neurology Department of BIRDEM General Hospital during the period of January 2019 to December 2020. Clinical assessment and relevant investigations were done and data were collected regarding their etiological diagnosis. Data were analyzed using statistical package for the social sciences (SPSS) version 23.*

Results: *Total admission during the study period was 2920 and among them, 100 patients (male 62, female 38) were having their first symptomatic seizures giving a prevalence of 3.4%. They were between 18 to 82 years of age. The main etiology of acute symptomatic seizure was metabolic encephalopathy (42.0%) .It was followed by acute cerebrovascular disease (31.0%) and acute CNS infection (16%) . Acute cerebrovascular disease and metabolic encephalopathy were predominant causes of symptomatic seizure among the elderly and CNS infections among the middle aged adults. The majority (70.0%) of patients had generalized onset seizures. Focal seizures and focal to bilateral tonic clonic seazure were present in 22% and 8% of the patients respectively.*

Conclusion: *This study showed that metabolic encephalopathy, acute cerebrovascular disease and CNS infections were the prominent causes of acute symptomatic seizures. Treatment strategies should aim for promt identification and management of these conditions as seizures may not recur when the underlying cause has been removed or the acute phase has elapsed.*

Key words: *acute symptomatic seizures, etiology, metabolic encephalopathy, acute cerebrovascular disease, acute central nervous system infection.*

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INTRODUCTION

Acute symptomatic seizures (ASS) are defined in a recent recommendation from the International League Against Epilepsy (ILAE) as clinical seizure events, occurring in close temporal relationship with an acute central nervous system (CNS) insult, which may be metabolic, toxic, structural, infectious or due to inflammation.[1] Seizure events occurring within one week of stroke, traumatic brain injury, anoxic encephalopathy or intracranial surgery are causes of ASS. Symptomatic seizures also can occur at first identification of subdural hematoma, in the presence of an active CNS infection or during an active phase of multiple sclerosis or other autoimmune diseases. In addition, ASS may appear in

the presence of severe metabolic derangements (documented within 24-h by specific biochemical or haematologic abnormalities), drug or alcohol intoxication or withdrawal or exposure to a well-defined epileptogenic drug.[1] Such seizures are considered to be an acute manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed.

Population-based studies showed that the cumulative risk for acute symptomatic seizures from birth to 80 years of age is 3.6% and age-adjusted incidence is 29 to 39/ 100,000 person years.[2,3] Acute symptomatic seizures represent 40% of total seizures, 40% of all first seizures and 50% to 70% of status epilepticus episodes.[2-4]

When seizures complicate acute neurological disorders, they add an additional layer of complexity to patient management. The knowledge of the etiologic risk factors of acute symptomatic seizures in third-world countries will invariably contribute to the effort aimed at preventing and managing medical conditions frequently complicated by seizures. Currently, there is dearth of information on the epidemiology of acute symptomatic seizures among adult medical admissions in Bangladesh. This study aimed to determine the frequency of presentation and etiology of acute symptomatic seizures among adults.

METHODS

Study design and patient population

This cross-sectional study was done at the Department of Neurology of BIRDEM General Hospital, Dhaka, Bangladesh from January 2019 to December 2020. Hospitalized adult patients with new onset seizures were consecutively included in this study.

Inclusion criteria

Adult patients (>18 years) admitted with new onset seizure fulfilling the following criteria were included in the study:

1. Patients with seizure events occurring within one week of stroke.
2. Patients with seizure events occurring during acute and severe electrolyte and metabolic derangements with specific cut off value such as: hypoglycemia [serum glucose <36 mg/dl (2.0 mM/L)] or hyperglycemia [serum glucose >450 mg/dl (25 mM/L) associated with ketoacidosis (irrespective of duration of diabetes)], hyponatremia [serum sodium <115 mg/dl (<5mM/ L)], hypocalcaemia [serum calcium <5.0 mg/dl (<1.2 mM/L], hypomagnesemia [serum magnesium <0.8 mg/dl (<0.3 mM/L)], uraemia [BUN <100 mg/dl (>35.7 mM/L)] and serum creatinine >10.0 mg/dl (>884 ìM/L).[1] When there was suspicion that the seizure may be acute symptomatic due to a metabolic derangement but the proposed cut offs were not met, seizures were placed into an "unknown" category but excluded as epilepsy.
3. Patients with hepatic encephalopathy and seizure occurring during the period of overt neuro-psychiatric symptoms in a patient with history of liver disease.
4. Patients with hypertensive encephalopathy and seizure occurring during severe elevation of blood pressure, altered mental status or evidence of diffuse brain dysfunction followed by prompt response to antihypertensive therapy.
5. Patients with an active CNS infection presenting with seizures.
6. Patients with history of drug abuse (alcohol, benzodiazepines or related sedative drugs) presenting with seizure along with other symptoms of withdrawal, such as tremors, sweats and tachycardia.

Exclusion criteria

Patients with epilepsy, cases of traumatic brain injury (TBI) including intracranial surgery, anoxic encephalopathy and eclampsia were excluded from this study. Cases of seizures due to brain tumors that presented during the period under review were excluded as acute symptomatic ones since they belong to the group progressive symptomatic according to the proposed ILEA definition.[1]

Selection of patients

Upon screening, the selected patients who met the inclusion criteria were explained about the purpose of the study. Participation was voluntary and they were allowed to refuse or withdraw from the study. Only

patients who met the eligibility criteria and gave consent were recruited. During this time, we found 121 cases of acute symptomatic seizures, of whom 7 denied to participate. Among 114 enrolled patients 4 expired and 10 were excluded according to exclusion criteria. Finally, the remaining 100 cases were available for analysis.

Data collection

Data included demographic data (age and sex), relevant history and clinical examination findings, available investigation results and diagnosis were collected using a semi-structured questionnaire.

Statistical analysis

Collected data were analysed using statistical package for the social sciences (SPSS) version 23 (SPSS Inc., Chicago, IL, USA). Relevant percentages, frequencies, means and standard deviations were calculated. Findings were represented in tables and figures.

RESULTS

Total admission during the study period was 2920 and among them, 100 patients (male 62) were having their first symptomatic seizures (3.4%). The patients were between 18 and 82 years of age with a mean age of 57.2±12.7 years. One-third (31.0%) patients belonged to age 51-60 years.

The most common etiology of acute symptomatic seizure in the study population was electrolyte and metabolic derangements and others are shown in Table I. Hyponatraemia and hyperglycemia with ketoacidosis was found in 33.2% and 26.2% of the patients respectively with metabolic encephalopathy.

Table I Etiological profile of acute symptomatic seizure

Disease class	Frequency (N=100)	Disease	Frequency (N=100)	Percentage
Electrolyte and metabolic derangements *	42 (42.0%)	Hypoglycemia	6	14.28
		Hyperglycemia with ketoacidosis	11	26.20
		Hyponatremia	14	33.2
		Hypocalcaemia	03	7.1
		Hypomagnesaemia	01	2.4
		Uremia	05	11.9
		Hepatic encephalopathy	02	4.8
Cerebrovascular disease	31 (31.0%)	Intracerebral hemorrhage	08	25.8
		Haemorraghic infarct	05	16.1
		Ischemic stroke	17	54.8
		Cerebral venous thrombosis	1	3.2
Acute CNS infections	16 (16%)	Meningo-encephalitis	16	100.0
Drug withdrawal and toxic insults	1 (1%)	Alcohol withdrawal	01	100.0
Others	8 (8%)	Hypertensive encephalopathy	01	12.5
		Reversible posterior Leukoencephalopathy	02	25
		Sepsis associated Encephalopathies	05	62.5
Unknown	03 (3%)	—	03	100

Etiology of acute symptomatic seizures varied with age as shown in Figure 1. Cerebrovascular disease and metabolic derangements were predominant causes among the elderly and cerebral infections among the middle aged adults. Symptomatic seizures due to metabolic derangement appeared to be distributed among all age groups predominantly occurred in >50 age group and those aged 50 years and above accounted for 67.4% (*n*= 29/43) of cases. Seizures due to cerebrovascular disease peaked at >50 age group and those aged 50 years and above accounted for 80.7% (*n* = 25/31) of cases of seizures due to stroke. Symptomatic seizures due to acute CNS infection peaked at 41– 50 age group and those aged above 40 years accounted for 100.0% (n= 16/16) of seizures due to cerebral infection.

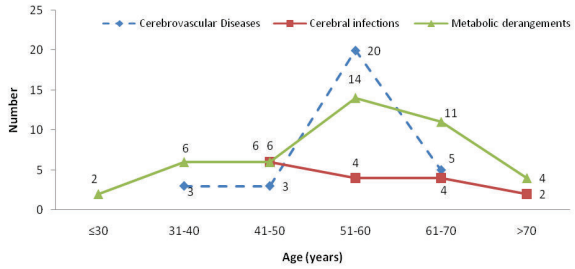

Figure 1 Age distribution of the 3 major causes of acute symptomatic seizures

Etiology of acute symptomatic seizures varied among male and female participants are shown in Figure 2. Cerebrovascular disease was more frequent among male patients. The metabolic parameters in cases of acute symptomatic seizures are shown in Table II.

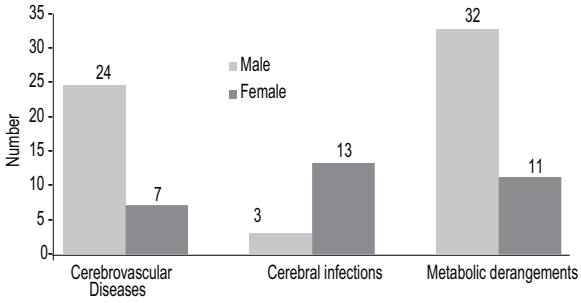

Figure 2 Sex distribution of the 3 major causes of acute symptomatic seizures

Table II Metabolic parameters of the participants with acute symptomatic seizure (N=42)

Investigations	Mean±SD
SGPT (U/L)	93.3±20.4
S. Creatinine (mg/dl)	10.33±0.96
Sodium (mmol/L)	111.3±6.7
Magnesium (mmol/L)	0.56±0.15
S. Calcium (mg/dl)	8.8±0.8
RBS (mmol/L)	22.4±7.1
HbA1c (%)	9.4±2.9

SGPT – serum glutamate pyruvate transaminase, RBS – random blood sugar

Thirty one patients (31 %) with a stroke experienced a seizure within one week of an acute stroke. The frequency varies with the nature of stroke as shown in Table III. The majority (70.0%) of patients had generalized onset seizures. Focal onset seizures and focal to bilateral tonic clonic was the seizure type in 22 % and 8 % of the patients respectively. The distribution of different seizure types varied among the major etiologies of acute symptomatic seizure in the study population which is shown in Table IV.

Table III Stroke subtypes in the participants with acute symptomatic seizure (n=31)

Disease class	No of cases	Disease	Frequency	Percentage
Cerebrovascular disease	31	Intracerebral hemorrhage	08	25.8
		Cerebral infarct with hemorrhagic transformation	05	16.1
		Ischemic stroke	17	54.8
		Cerebral venous Thrombosis	1	3.2

Table IV Types of seizure in major causes of acute symptomatic seizures

Types of seizure	Cerebrovascular lesions	CNS infections	Metabolic derangements
Generalized Onset seizures	13	15	36
Focal Onset seizures	14	2	4
Focal to bilateral tonic clonic	4	0	2

DISCUSSION

Epilepsy is a common disorder, occurring in all countries and all age groups. When a person has an epileptic seizure it is often believed that he or she suffers from epilepsy. However, epilepsy is defined as a condition with recurrent, unprovoked seizures. In the most recently updated definition of epilepsy according to the ILAE, epilepsy is a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24-h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.[5] When seizures are assumed to be provoked, they fall into another category termed symptomatic seizures[1] and the medical investigation, treatment of these seizures differs considerably from those of unprovoked seizures. The prognosis after unprovoked seizures and ASS differs with regard to the risk of seizure recurrence and mortality; therefore, it is essential to define the underlying conditions in which acute symptomatic seizures occur.[6]

This study was undertaken to determine the etiology of cases distinguished as ASS among adult patients. 100 of 121 patients who fulfilled the inclusion criteria were analyzed. These cases accounted for 3.42 % of the 2,920 admissions during the period under review. The frequency of cases corresponded to that of large population based studies.[2,3] In this study, it was observed that most of the study subjects (62%) were male and maximum (31.0%) were in the age group of 51-60 years. This finding was consistent with previous studies.[2]

Electrolyte and metabolic derangements were the most common cause of acute symptomatic seizures in the study population accounting for 42% (n=42/100) of cases. Other major causes of ASS were acute cerebrovascular disease (31.0%) and acute cerebral infections (16%). In another study, the main causes of acute symptomatic seizures are acute stroke (16%), TBI (16%), CNS infection (15%), medication, alcohol and illicit drugs (14%), electrolytic and metabolic disorders(9%), encephalopathy (5%) and eclampsia (2%).[2] Infectious causes were the most frequent cause of acute symptomatic seizures in study conducted in NAUTH of Nnewi in Southeast Nigeria accounting for 36.2% of cases which was similar to a report from India.[8] The difference in incidence of events in our study population may be because the cases were selected from neurology wards of a tertiary referral hospital.

ASS occurred within 24 hours of documented severe selected metabolic derangements as in many previous studies.[9-11] Severe hypoglycemia and hyperglycemia with ketoacidosis i.e. diabetic metabolic emergencies contributed to 40.5% (17/42) of cases. Moderate to severe electrolyte imbalance accounted 42.8% (18/42) of cases of ASS. Near similar findings were observed in a study done by J. Narayanan et al.[8] ASS has also been reported in connection to other rare causes including thyrotoxic storm and porphyria.[12] On the other hand, moderate alteration of urea, creatinine and serum glucose levels was found in some cases of ASS.[13]

In our study, stroke was a common cause of acute symptomatic seizures accounting for 31% (n=31/100) of cases. Ischemic stroke accounted for 54.8% of post stroke seizures while 25.8% cases were due to primary intracerebral hemorrhage. In another prospective series, seizures occurred in 4.4% of 1000 patients, including 15.4% with lobar or extensive intracerebral hemorrhage, 8.5% with subarachnoid hemorrhage, 6.5% with cortical infarction, and 3.7% with hemispheric transient ischemic attacks.[14] A prospective study revealed that the frequency of acute symptomatic seizures is almost twice in hemorrhagic stroke [subarachnoid hemorrhage (SAH) 8% and intracerebral hemorrhage (ICH) 7.3%] compared with ischemic stroke (4.2%).[15]

Acute CNS infection accounted for 16% (n=16/100) of cases of acute symptomatic seizures in this present study. Infectious causes were the most frequent cause of ASS in other studies conducted on Nigeria and India accounting for 36.2% (n=34/94) of cases and 32% (n=21/66) respectively.[7,8] In both studies, meningo-encephalitis ranked highest among the infective causes of acute symptomatic seizures. Acute CNS infection was based on documentation of fever, headache, focal neurological deficit or alteration in the level of consciousness and signs of meningism on examination and positive cerebrospinal fluid (CSF) features indicating CNS infection in the presence of positive Gram stain or culture from CSF and/ or a positive blood culture or suggestive involvement on computed tomography or magnetic resonance imaging. It is reported that the risk of acute symptomatic seizures occurring in patients with acute CNS infections is more with encephalitis than meningitis but differentiation of these entities was not possible in most cases.[2,16]

In our study, alcohol related causes were implicated in 1 case of ASS. In contrast, in some studies, it can represent as much as one-third of total hospital admissions due to seizures.[17] Other causes of ASS included hypertensive encephalopathy, reversible posterior leukoencephalopathy and sepsis associated encephalopathies.

Majority (70.0%) of patients in this study experienced generalized onset seizures and the finding was consistent with other studies. Post stroke seizures were mostly focal and this finding was comparable to other studies.[18,19] Of them, 30.9% (n=13/42) had focal to bilateral tonic clonic evolution. In a large series of patients with post stroke seizures, 9% had status epilepticus.[20] Status epilepticus was not observed among our study participants. In this study, acute CNS infection presented with generalized onset seizure, although the main seizure type associated with herpes simplex encephalitis(HSE), the most common type of sporadic encephalitis are focal seizures followed by generalized seizures .[21] Study on larger population would be needed to validate this result.

Study limitations

This study however had several limitations. The study was among medical admissions and so did not include etiologic risk factors like traumatic brain injuries or brain tumour which are managed primarily by the neurosurgical teams or eclampsia which was managed by obstetrician. This study was also limited by unavailability of high yield neurologic investigative modalities (like serological test, electroencephalography, viral studies, neurovascular imaging and others) that would have enhanced accurate delineation of the differential diagnosis of acute symptomatic seizures. However, not withstanding these limitations, the findings afford a baseline for further studies on this subject in developing nations.

Conclusion

This study showed that metabolic encephalopathies due to acute and severe electrolyte imbalances and metabolic derangements, acute cerebrovascular disease and CNS infections can manifest with seizures, which may be the sole presenting symptom in adults during admission. The risk of acute symptomatic seizures in males was higher and the seizure type was mostly generalized onset according to this study. It is crucial to rapidly identify all insults possibly involved, treat underlying diseases, revert corrigible factors and in case of central nervous system involvement, use antiepileptic drugs during the acute period. Appropriate and successful therapeutic management, risk of epilepsy, and increased risk of mortality depend largely on the rapid identification of the selective insult responsible for acute symptomatic seizure.

Conflicts of interest: Nothing to declare

Authors' contribution : RH planned the study and draffed manuscript. MRH collected data. MSHK, DA and MRI reviewed the paper.

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