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Original Research Article

Clinical and investigational study for the aetiological evaluation of patients in nontraumatic altered sensorium and its outcome

Siba Narayan Jali, Sachida Nanda Nayak, Biju K. Alexander, Diptimayee Tripathy, Bijaya K. Behera*

Department of General Medicine, MKCG Medical College and Hospital, Berhampur, Odisha, India

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***Correspondence:**
Dr. Bijaya K. Behera,
E-mail: drbkbehera@gmail.com

ABSTRACT

Background: Apart from head injury many patients present to the tertiary care hospital in unconscious state, the etiology of which is obscure in most of the cases. The present study was conducted with on objective to provide insight into the clinical features and diagnostic methods to know the aetiology of patients with non-traumatic cases of altered sensorium and to study the outcome of these patients.
Methods: This is an observational study on 100 patients of altered sensorium of non-traumatic origin during the period from October 2012 to September 2014 conducted in the Department of General Medicine, MKCG Medical College Hospital, Berhampur, Odisha, India. All patients were selected for the study based on the inclusion exclusion criteria. Detailed history, clinical evaluation, laboratory investigations like neuroimaging studies etc. were carried out. Statistical data analysis was done using Graph pad Prism 6 and Microsoft Excel. P value <0.0001 was considered statistically extremely significant.
Results: Out of 100 patients of altered sensorium, 64 were males and 36 were females. All patients were in the age group of 19 to 89 years. Cerebrovascular accident was the most common aetiology of altered sensorium followed by metabolic encephalopathy and infection. Altered sensorium in patients with CVA carries a high mortality. Metabolic causes and younger age indicated a better prognosis, patients with low (Glasgow Coma Score) GCS score of 3 to 4 had poorer prognosis.
Conclusions: The results suggest that clinical assessments yield accurate predictive information about the potential for recovery in cases of altered sensorium. So, this study concludes that empirically based estimates of prognosis in the neurologically severely ill provides great reassurance to those involved in a decision-making process, including patients' families and physicians.

Keywords: Altered sensorium, Brain stem reflexes, Glasgow coma score, Neuro ophthalmic signs

INTRODUCTION

Altered sensorium is the most common and striking problems in general medicine. It accounts for a substantial portion of admissions to emergency wards. There is a continuum of states of reduced alertness, the mild form confusion to the severe form being coma. Coma, defined as a deep sleep like state with eyes closed from which the patient cannot be aroused.[1]

The terms confusion, obtundation and lethargy all imply mild disturbances of arousal, but are too imprecise to be of clinical value. More important is the use of coma scales such as Glasgo coma scale, which indicates the

severity of coma using a number of easily identifiable behavioral features.[2]

Normal consciousness requires both arousal and cognition. Arousal is mediated by the reticular activating system (RAS), which is primarily located in the brain stem. Cognition is a function of properly working cortical hemispheres. Derangements of arousal can present as either depressed (lethargy, stupor, coma) or elevated hyper vigilant, agitated, may be seizure?) Derangements of cognition run the spectrum from "just not as sharp as usual" to confusion, amnesia, hallucination and detachment from reality, a deficit in the level of consciousness suggest that both of the cerebral hemisphere or the reticular activating system have been injured. Altered mental status is never a disease state itself but it correlates to increased morbidity and mortality, thus it is a valuable measure of patient's neurological status.[3]

An altered sensorium can result from various causes including cerebrovascular accident, metabolic disorders like diabetic ketoacidosis, uremia, electrolyte imbalance (hypo or hyper natremia) etc., dehydration, alterations in the clinical environment of the brain (e.g. exposure to toxins and poisons etc.), CNS infections, in sufficiently oxygen or blood flow in the brain and excessive pressure within the skull and intracranial neoplasm are other causes which can alter consciousness.[4]

The "altered sensorium" label may be given to patients with seizures, speech difficulties, generalized weakness, anger management issues, hemiparesis, psychosis, etc. Some focal neurological deficits can be mistaken for alterations in consciousness. Dysarthria and aphasia (receptive, motor or mixed), spatial neglect syndromes, even hemianopsias and hemiparesis can be mistaken as confusion if not looked at closely. Functional (psychiatric) changes in behavior (like depression or fugue states) can be difficult to distinguish from organic causes of behavioral changes. Much of "medical clearance for psychiatry" deals with this conundrum. When in doubt, it can be assumed a medical cause until it is clearly ruled out.[4]

Altered sensorium poses a great challenge in the emergency department many of which require timely intervention. A structured approach to the evaluation of these patients frequently leads to satisfying answers. With the advent of neuroimaging studies, special lab investigations and extensive clinical examination, the different etiologies and their prognosis can be predicted. The aims and objectives of the study were to find out the etiology of patients with non-traumatic causes of altered sensorium, to know the outcome of these patients.

METHODS

The present study was conducted from October 2012 to September 2014 in the department of general medicine, MKCG Medical College, Hospital, Berhampur, Odisha, India. It was an observational study design with a sample size of 100. The work was carried out after the study protocol was approved by the Institutional Ethics Committee. The study population included patients of altered sensorium of non-traumatic origin based on inclusion exclusion criteria. Informed consent was obtained from all the patients (either the patient or first degree relative of the patient). All patients underwent full medical and neurologic clinical evaluation at the time of admission (Time of admission to study was arbitrarily taken as time of first neurologic assessment). Neurologic condition was judged by evaluating GCS score and neuro ophthalmic signs using criteria developed by Plum and Posner and Teasdale and Jennette (Glasgow Coma Scale).[5]

The total coma score of the patient was calculated by adding up the three scores and it was taken to reflect the depth of unconsciousness (lower the score deeper the coma). Neuro ophthalmic signs like oculocephalic reflex, oculovestibular reflex, pupillary reflex and corneal reflex of all patients were evaluated: Oculocephalic reflex-tested by rotating the head from side to side and observing the position of eyes. If the yes moves conjugately to the opposite direction of the head movement, the response is positive and indicate an intact pons. Oculovestibular reflex-tested by the instillation of ice-cold water into the external auditory meatus having confirmed that there is no tympanic rupture. A normal response is the development of nystagmus with the quick phase away from the stimulated side and it suggest an intact cerebropontine connections. Pupillary reflex-Bilaterally dilated and unreactive pupils, indicates severe midbrain-3rd nerve compression. Unilateral miosis in coma has been attributed to dysfunction of sympathetic efferent. Corneal reflex-normally a unilateral stimulus provokes bilateral blinking. Absent reflex is an early sign of 5th cranial nerve or pontine lesion.[6] The outcome at the end of one month was graded and recorded. The patients discharged earlier to one month were called at the end of one month for grading outcome. The following outcome were identified viz, death, persistent vegetative state (awake but unaware), severe disability (dependent but conscious), moderate disability (independent but disabled) and good recovery Jennett B et al and Bond M et al.[7] No patient with persistent vegetative state was encountered and hence authors graded the outcome into 3 categories:

- Outcome 1: Death
- Outcome 2: Recovery with functional disability
- Outcome 3: Good recovery

The general examination in short, risk factors, the neurologic profile at the time of admission, important positive investigation findings, the diagnosis and outcome at the end of one month, of all the cases studied are presented in a tabular form. Then all the cases were followed daily till discharge or death.

Inclusion criteria

- Patients whose altered sensorium lasted at least for 6hours,
- Patients more than 15 years of age.

Exclusion criteria

- Patients in altered sensorium due to head trauma,
- Transient unresponsiveness of syncope or the unresponsiveness of imminent death,
- Patients with transient post ictal unconsciousness,

Statistical analysis

Statistical data analysis was done using graph pad Prism version 6 and Microsoft Excel. Frequency and percentage were used for categorical variables. Mean and standard deviation were used for describing continuous variables. Inferential statistical tools like Chi-square test and student's t test were used. P value <0.0001 was considered statistically extremely significant.

Investigations

Complete hemogram, random blood sugar, serum electrolytes (sodium, potassium, calcium, magnesium), ABG analysis, bun, serum creatinine, thyroid function test, toxic screen for suspected poisoning patients.

Imaging

Plain chest x-ray PA view, CT scan of brain, MRI.

Special Investigations

CSF study, EEG, ECG, 2D Echocardiogram, serum cortisol, vit B12 level were also done for suitable patients. All available clinical and laboratory data were used to ascertain cause of altered sensorium.

RESULTS

A total number of 100 patients of altered sensorium were enrolled and studied. 64 were males and 36 were females, the male female ratio being 1.5:1.

Table 1: Age and gender distribution of 100 cases of altered sensorium.

Age group (years)	Male	Female	Total	Total
15-20	0	2	2	100
21-30	8	4	12	
31-40	10	8	18	
41-50	12	4	16	
51-60	12	8	20	
60 and above	22	10	32	

The maximum number of patients who had altered sensorium were in the age group of 60 years and above, n=32 (32%) followed by the age group of 51 to 60 years n=20 (20%). The mean age of patients with altered sensorium was 58 years. Patients who were above 30 years had one or other risk factors which contributed to the altered sensorium (Table 1). Table 1 shows majority of patients were in the age group of 60 and above. Among 100 cases, majority of the older age group people (>40 years) have one or more risk factors. Therefore, resulting in increased incidence of altered sensorium among these groups as well as the poor outcome also.

Table 2: Risk factor distribution among cases.

Risk Factors	Males	Females	Total
Hypertension	23	10	33
Diabetes mellitus	16	12	28
Alcohol	24	1	25
CKD	5	2	7
Smoking	6	0	6
Diuretic therapy	2	3	5
HIV (CD4<250)	4	0	4

Hypertension forms the most common risk factor in this study, (n=33) which results in increased incidence of stroke hypertensive encephalopathy followed by diabetes (n=28) causing ketosis or hyperosmolar coma, alcohol consumption (n=25) which have a role in hepatic encephalopathy, CKD (chronic kidney disease), n=7 (Table 2).

Table 3: Aetiology distribution.

Diagnosis	Males	Females	Total
CVA	25	13	38
Haemorrhage	10	4	14
Infarction	12	6	18
SAH	3	3	6
Metabolic	20	8	28
Hepatic encephalopathy	13	1	14
Hypoglycaemia	3	1	4
Hyponatremia	2	4	6
Ketosis	1	2	3
Hypoxia	1	0	1
Infection	13	11	24
Cerebral malaria	4	8	12
TB meningitis	2	3	5
Viral meningitis	2	0	2
Fungal meningitis	1	0	1
Brain abscess	3	0	3
Neurocysticercosis	1	0	1
Others	6	4	10
Drugs and Toxins	3	3	6
SOL	1	1	2
Wernickes encephalopathy	1	0	1
Unknown	1	0	1

Among 100 cases of altered sensorial, cerebra-vascular accidents (CVA) were the most common cause n=38 (38%) followed by metabolic causes n=28 (28%), infection n=24 (24%) and other causes n=10 (10%) (Table 3).

Table 4: Aetiology and outcome.

Aetiology	Outcome			P Value
	1	2	3	
CVA	21	7	10	0.0012
Metabolic	5	1	22	
Infective	4	4	16	
Others	3	1	6	

Among 100 cases of altered sensorium, cerebrovascular accidents were the most common cause, n=38 (38%) followed by metabolic causes, n=28 (28%), infection, n=24 (24%) and other causes, n=10 (10%). The detail description of various causes and its outcome are described below (Table 4).

Among the studied cases, cerebrovascular accident stands the most common cause, which included hemorrhage, ischemic infarcts and SAH. Among the cerebrovascular accident, infarction was the most common cause (47.36%) followed by hemorrhage (36.84%) and SAH (15.80%). The patients who suffered CVA had definitive risk factors like diabetes mellitus, hypertension, smoking etc. Infarction showed good prognosis (55.55%) when compared with hemorrhage and SAH (Table 5).

Table 5: Cerebrovascular accident aetiology and outcome.

CVA aetiology (no=38)	Males	Females	Outcome 1		Outcome 2		Outcome 3	
			No	%	No	%	No	%
Haemorrhage	10	4	12	85.71	2	14.29		--
Infarction	12	6	4	22.22	4	22.22	10	55.55
SAH	3	3	5	83.33	1	16.66	--	--
Total	25	13	21	55.26	7	18.42	10	26.31

Table 6: Age and outcome.

Age group (in years)	Outcome 1		Outcome 2		Outcome 3	
	Number	%	Number	%	Number	%
15-30	2	14.28	1	7.14	11	78.58
30-60	11	20.37	11	20.37	32	59.26
Above 60	20	62.50	1	3.12	11	34.38

P value = 0.0002 (very significant)

In the age group between 15-30 years mortality was 14.28% and in the age group of 60 and above mortality was 62.50%. Thus, in this study younger patients had a more favorable outcome when compared to the elderly. Elder patients with other added risk factors like diabetes mellitus, hypertension, chronic kidney disease, smoking, alcohol, etc.

All added to the mortality and recovery. Young patients with immunocompromised status showed poor recovery which was mainly dependent on the CD4 count. But overall, young patients showed good recovery (Table 6).

The total coma score of all the patients were calculated by adding up to three scores and it was taken to reflect the depth of unconscious (lower the score deeper the coma) (Table 7).

Revised GCS (2014): From G Teasdale et al. The Glasgow Coma Scale at 40 years standing the test of time. Lancet Neurol 13:844, 2014. In the present study out 100 patients, all those who had GCS score of 3 and 4 (n=28) showed outcome 1 (death), 72 had GCS score of 5 and above, out of those 72 cases, 5 died and 54 had full recovery with P value of <0.0001 which shows significant.

Table 7: Glasgow Coma Scale.

Eye opening (E)		Verbal response (V)		Best motor response (M)	
Spontaneous	4	Oriented	5	Obeying Commands	6
To speech	3	Confused	4	Localizing	5
To pressure	2	Words	3	Normal Flexion	4
None	1	Sounds	2	Abnormal Flexion	3
		None	1	Extension	2
				None	1

The lower the coma scores of 3 and 4, the death rate is more but it was not a specific indicator of prognosis taken alone. Coma score helped to know the effect of pathology on RAS and its effect on ocular and vestibular reflexes. It also helped to know whether pathology is worsening or

improving with treatment. GCS score helps to compare the numerical score day after day and guide the line of treatment (Table 8).

The commonest cause of altered sensorium in the present series is cerebrovascular accident (hemorrhage, ischemia, SAH) 38% (Table 10).

In the present study oculocephalic reflexes (OCR) were present in 71 cases and absent 29 cases. Among the absent OCR cases, 96.55% (n=28) died (out-come 1), where as in those cases (n=71) with intact reflex 76% had full recovery (outcome 3) and 17% had moderate disability (outcome 2) with P value of <0.0001 proving significance (Table 11).

Table 8: Glasgow Coma score and outcome.

Outcome	GCS-score			P -value
	3	4	5 and above	
1	18	10	5	<0.0001
2	0	0	13	
3	0	0	54	

There are no studies available that has data on non-traumatic altered sensorium and age group and gender influence. The relative frequency of different disease entities that was responsible for altered sensorium in the present study has been compared with Plum and Posner (1981) and Srinivasan K et al (Table 9).[8]

Table 9: Comparative study between present, Plum and Posner and K. Srinivasan K.[8]

Type of lesion	Plum and Posner		Srinivasan K et al		Present study	
	No of cases	%	No. of Cases	%	No. of cases	%
Toxic/ metabolic/infective	326	65.2	93	40	62	62
Structural	166	33.2	138	60	38	38
Psychogenic	8	1.6	-	-	-	-

Table 10: Comparison between Plum and Posner and present study based on aetiologic diagnosis.

Diagnosis	Plum and Posner		Present study	
	N	(%)	N	(%)
Haemorrhage	44	8.8	14	14
Ischemia	9	1.8	18	18
SAH	13	2.6	6	6
Hypoxia	13	2.6	1	1
Infective	14	2.8	24	24
Drugs/toxins	149	24.8	7	7
Hepatic coma	17	3.4	14	14
Ketosis	12	2.4	3	3
Others	196	39.2	13	13

Table 11: Oculocephalic signs and outcome.

Outcome	Oculocephalic reflex				P Value
	Absent		Present		
	No. of cases	%	No. of cases	%	
1	28	96.55	5	7.04	<0.0001
2	1	3.45	12	16.90	
3	-	-	54	76.06	

DISCUSSION

Hundred patients of altered sensorium of non-traumatic origin were studied based on aetiology and clinical signs and were followed prospectively for a month and their outcome determined.

In the present study maximum patients who had altered sensorium were in the age group of 60 years and above n=32 (32%) followed by the age group 51-60 years n=20 (20%). The mean age of patients was 58 years. Among the 100 cases of altered sensorium, 64 were males and 36 were females. The male female ratio is 1.5: 1. There are no studies available that has data on non-traumatic altered sensorium and age group and gender influence. Although none of the altered sensorium are known to have a male predominance, this apparent male predominance can be attributed to the male dominated social system where a sick male gets preferential medical attention.

The relative frequency of different disease entities that was responsible for altered sensorium in the present study has been compared with that of Plum and Posner (1981) and Srinivasan K et al, (Table 9 and 10).[9] (Table 9 and 10) reveals that commonest cause of altered sensorium in the present series is cardiovascular accident (Hemorrhage, Ischemia, SAH) (38%). The next in order of frequency are metabolic (hepatic encephalopathy, hyponatremia, hypoglycemia etc.) 28%, infective (24%) and others (drug/toxins etc.) (10%), The order of frequency in Plum and Posner series is exogenous toxins (29.8%) CVA (13.2%), hepatic coma (3.4%) and infections (2.6%).

In our series, infective cause formed the third main cause of altered sensorium, but in the K. Srinivasan study infection (50%) is the main cause.[8] Infective causes were much less in Plum and Posner series. This reflects the difference in geographic distribution of infections particularly that of severe malaria, TB meningitis etc.

The relation of cause of altered sensorium to outcome in the present series has been outlined in table showing etiology and outcome. In present study, cerebrovascular accident was the most common cause (38%), followed by metabolic (28%), infective (24%) and other causes (10%). Cerebrovascular accident: presence of any degree of altered sensorium substantially reduces the chance of a good outcome of patients with ischemic stroke and a poor chance of outcome in patients with cerebral hemorrhage.

Among Marquardsen's 769 patients, less than 1% of those admitted in unresponsive altered sensorium (coma) survived beyond 5 days, and even among those who were nearly drowsy 71% died within three weeks. These poor results reflect a high proportion of acute cerebral hemorrhage.

Among 153 patients studied by Carter 75% of those in coma had intracranial bleeding who all showed in high mortality rate. Similar finding was noted in present study in which all 3 patients with Intercranial bleed showed 100% mortality. Obtundation, stupor, coma with ischemic stroke showed a poor outcome as equally as poor as intracranial bleed. Carter reported that among 95 patients with cerebral infarction in coma for less than 24 hours, 44% died with 4 weeks.[9]

Similarly, in present study patient who presented with infarction and altered sensorium not lasting more than 24 hours showed good recovery. This was true among present study in which ten patients with ischemic infarction showed good recovery. More long-standing unresponsiveness continuing up to 48hours led to a mortality of 86% and when over 48hours led to a mortality of 95%.

Cooper ES et al, and associates gave similar figures and even Jones and Milliken noted that addition of altered sensorium with hemiplegia increased the mortality from 2 to 41%.[10,11] Oxbury, Greenhall and Grainger found that any alteration in consciousness with ischemic stroke predicted at least a 30% mortality and the death rate climbed as coma descended.[12] In present series among 18 ischemic strokes, only 4 died with mortality of 22.22%. The case of ischemic stroke which expired had presented in a deeply comatosed state with wide area of infarction in MCA territory.

Level of consciousness is of major importance in anticipating outcome from subarachnoid hemorrhage. According to Richardson the mortality in the first 6 months is 29% for alert patients, 55% for drowsy patients, 71% for stuporous patients, and 90% for patients in coma.[13] Age is important, young and alert patients have a mortality one third that of elderly Mc Kissock et al.[13] In the present study of the 6 patients who had SAH with altered sensorium at the time of presentation 5 died with a mortality of 83.33%.[13] Death among all 5 patients was seen in 1st week of their hospital stay.

Coma score and outcome

The lower the coma score of 3 and 4, the death rate is more but it was not a specific indicator of prognosis taken alone. Patient with GCS score of more than 6 to 8 were 7 times more likely to waken than those with a score of 3 to 5. GCS less than four has high mortality. This was seen in a study done by Sacco RL, Gool V R et al.[14] Thus GCS helps to predict outcome and identification of comatose patients at high risk for death or severe disability. Patients with abnormal brain stem response, absent verbal response, absent withdrawal response to pain on day 3 showed more mortality. A study done on 596 patients by Hamel MB, Goldman L et al, showed the absence of above clinical signs carries poor outcome.[15] The risk stratification approach offers physician, patient and patients family information that may prove useful in-patient care decision and resource allocation. In the present study GCS score of 4 and below showed 100% mortality whereas GCS 5 and above showed 11.11% mortality.

Chance of regaining an independent existence was greater in response to noxious stimuli or who had attained any of the following- orienting eye moments, normal response to oculcephalic/oculovestibular stimulation, or normal muscle tone. This was also proved the same in a study done by Bates D, Caronna JJ et al. Patient with absent brain stem reflexes died early which was also the conclusion in a study done in CMC Vellore by John G et al.[16]

Neuro ophthalmologic signs and outcome

The relation of neurophthalmologic signs like oculocephalic response, oculovestibular response, pupillary and corneal reflexes have been shown in table showing the neuro ophthalmologic signs and outcome. It is apparent from the tables that absence of any of these is a poor prognostic indicator. The absence of oculocephalic, oculovestibular response, pupillary and corneal reflexes suggested poor prognosis with a mortality of 96.55%, 96.66%, 93.55% and 88.24% respectively.

Table showing combined absence of OVR, OCT, Pupillary and corneal reflex shows that all the 28 patients with absent oculovestibular, oculocephalic, papillary and cormeal reflex had a mortality of 100%. Even Plum and Carona's finding in their study of 48% patients was similar.[17] In Levy DE et al, series, 120 out of 500 had similar findings, and only none of them regained consciousness to die 2 weeks later.[18] Thus, the accuracy of predictability of death increases when combination of signs rather than when single clinical sign is used.

CONCLUSION

The present study was concerned with the identification of the aetiology and the minimal clinical data required to

make a prediction of outcome in cases of altered sensorium. The results show that with timely intervention and accurate management most of the aetiologies like metabolic and infective causes will show favorable outcome. Cerebrovascular accident was the most common cause (38%) followed by metabolic (28%), infective (24%) and others (10%in this study. Systematic clinical assessment like GCS score and neuroophthalmic signs can yield predictive information about the potential for recovery in cases of altered sensorium. So, this study concludes that empirically based estimates of prognosis in the neurologically severely ill provides great assurance to those involved in a decision-making process including patients, families and physicians. Knowledge of potentially favorable outcome greatly improves the morale and associated level of care on a cost-effective basis.

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