International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 07 (D); July 2019; Page No.19557-19562
DOI: http://dx.doi.org/10.24327/ijcar.2019.19562.3782

Research Article

AN OBSERVATIONAL STUDY ON COGNITIVE IMPAIRMENT AND BEHAVIOURAL STATUS IN CHRONIC EPILEPSY

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A R T I C L E I N F O

Article History:

Received 6th April, 2019
Received in revised form 15th May, 2019
Accepted 12th June, 2019
Published online 28th July, 2019

Key words:

Epilepsy, cognitive impairment, anti-epileptic drugs

A B S T R A C T

Introduction: Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness withor without convulsions associated with abnormal electrical activity in the brain. Epilepsy is associated with cognitive and behavioural functions. Cognitive functions and behavioural disturbance are more frequent in epileptic patients with frequent seizures and associated neurological or mental abnormalities than in general population.

Materials and methods: A prospective observational study was conducted for a period of 6months in the Department of Neurology MGM Hospital, Warangal region. Chronic epilepsy patients attending the hospital were enrolled in the study and the data was collected from patient profile forms, direct communication with patients and their care givers. The patient data was collected in the data collection form by considering the study parameters.

Results: A total number of 196 chronic epileptic patients were included in the study. The level of impairment was found as severe in 27.55 % patients, mild in 27.04 % and 44.40 % patients had no cognitive impairment. Of all the patients observed in our study, 51 patients had abnormal behaviour.

Conclusion: Patients with long term uncontrolled seizures, increased seizure frequency, prolonged duration of epilepsy, long term use of antiepileptic drugs, higher doses of antiepileptic drugs, onset of epilepsy in early age, polytherapy were found with poor behavioural status. Pharmacist has a vital role in neurology department in counselling the patient about disease, medication adherence, counselling for regular visits to doctor and for proper dose adjustments.

INTRODUCTION

Epilepsy is a disorder of the central nervous system characterized by periodic loss of consciousness with or without convulsions associated with abnormal electrical activity in the brain. Epilepsy is characterized by repeated seizures due to a disorder of the brain cells (1). It is estimated that 20 lacks in United States of America and 3 lacks in United Kingdom (2).Nearly 12 million people with epilepsy are expected to reside in India (3).Seizures results from transient abnormal synchronization of neurons in the brain that disrupts normal patterns of neuronal communication and results in electrical discharges in the EEG. This disruption can produce various symptoms and signs that depend on the site of origin of the seizure (epileptic focus or zone) and its connections (4). Signs and symptoms due to abnormal excessive neuronal activity in the brain.

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Depending on which areas of the brain are involved, epileptic seizures may consist of loss of awareness with body tremors, confusion, and difficulty in responding; visual or other sensory symptoms; isolated posturing or jerking of a single limb; or brief loss of awareness. Seizure origin, pattern of spread, and brain networks involved determine the signs and symptoms of a seizure (5).

Epilepsy is associated with cognitive functions which includes memory, attention, concentration, language abilities, information processing, reaction time, spatial and emotional memory, psychomotor speed and specific learning disorders such as those affecting reading, writing or mathematical skills. Behavioural disorders include depression, psychosis, personality disorders, aggression, anxiety, mood changes, self-injurious behaviour and attention deficit hyperactivity disorder are more frequent in epileptic patients with frequent seizures and associated neurological or mental abnormalities. Cognitive functions are more frequently impaired in epileptic population than in general population (6). Prolonged and recurrent seizures cause and exacerbate cognitive impairment(7).

Causes for neuropsychological deficiencies in epilepsy are use of multiple antiepileptic drugs, multiple seizure episodes, epileptiform activity, symptomatic/cryptogenic aetiology (seizure occurrence with stroke, toxin, infection / unknown cause). Epileptic patients with these risks are three times more likely to develop neuropsychological deficiency (8).Seizure type, seizure control, dose of AED and duration of therapy associated with cognitive impairment. Polytherapy, early onset of seizures, poor seizure control was associated with significant impairment of attention and concentration. Among these polytherapy, early onset, poor control has adverse influence on brain function. Seizure type, AED type, dose of AED, duration have less impact on cognitive function (9).Compared with monotherapy, polytherapy was associated with worse overall performance of cognition (10).

MATERIALS AND METHODS

Our study was a prospective observational study carried out for a period of 6months at Mahatma Gandhi Memorial Hospital after obtaining approval from Institutional Ethics Committee. Chronic epilepsy patients attending the hospital were enrolled in the study. All the patients with chronic epilepsy prescribed with antiepileptic drug and age below 60years were included in the study. Exclusion criteria includes patients elder than 60 years of age, patients on medication other than antiepileptic drugs, fresh attack of seizures. The patient data was collected from patient profile forms, direct communication with patients and their care givers. The data collection form by considering the study parameters.

RESULTS

Of 196 chronic epilepsy patients 26.02% were with behavioural abnormality. According to MMSE it was found 27.55% are with severe cognitive impairment, 27.04% with mild impairment and 45.40% are without cognitive impairment. As per MoCAscale 25% are with severe cognitive impairment, 42.85% are with mild cognitive impairment and 32.14% are without cognitive impairment.

Among 196 patients, 118 were females and 78 were males. In our study 27.19% of patients were on monotherapy, 36.73% were on dual therapy and 35.71% of patients were on polytherapy. Cognitive impairment is mostly associated with polytherapy.

The study was divided into various groups according to their onset of age of epilepsy. In the study population it was observed that, at the age group of 0-5years both men and women were 41, followed by the age 6-10years (30), 11-15years age group were 35, 16-20years age group were29, 21-25 years (16), 26-30years (20), 31-35 years (8), 36-40 years (6),41-45 years (6) and 46-50 years (5) it was observed that cognitive and behavioural impairment is mostly seen in cases with early onset of age.

Of 196 patients, 27.55 % (54) patients were on one AED, 35.71 % (70) were on two AED's, 21.42 % (42) were on three AED's, 11.73 % (23) were on four AED's, 3.06 % (6) were on five AED's and 0.5 % (1) were on six AED'S.

Of all the patients many were with confused mindset with percentage of 67.34%. Out of all 196 patients, 21.42% patients do not depend for their daily activities and 78.57% depend on others for their daily activities.

Of all cases most of the patients have the seizure episode for nearly 10min. Amongst 196 patients, 59 had<5 episodes of attack followed by 40 patients with <10 episodes, 28 patients with <20 episodes, 34 patients with <30 episodes, 16 patients with <40 episodes and 19 patients with >40 episodes of seizures. Severity of cognitive and behavioral impairment are directly proportional with duration and frequency of attacks. Abnormality in alertness was observed in 39.79% of study populations.

Of 196 patients, 29.59 % (58) patients were with abnormality in immediate word recall and 70.40 % (138) patients were without abnormality in immediate word recall. 64.28 % (126)of patientswere classified as experiencing abnormality in delayed word recall and 35.71 % (70) patients are classified as without abnormality in delayed word recall.

Headache: Of 196 patients, 5.10 % (10) had headache before seizure attack, 6.12 % (12) had after attack, 37.24 % (73) patients had headache before and after attack and 51.53 % (101) patients were without headache.

Aura: In terms of aura, 86 patients were with aura phase and remaining are without aura phase. The number of patients with sleep disturbance is 32.14 % and the patients without sleep disturbance are 67.85 %.Among 196 patients, patients injured with epilepsy are 79 and patients without injury are 117.

Mostly prescribed drugs for the treatment are levetiracetam 34.18 % (67) while oxcarbazepine 1.02 % (2) is the least prescribed drug. Other drugs such as sodium valproate 17.34 % (34), carbamazepine 16.83% (33), clobazam 5.61% (11), clonazepam 5.61% (11) and oxcarbazepine 1.02 % (2) were also prescribed for the treatment of epilepsy.

Of all, 61.22 % (120) were without any impairment in verbal fluency and 38.77 % (76) were with impairment in verbal fluency.Among 196 patients,33.67 % (66) patients were education dropouts, 41.83 % (82) patients were uneducated and 24.48 % (48) patients did not have any problem in education.Of 196 patients, 38.26 % (75) patients were with changes in appetite and 61.73%(121) patients were without any change in appetitie.Out of 196 patients, 30.10 % (59) consumes alcohol and 136 69.38 % (136) do not take alcohol.

Table 1 Patients on Monotherapy, Dual therapy and Combination therapy of anti-epileptics

Type of Therapy	Number of patients	Percentage
Monotherapy	54	27.19
Dual therapy	72	36.73
Poly Therapy	70	35.71

Table 2 Distribution according to the age

Onset of epilepsy with age group	Onset of age	Percentage
0-5	41	20.91
5-10	30	15.30
11-15	35	17.85
16-20	29	14.7
21-25	16	8.16
26-30	20	10.20
31-35	8	4.08
36-40	6	3.06
41-45	6	3.06
46-50	1	0.51

Table 3 Distribution according to patients on No of AED's

Number of patients	On number of AED's	Percentage
54	*1*	27.55
70	2	35.71
42	3	21.42
23	4	11.73
6	5	3.06
1	6	0.5

Table 4 Categorization of MMSE scores

Score categorization	No. of patients	Percentage
Severe (<17)	54	27.55
Mild (18-23)	53	27.04
No impairment (24-30)	89	45.40

Table 5 Categorization of MoCA scores

MoCA Score categorization	No. of patients	Percentage
Severe (<17)	49	25
Mild (17-25)	84	42.85
No Impairment (26-30)	63	32.14

Table 6 Distribution based on duration of Attack

Duration of attack	Number of patients	Percentage
0-10min	130	66.32
11-20min	29	14.79
21-30min	30	15.30
31-40min	3	1.5
41-50min	5	2.55
51-60MIN	2	1.02

Table 7 Distribution based on visual and verbal impairment with chronic epilepsy

Impairment	Number of Patients	Percentage
Visual impairment	19	9.69
Verbal impairment	13	6.63
Visual and verbal impairment	66	33.67
No Impairment	98	50

Table 8 Drugs prescribed for the patients

Name of the drug	Number of patients	Percentage
Levetiracetam	67	34.18
Phenytoin	45	22.95
Sodium valproate	34	17.34
Carbamazepine	33	16.83
Clobazam	11	5.61
Clonazepam	11	5.16
Oxcarbazepine	2	1.02

Table 9 Frequency of attacks

Frequency of attacks	No. of patients	Percentage
<5	59	30.10
<10	40	20.40
<20	28	14.28
<30	34	17.34
<40	16	8.16
>40	19	9.69

DISCUSSION

Drugs prescribed: As per *Clare M. Eddyet.al.,* 1st generation or conventional Anti-epileptic drugs cause the great cognitive toxic potential (11).According to *P.S. Fastenauet.al .,* 14.9 % are on valproic acid followed by 14.9 % on oxcarbazepine (8). In our study we found that highest number of patients (33 %) are on levetiracetam followed by on phenytoin, sodium valproate, carbamazepine, clobazam, clonazepam and to least on oxcarbazepine. This was in contrast to the study conducted by *Rupa Joshi. et.al.,* in which highest number of patients are on phenytoin followed by sodium valproate, levetiracetam, carbamazepine, clobazam, oxcarbazepine and to the less number are on lamotrigine and phenobarbital (12). Levetiracetam was mostly prescribed drug due to its safety profile and efficacy.

Sleep disturbance: In our study, 32.14 % patients experienced sleep disturbance, like excessive sleepiness, difficulty in maintaining sleep. 67.85 % patients had no sleep disturbance. These results are similar with study conducted by *ZohrehYazdi et al.,* who reported that among 152 epilepsy patients, insomnia and excessive day time sleeping was observed in 38.1 % of patients (13). It was found that sleep quality in epilepsy patients was worse than normal people. Seizures during the night cause tiredness and result in inadequate sleep. Lack of sleep can affect concentration and contribute to memory difficulties.

Type of therapy: In our study majority of patients are on dual and polytherapy i.e., 36.73 % and 35.71 % respectively. AED polytherapy is associated with worse cognitive outcomes. Combination of AED's with different modes of action result in higher apoptosis of brain cells compared to monotherapy. Depression of synaptic neurotransmission is the common function of AED's which alter signaling of neurons resulting in cognitive defects. Long term use of AED polytherapy reduces alertness and slows down memory processing. A study conducted by *Lindsay A. Milleret.al.,* showed that 52.70 % are on polytherapy (10). This difference was due to improved efficacy and higher rate of seizure control with two AEDs over monotherapy. Patients reported improved quality of life and better seizure control after shifting to dual therapy and polytherapy.

Gender: In our study female were 60.2 % and male were 30.7 %. This was similar to the study conducted by *Joanne Tayloret.al.,* where males were 36.2 % and females were 63.2 % (14). In contrast to this, study conducted by *Paul J. Rathouzet.al.,* included 40 male patients and 29 female patients. Social problems, poor health care, cultural beliefs are more in women compared to men (15). Low awareness of disease and less literacy rate of female compared to male could also be the reason.

Frequency of attacks: Study conducted by *P.S. Fastenauet.al.,* showed that 30.2 % of patients are with multiple seizures episodes (8). Patients with multiple seizure episodes have four times more risk for cognitive and behavioral impairment. According to *Yoshimi Sogawaet.al.,*40 % of patients were with multiple seizure episodes (16). Similarly, in our study 49.47 % of patients are with multiple seizure episodes. Uncontrolled seizures impair cognitive function. Prolonged and frequent seizures impair brain maturation resulting in abnormal functioning of brain and the patients show behavioral abnormality.

Headache with epilepsy: According to *Christoph J. Schankinet.al.,* 47.10 % had experienced headache with epilepsy (17). Similarly, in our study 48.41 % experienced headaches before and after the seizure episodes. This is because both headaches and epilepsy have the common triggers such as alcohol, menorrhagia and irregular sleep pattern. Headaches and epilepsy even have some common pathophysiological mechanisms that is increased excitability of

the cortex accounting for increased risk of migraine and epilepsy. Headache and epilepsy have the common pathophysiological mechanisms which includes imbalance between excitatory and inhibitory neurotransmitters that result in altered brain function.

Change in appetite: As per study of *Rupa Joshi. et.al.,* it was shown that 9.47 % had loss of appetite and in contrast our study shown 38.26 % had appetite changes (i.e., loss of appetite and increased appetite) (12). The changes in appetite are due to the side effect of anti-epileptic drugs.

MMSE and MoCA scales: In a study conducted by *KayceeM et.al.,* MMSE and MoCA scales are used to assess the cognitive assessment in diabetic ketoacidosis patients (18). This study was done in elderly patients of mean age of 35-83 years. In contrast our study was done to assess cognitive level in chronic epilepsy patients using same MMSE and MoCA scales. The scores of MMSE are lower than MoCA this was similar to this study. The difference in scores in our study was due to difference in patient education level. According to MMSE scale our study stated that 27.55 % are with severe cognitive impairment followed by 27.04% with mild and 45.40 % patients without cognitive impairment. According to MoCA scale 25 % are with severe cognitive impairment, 42.85% with mild and 32.14 % are without cognitive impairment. Failure of neuronal network flexibility contribute to memory impairment.

Hyperactive and drowsiness: Study conducted by *Tuba CelenYoldaset.al.,* reported behavioral problems in children with epilepsy (19). Similarly, in our study the information collected from the patient care givers and patient's demographics stated that chronic epilepsy patients are aggressive, drowsy and with dull mood most of the times. This might be due to neurological abnormalities with prolonged uncontrolled seizures.

Verbal fluency: According to *Chris Taiblyet.al*., 34.5 % patients in their study had impaired verbal fluency (20). Verbal fluency was significantly impaired in chronic epilepsy patients. Similarly, in our study 31.77 % patients are with impaired verbal fluency. Defect in verbal fluency was due to abnormalities in functional networks of the brain. This deficit might be due to neuronal loss in multiple regions of the brain, destruction of afferent nerve connection, alteration in language networks in chronic epilepsy. The presence of epilepsy during childhood impact brain development, affect areas such as executive function, attention and language. This may be the cause of differences in language development.

Alertness: According to study done by *FilippoDonati et.al.,* alertness and attention in epilepsy patients was 48 % as per MMSE scale. Similarly, in our study alertness and attention was found to be 39.79 % (21). The defect in alertness and attention in chronic epilepsy patient is might be due to defect in processing speed and neuronal network abnormalities in the cortex region of the brain. The defect in alertness and attention is also due to long term use of anti-epileptic drugs that impairs concentration, learning skills, alertness, attention.

Social status: A study conducted by B*ruce P. Hermann et.al.,* stated that 32.10 % are at social-behavior risk. Similarly, in our study 21.42 % of patients depend on others for social and economic life (22). Chronic epilepsy is associated with abnormalities in cognition and social-behavior. Seizure attack cause defect in the normal function of the brain. Area of brain affected with seizures reflects the symptoms accordingly. Chronic epileptics have poor quality of life which eventually affects the social life of patient and the patient depends on others for their daily activities.

Epilepsy impact on education: A study conducted by *YashimiSogawaet.al.,* shown worse educational outcomes in children with epilepsy along with comorbid psychiatric disorders even with special education to them (16). In contrast, our study included only chronic epilepsy patients without comorbid conditions and we found that 33.67 % are education dropouts and 24.48 % had no issue with education. Academic underachievement and education dropout were due to poor memory functions, decreased learning skills. Developing brains are more vulnerable to long term consequences of antiepileptic induced cognitive impairment.

Onset of age: As per study conducted by *K. Jayashreeet.al.,* cognitive impairment was mostly seen with early onset of age, and we also observed the same (9). However, majority of epilepsy patients with cognitive and behavioral impairment were with early onset of age (less than 5years) and with frequent uncontrolled seizures. A study conducted by *Paul J Rathouzet.al.,* stated that presence of childhood epilepsy affects cognition (15). Our study has shown the same. As per our study, 20.9 % patients had onset of epilepsy in less than 5 years of age. The age at onset of seizures has a significant impact on cognitive side effects. Seizures occurred in early stage of life show significant adverse effects on cognition.

Behavioral impairment: Behavioral or emotional problems have reported with neurological disorders. A study conducted by *Daniel L. Keeneet.al.,* reported that 39.33 % had significant behavior problems (23). In a study conducted by *Tuba CelenYoldaset.al.,* reported 60 % behavioral problems in children with epilepsy (19). A study conducted by *Simon N Kariukiet.al.,* reported 52 % of behavioral problems. In contrast our study was done not only children it included the age group of 5-60years patients and our study stated abnormality in behavior in 26.02 %. Behavioral disorder is more frequent in epilepsy patients with associated neurologic and mental abnormalities. Defect in the behavior of chronic epilepsy patients is due to structural and functional deficit. Suppression of synaptic neurotransmission via blockade of glutamate and activation of GABA receptors triggers neurodegeneration. Depression of synaptic neurotransmission is the common action of antiepileptic drugs which cause neurodegeneration in the developing brain and result in abnormality in behavior.

Alcohol intake: As per *Xinjun Liet.al.,* most of the male patients are alcoholic (25). This was similar to our study in which majority male and few females consume alcohol. Alcohol intake or abuse is a risk factor for epilepsy as higher alcohol consumption worsens epilepsy. Alcohol intake increase the risk of accident injuries which is the cause of traumatic seizures. Seizures are common complication of head injuries.

Injury with epilepsy: Accidents and injuries are slightly more frequent among people with epilepsy. According to *Torbjorn Tomson et.al.,* there is increased risk for injuries to the epilepsy patients. Similarly, in our study 40 % of epilepsy patients are injured (26). Epilepsy patients are more prone to traffic accidents in drivers with epilepsy. Increased risk is probably most prevalent in patients with prolonged frequent

seizures, most often in combination with associated handicaps. Absence of aura phase in seizure causes majority of injuries. Most of the patients are severely injured and are with poor quality of life.

Verbal memory: As per *P.S. Fastenauet.al.,* study, verbal memory was 23 %. Similarly, in our study we found that 30 % patients had impaired verbal memory (8). In our study 30 % patients are with impaired immediate word recall and 64.28 % patients are with delayed word recall. Abnormalities in the temporal or frontal lobes of the brain are the most common reason for memory problems in people with epilepsy. Left temporal lobe is important for verbal memories such as learning names and remembering. The right temporal lobe is important for visual memories like remembering a person's face or finding way to a place.

Frequency of attacks: In our study it was found that patients with higher frequency of attacks are with poor memory performance compared to patients with lesser number of attacks. Uncontrolled seizures have cumulative effects on cognition. Our study observed that patients with repeated and prolonged attacks have decline in intellectual performance. This might be due to structural changes in the brain associated with repeated seizures. This was similar to the study conducted by *K. Jayashreeet.al.,* which stated that impaired cognitive effects with poor seizure control (9). Uncontrolled seizures have deleterious negative effects on cognition and behavior, particularly in the developing brain.

CONCLUSION

Seizure frequency, duration of epilepsy, long term use of antiepileptic drugs, higher doses of antiepileptic drugs, onset of epilepsy in early age, polytherapy, unaware of triggering factors, poor compliance to medication heightened the risk for cognitive and behavioral impairment (Impairment in verbal memory, visual memory, attention, executive function, processing speed, verbal fluency, poor learning skills, writing and reading skills, spontaneous speech, repetition of words). Early intervention of seizures, rationale choice of antiepileptic of drugs with proper dose tapering, reducing drug toxic level results in better cognitive outcomes of patients. Adverse effects of antiepileptic drugs can be avoided by slow titration to the lowest effective dose and by avoiding polytherapy. Pharmacist have a vital role in neurology department in counselling the patient about disease, medication adherence, counselling for regular visits to doctor and for proper dose adjustments.

Abbreviations

MGM: Mahatma Gandhi Memorial
EEG: Electro Encephalogram
AED: Anti-Epileptic Drugs
MMSE: Mini Mental State Examination
MoCA: Montreal Cognitive Assessment
GABA: Gaba Amino Butyric Acid

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How to cite this article:

Mayuri B *et al* (2019) 'An Observational Study on Cognitive Impairment and Behavioural Status in Chronic Epilepsy', *International Journal of Current Advanced Research,* 08(07), pp. 19557-19562. DOI: http://dx.doi.org/10.24327/ijcar.2019.19562.3782

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