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Clinical Profile and Aetiological Analysis of Late Onset Seizure: A Study Conducted At Tertiary Care Institute

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Abstract

Context: The elderly are the most rapidly growing segment of the population. When compared to other age groups, the incidence and prevalence of seizures and epilepsy are higher in the elderly. Clinical manifestations and causes of seizures are different in older age group than in younger ones. In addition, establishing the diagnosis of seizures in old age can be more difficult than in younger people because of the extensive range of differential diagnoses. *Aims:* To analyse and find out the various aetiologies and clinical characteristics of late onset seizure. *Settings and Design*: This was an observational study, designed to analyse patients more than 60 years of age and who presented with new onset seizure in their lifetime. The sample size was 80 and the study period was from December 2016 to February 2018. Clinical data was collected from patients and witnesses in a systematic manner and added to a database, which included a checklist of seizure antecedents and the symptoms associated with seizure. *Methods and Material*: Total number of 80 patients whose age ranged from 60 to 84 years were included. Analysis initiated with history, neurological examination and clinical examination of other systems. Investigations like blood sugar, urea, serum creatinine, sodium, potassium, calcium, magnesium, 12 lead electrocardiography and other relevant investigations were carried out. All the patients underwent neuroimaging with CT brain. Interictal EEG was done for all the patients. *Statistical analysis used*: The data was entered in MS Excel and appropriate simple frequencies and statistical were used for data analysis. *Results*: Aetiologies found in this study were: seizure due to metabolic disturbances 33.7%, cerebrovascular disease 26.2%, malignancy related seizures 6.2%, seizure in calcified cerebral granuloma 3.7%, others 7.5%. In remaining 22.5% patients, cause could not be found (idiopathic seizure). Generalized tonic clonic seizure (GTCS) was the commonest semiology, seen in 83.8% patients and focal seizures in 12.5% patients. In remaining 3.8% patients, started as focal followed by secondary generalisation. EEG abnormalities were noticed in 25 patients. CT brain abnormalities were noticed in 28 patients. *Conclusion:* Our study illustrates the various causes and clinical characteristics of late onset seizure. In a patient with late onset seizure, all efforts to identify the aetiology should be made out. Thorough search to rule out metabolic disturbances and other treatable causes for seizures should be given early priority. Blood biochemistry, CT brain and EEG are indispensable in patients more than 60 years with new onset seizures.

Keywords: Seizure; Late Onset; Elderly; Aetiology; Stroke; Metabolic Disturbances and Neuroimaging.

Introduction

Late onset seizures are the new onset of seizures in the elderly people. The elderly are the most rapidly growing segment of the population. When compared to other age groups, the incidence and prevalence of seizure and epilepsy are more in the elderly [1,2]. The incidence of seizures in patients over age of 60 was estimated at 50 to 100 per 100,000 per year in one study [3] and presently old age is considered to be the most common period in lifetime to develop seizures [4]. Among the diseases affecting the brain in the elderly, epilepsy constitutes the third most common disease, next to stroke and dementia [5,6]. Seizure is more likely to develop in older age group because age itself is a risk factor for development of seizure [7]. Age has epileptogenic effect on neurons [8]. Moreover, risk factors for seizure and epilepsy are more common as people age.

Seizures and epilepsy can have a profound physical and psychological impact in old age, with

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a substantial negative effect on quality of life which results in role problems (e.g., grandparenting), employment, social embarrassment, and safety. Many elderly patients tend to deny their history of seizures or do not report it immediately due to the fear of social consequences, of losing their driving license, social stigmatization or they may think the event was not seizure. The situation is further complicated by the fact that elderly may have many other comorbidities, age-related changes in pharmacokinetics, possible risk of drug-drug interaction and the adverse effects of medications used to treat seizures.

When compared with younger patients, the causes are more structural in elderly. For instance, the most common cause of provoked seizures in elderly people is acute stroke [9]. Likewise the postictal deficits often are prolonged [10]. Also the clinical manifestations of seizures and the psychosocial impact of the diagnosis can be different in older people. For example, complex partial seizures presenting as confusion may be misdiagnosed as psychiatric symptoms. In addition, elderly people with epilepsy have two to three times higher mortality than the general population. Establishing the diagnosis of seizures in old age can be more difficult than in younger patients, due to the extensive range of differential diagnoses like syncope, transient ischemic attack, cardiac arrhythmia, metabolic disturbances, transient global amnesia, neurodegenerative disease, rapid-eye-movement sleep behaviour disorder, and psychogenic disorders.

Hence, thorough understanding of the aetiologies and the clinical characteristics is essential for the proper management of late onset seizure.

Aims

1. To analyse the various aetiologies of late onset seizure
2. To find out the clinical characteristics of late onset seizure
3. To compare the clinical data with other studies

Settings and Design

This study was conducted at Government Mohan Kumaramangalam Medical College Hospital, Salem district of Tamilnadu, India, a tertiary care teaching institute, during the period of December 2016 to February 2018 for 15 months. The study was approved by our institutional ethical committee. The study was an observational study, designed to analyse patients more than 60 years of age and who presented with first seizure in their lifetime. The sample size was 80. All the subjects were explained about the nature of the study and informed consent was obtained. Clinical data was collected from patients and witnesses in a systematic manner as per proforma and added to a database, which included a checklist of seizure antecedents and the symptoms associated with seizure.

Materials and Methods

Patients admitted in intensive medical care unit and general medical wards were taken for study. Seizure due to traumatic etiologies were not included. Similarly patients with known surgical conditions (like tumour, abscess, etc.) were not included as they are directly getting admitted in surgical side. At the same time, patients admitted in medical wards with seizure, incidentally found to be having surgical conditions like space occupying lesions were included. Patients with acute central nervous system infections were not included in this study. After the treatment for seizure and stabilisation of the general conditions, analysis was initiated with history, neurological examination and clinical examination of other systems. Investigations like blood sugar, urea, serum creatinine, sodium, potassium, calcium, magnesium, 12 lead electrocardiography and other relevant investigations were carried out. All the patients under went neuroimaging with CT brain and MRI brain was done for few patients. Interictal EEG was done for most of the patients. All the results and statistics were analysed.

Statistical analysis used

The data was entered in MS Excel and appropriate simple frequencies and statistical were used for data analysis.

Results

Total number of about 80 consecutive patients were taken up for the study and whose age ranged from 60 to 84 years. Among them, male patients were 41 (51.3%) and female patients were 39 (48.7%). Demographic profile reveals patients between the ages of 60 and 69 years were 49 (61.3%), those between 70 years and 79 were 26 (32.5%) and 5 (6.2%) patients were in the group of 80 and above years. Results are tabulated as follows:

Table 1: Showing various aetiologies of late onset seizure

No	Aetiology	Number of Patients	%
1	Metabolic Disturbances	27	33.7
2	Cerebrovascular Disease	21	26.2
3	Idiopathic Seizure	18	22.5
4	Malignancy Related Seizure	5	6.2
5	Seizure In Calcified Cerebral Granuloma	3	3.7
6	Others	6	7.5
	Total	80	

Table 2: Showing demography of various metabolic disturbances presented with seizure

No	Causes	Male	Female	Total
1	Non Ketotic Hyperglycemia	9	7	16 (59.2%)
2	Hypoglycemia	1	2	3 (11.1%)
3	Uremia	2	1	3 (11.1%)
4	Renal Failure + Hyperglycemia	2	1	3 (11.1%)
5	Hyperglycemia + Hyponatremia	0	1	1 (3.7%)
6	Hyperglycemia + Substance Abuse	1	0	1 (3.7%)
	Total	15	12	27

Table 3: Showing demography of seizure due to cerebrovascular disease

No	Causes	Male	Female	Total
1	Seizure in Acute Stroke	4	3	7
2	Post –Stroke Seizure	5	3	8
3	Acute Stroke + Hyperglycemia	2	1	3
4	Post-Stroke + Hyperglycemia	0	1	1
5	Post-Stroke + Hypoxia	0	1	1
6	Post Stroke + Renal Failure	1	0	1
	Total	12	9	21

Table 4: Showing demography of malignancy related seizure

No	Causes	Male	Female	Total
1	Meningioma	0	2	2
2	Meningioma + Hyperglycemia	0	1	1
3	Carcinoma Cervix	0	1	1
4	Carcinoma Breast with DM	0	1	1
	Total	0	5	5

Table 5: Showing various other causes associated with seizure

No	Causes	Male	Female	Total
1	Dementia	1	0	1
2	Alcohol Withdrawal	1	0	1
3	CAD	0	1	1
4	Hypoxia	1	0	1
5	Pul.TB Defaulter	2	0	2
	Total	5	1	6

Table 6: Showing semiology of seizure

GTCS	Focal	Focal With Secondary Generalisation	Total
67 (83.8%)	10(12.5%)	3 (3.8%)	**80**

Table 7: Showing findings in CT scan Brain

No.	CT Scan Brain Findings	Number of Patients
1	Normal Study	41 (51.2%)
2	Age related Cerebral Atrophic Changes	11 (13.7%)
3	Chronic Infarct / Gliosis	11 (13.7%)
4	Acute Infarct	10 (12.5%)
5	Meningioma	3 (3.7%)
6	Calcified Cerebral Granuloma	3 (3.7%)

Table 8: Showing findings in Interictal EEG

No	EEG Findings	Number of Patients
1	Total Number of Patients Underwent EEG	79 (98.7%)
2	Normal Record	54 (67.5%)
3	Focal Spikes	6 (7.5%)
4	Focal Slow waves	7 (8.7%)
5	Diffuse Slow waves	12 (15%)

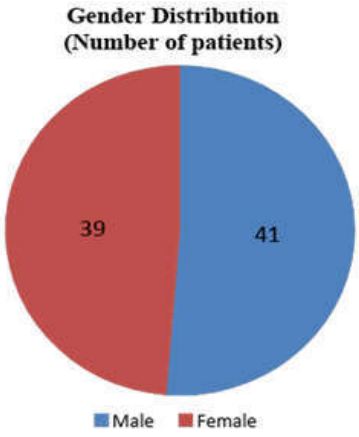

Chart 1: Showing the gender distribution

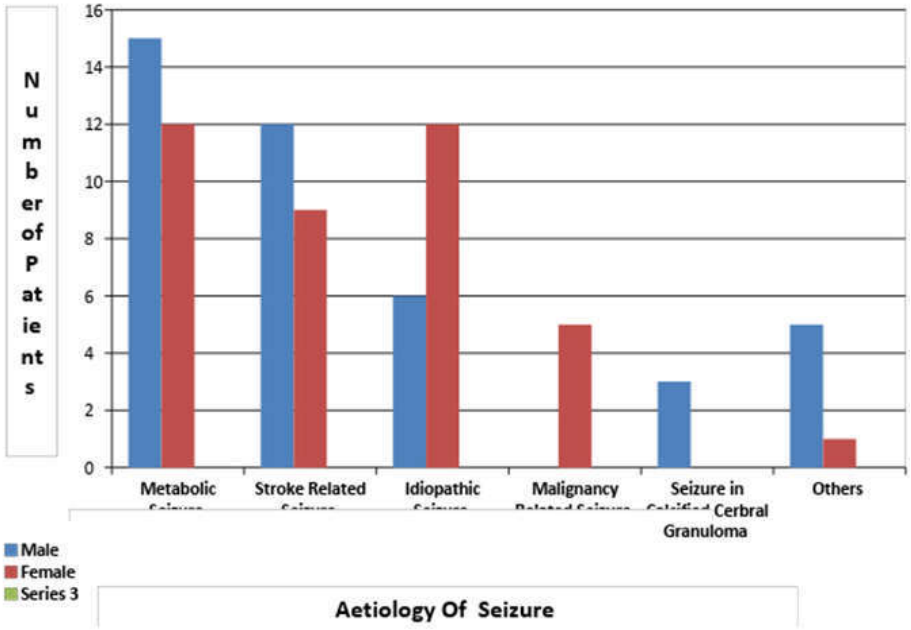

Chart 2: Demonstrating various aetiologies and number of patients in each category

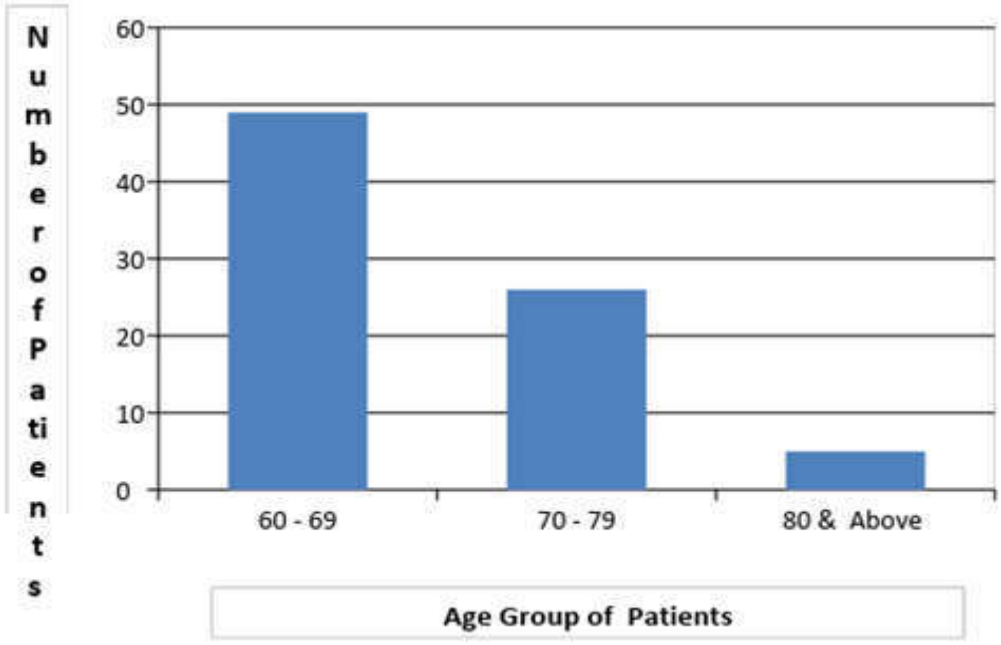

Chart 3: Showing number of patients different age groups

Discussion

Causes of seizure in the elderly are cerebrovascular disease, metabolic or electrolyte disturbances, head injuries, neurodegenerative disorders (such as Alzheimer's disease), alcoholism and other substance abuse, central nervous system infections, brain tumours. But in 25-40% patients, there is no obvious underlying aetiology, that is idiopathic seizure [11]. In a study done by Vercelletto P et al., in 50% of the cases the aetiology was not obvious [12].

Among these, cerebrovascular disease is the most common aetiology leading to the development of seizures and epilepsy in older adults [13,14,15]. According to Kramer G, stroke accounts for up to 50% of cases where a cause can be identified and the risk of epilepsy increases up to 20-fold in the first year after a stroke [16]. But in contrast to this, in our study, cerebrovascular disease constitutes the second common cause (26.3%) of seizures. Usually seizures may occur at the onset of stroke or may follow stroke (post stroke seizure). In our study, seven acute stroke patients presented with seizure. Three of them had infarct with haemorrhagic transformation and four had ischemic stroke. According to Rowan AJ et al. [17] ischemic stroke is more associated with seizure. No patients with acute intracerebral haemorrhage were presented with seizure in our study. Also we had eight "post stroke seizure" patients. They had been treated for stroke in the past one month to eight months period and presently were admitted for seizure. Usually these post stroke seizures are relatively more common in haemorrhagic stroke than in ischemic stroke. In haemorrhagic stroke, 8% of patients will develop seizures within two weeks whereas in ischemic stroke 5% will develop seizure within two weeks [18]. In our study we couldn't get the old records of these 'post stroke seizure' patients to find out whether the previous stroke was ischemic or h haemorrhagic.

Three diabetic patients presented in acute stroke with seizure. All of them were diagnosed to have ischemic cerebral infarct. Apart from these, a 65 years old diabetic woman who was treated for stroke (left hemiplegia) about 6 months ago presented with left focal seizure. Her blood sugar was 159 mg% and her CT scan brain demonstrated chronic infarct in right parietal region. Another 66 years old woman who was a known case of bronchial asthma for the past ten years and who was treated for stroke two months ago presented with acute exacerbation of asthma with one episode of seizure. Arterial blood gas analysis revealed hypoxia. A 75 years old man treated for stroke 6 months ago and presently was admitted in renal failure and left focal seizure. His CT scan brain demonstrated right parietal gliosis. These three cases demonstrate the fact that the coexisting diseases increase possibility of development of seizure.

Regarding the other aetiologies of seizure, metabolic causes play an important role. Acute

metabolic and electrolyte disturbances are common in elderly patients because of multiple comorbidities and polypharmacy. These metabolic disturbances can precipitate seizure and they include hypoglycaemia, nonketotic hyperglycaemia, uremia, hyponatraemia, hypocalcaemia, hepatic failure, etc. [19] Among these, non-ketotic hyperglycemia (NKHG) is an important cause of seizure [20,21]. High blood sugar causes hyperexcitability of the neurons and the overexcited brain can seize. Interestingly in our study, seizures due to metabolic disturbances was the commonest aetiology noticed. Among the total number of 80 patients, 27 cases (33.8%) were due to metabolic disturbances. In this, non ketotic hyperglycemia caused seizure in more number (15 patients - 55.6%) of patients. All of them were diabetic patients with poor glycaemic control and they satisfied the inclusion criteria of NKHG: hyperglycemia with no evidence of ketosis, seizures that disappeared when hyperglycemia was controlled and the absence of lesions in cerebral imaging that may explain seizures [22]. All of them recovered with insulin and diabetes management along with short course of antiepileptic drugs. Studies demonstrate, seizure due to hypoglycaemia is more common than NKHG [23].But in our study, seizure due to (NKHG) was more (15 patients – 55.6%) than seizure due to hypoglycaemia (3 patients– 11.1%). Similarly, studies demonstrate, focal seizures are more common in NKHG [24]. But in our study GTCS was more common semiology in NKHG than focal seizure.

In addition, though hyponatremia is a common cause of seizure, in our study we had only one patient, a 75 years old newly diagnosed diabetic woman who showed hyponatremia (serum Na+: 122 meq/l) along with hyperglycemia (blood sugar: 196 mg%). Another 60 years old diabetic man who was an alcoholic and substance ("HANS") abuser presented with hyperglycemia and seizure and was treated accordingly. In these two patients seizure could have been due to add on factors along with hyperglycemia.

Next to diabetes mellitus, uremia constitutes an important metabolic cause. 3 patients (11.1%) known case of renal failure presented with seizure. 3 more patients who were diabetic and getting treatment for renal failure as well, presented with new onset seizure.

Malignancy (primary cerebral tumour or cerebral metastasis) is another important cause of seizure in elderly. About 10.7% of epilepsy in older adults is related to cancer, not necessarily involving the nervous system [25]. The most common tumours found to produce seizures in later life are gliomas, meningiomas and metastases. In our study, we had totally 5 patients (6.25%) with 'malignancy related seizure'. (This looks small in number, because already diagnosed or known cerebral tumour patients usually were getting admitted in surgical side). Notably all of them were females. Among these two patients were cases of meningioma and one was a diabetic woman with meningioma (blood sugar at the time of admission was 556 mg%). One patient with ca cervix on radiotherapy and another one operated for mastectomy 12years ago were admitted for seizure. But in these two patients CT scan brain was normal.

Alzheimer's disease (AD) and other neurodegenerative conditions represent about 10% of new onset seizure in patients older than 65 [26]. Compared with healthy individuals of the same age, patients with sporadic AD have a 6- to 10-fold increased risk of developing clinical seizures during the course of their illness [27,28,29]. In terms of semiology, generalized convulsive seizures have been identified in 90% of the cases [30]. Some data suggest that 70% of seizures are complex partial seizures [31]. But in our study, we had only one patient with Alzheimer's disease who presented with GTCS and responded well with antiepileptic drug management. His interictal EEG demonstrated slowing (theta waves) of the normal background activity without any epileptiform discharges. His CT brain showed – diffuse cortical atrophy with dilated lateral and third ventricle with widened sulci.

Alcohol withdrawal seizures are not uncommon in this population [18]. In our study, alcohol consumption history was there in many patients (30 patients– 37.5%). But many of them were reducing the consumption quantity and few stopped consuming recently. None of the female patients consumed alcohol. Among the total number of 41 male patients, 30 (73.2%) had alcohol consumption history. Interestingly in the 'idiopathic seizure' category all the 6 male patients were alcoholics. Hence alcohol would have played role in that category. Only one patient, 60 years old man who used to drink heavily on most of the days of a week was admitted and treated for alcohol withdrawal seizure.

Literature reveal a big list of drugs, like antipsychotics, antidepressants, antiarrhythmics, antibiotics, antituberculosis agents, antifungal agents, antimalarials, analgesics, vaccines, theophylline, etc, have been associated with seizure activity [32]. But in our study we didn't come across any drug induced seizure patients.

Though in other studies, calcified cerebral granuloma is not much discussed as an aetiology of seizure, we had three male patients (3.8%) whose CT scan brain showed calcified granuloma without perilesional edema. This is probably due to the endemicity of neurocysticercosis in this region.

Next comes the 'others' category which comprises 6 patients (7.5%) whom could not be classified in any of the above mentioned categories. One 60 years old woman who was admitted with seizure, normal CT brain and other parameters, was incidentally found to be a coronary artery disease on treatment. Likewise two pulmonary TB defaulters treated with anti tuberculosis treatment 6 months and two years ago respectively were presented with seizure. But their CT scan brain and other investigations were normal. In the above three seizure disorder patients incidentally the above comorbidities were noticed though the relevance could not be established. A 65 years old male patient, known case of chronic obstructive pulmonary disease (COPD) presented in acute exacerbation with seizure and with hypoxia. (A 60 years old man with alcohol withdrawal seizure and 68 years old man with dementia, these two come under this 'others' category had been described in previous paragraphs).

In remaining 18 (22.5%) patients, cause could not be found, that is idiopathic. (But many studies conclude idiopathic seizure is the major group [11,12]. Among them 6 were male patients and remaining 12 were females. In this, 5 patients (10.2%), belong to 60-69 years age group, 11 patients (42.3%) belong to 70-79 years age group and 2 patients (40%) belong to 80 and above years category. This is suggestive of increased incidence of idiopathic seizures is seen as the age advances. Interestingly, as mentioned earlier, all the 6 male patients were alcoholics. Hence alcohol might have played role in the development of idiopathic seizure.

Regarding the semiology of seizure, many studies conclude that most common seizures are focal in onset (either simple partial or complex seizures) in elderly. According to Vercelletto P et al., focal seizures are more frequent after the age of 60 [12]. In a study done by Hauser WA et al, up to 70% of seizures were focal, with or without secondary generalisation [26] and tonic-clonic seizures were less common and can occasionally were seen in idiopathic epilepsy syndrome. But in our study generalises tonic clonic seizure (GTCS) was the commonest pattern. It was seen in 67 patients (83.8%). Focal seizure was noted only in 10 (12.5%) patients and focal with secondary generalisation was seen in 3 (3.8%) patients.

Status epilepticus appears to occur more frequently in patients above 60 years and the morbidity and mortality of status epilepticus are significantly greater in this age group [11]. According to Brodie MJ et al., thirty per cent of acute seizures in elderly people present as status epilepticus, which carries a mortality approaching 40% [18]. In our study, 11 patients (13.8%) presented with status epilepticus. Among them, 5 were with non ketotic hyperglycemia and 2 were with post stroke seizure. Each one patient in following categories presented in status epilepticus: idiopathic seizure, seizure due to hypoglycaemia, seizure in acute stroke and seizure in meningioma. All the patients recovered with appropriate management.

Though EEG is a useful diagnostic tool in epilepsy, an interictal EEG in elderly patients has limited utility, showing epileptiform activity in only about one-fourth of patients [33]. In addition, nonspecific EEG abnormalities like intermittent focal slowing are seen even in many healthy older people [34]. Likewise, normal EEG do not rule out epilepsy, as EEG is normal in about one-third of patients with epilepsy, irrespective of age [35]. Activation procedures such as hyperventilation and photic stimulation does not improve the diagnosis in the elderly [31]. But video-EEG will be more useful in evaluation of possible epilepsy, as it allows accurate assessment of brain electrical activity during the events in question. According to McBride AE et al., video-EEG demonstrates epileptiform discharges in 76% of patients [32]. In our study, interictal EEG was done in all the eighty patients except one 62 years old woman, case of DM/meningioma who could not be followed. Results were focal spikes in 6 (7.5%) patients, focal slow waves in 7 (8.7%) patients and diffuse slow waves in 12 (15%) patients. In remaining 54 (67.5%) patients EEG was normal.

Neuroimaging is very essential in the evaluation of late onset seizure. MRI scan brain is preferred than CT, because of more accuracy. In our study, all the patients underwent CT brain and the findings were as follows: Normal study in CT brain noted in 41 (51.2%) patients. Age related atrophic changes noted in 11 (13.7%) patients, chronic infarct/gliosis was noted in 11 (13.7%) patients, acute infarct noted in 10 (12.5%) patients, meningioma was seen in 3 (3.7%) patients and calcified granuloma was noticed in 3 (3.7%) patients. Overall, CT brain abnormality noticed in 28 (35%) patients. CVA (either the acute or old) was the single most common aetiology uncovered in this study.

Recent progress in genetic analysis reveal family history plays an important role in the development of seizure in any age group [36,37]. In our study, family history of seizures was noticed in 5 (6.3%) patients - 3 post stroke seizure patients, one diabetic patient and one patient with uremia. Family history was there, mostly in the form of their children were seizure disorder patients except in one 60 years old man whose elder brother was an epileptic on treatment.

Conclusion

Management of older people with seizures and epilepsy requires thorough understanding of the aetiologies and the various medical and psychosocial aspects unique to this age group. Early priority should be given to find out the treatable causes like metabolic disturbances. Blood biochemical investigations, EEG, neuroimaging are indispensable in the diagnosis. Our study demonstrates the various aetiologies of late onset seizure. In many patients more than single aetiology, multiple factors played a role. Interestingly, some aetiologies referred to as 'commonest' in many other studies, conducted at various places, seen less commonly in our region. Moreover many studies in late onset seizure conclude, in nearly half of the cases, aetiology could not be made out, that is idiopathic. But in our study, idiopathic seizure constitutes only 22.5%. These informations give more light into the understanding of aetiology and changing trends of late onset seizure. But this study comprises relatively small number of patients. Hence further studies with large number of patients are needed.

Key Messages

Late onset seizure should be evaluated for aetiology. Neuroimaging, EEG and blood biochemistry are must for first seizure in elderly age group.

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