Original Research Article

Comorbid Neurocognitive Impairment in Patients with Epilepsy

Geetanjali Gupta[1], Raghav Kesri[2], Ankur Sachdeva[3], Yusuf Matcheswalla[4], Sagar Karia[5], Avinash De Sousa[6]

[1]Assistant Professor, Department of Psychiatry, ESIC Medical College, Faridabad, Haryana.
[2]Senior Resident, Artemis Hospital, Gurugram, Haryana.
[3]Associate Professor, Department of Psychiatry, ESIC Medical College, Faridabad, Haryana.
[4]Honorary Professor, Department of Psychiatry, Grant Medical College, Mumbai, Maharashtra.
[5]Assistant Professor, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai, Maharashtra.
[6]Research Associate and Consultant Psychiatrist, Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai, Maharashtra.
Corresponding author: Sagar Karia
Email – karia777@yahoo.com

ABSTRACT

Background: Epilepsy is a common chronic non-communicable neurological disorder in which the brain function is impaired. Cognitive function is more frequently impaired in people with epilepsy than in the general population. The neurocognitive outcome of epilepsy in children and adults is vital for social prognosis and quality of life assessment. Cognitive changes in epilepsy have multifactorial etiology, including the epilepsy itself, age at onset, duration of epilepsy, treatment of epilepsy, reaction to epilepsy and any associated brain dysfunction and /or damage. This study was conducted to check association of neurocognitive impairment with the socio-demographic factors and disease associated factors in patients with epilepsy.
Methodology: This study was a single centre cross-sectional study in which 96 patients were included. Severity of neurocognitive impairment was measured by Addenbrookes' Cognitive Examination- R (ACE-R) score.
Results: Out of 96 patients, neurocognitive impairment was seen in 23 (23.95%) patients. Conclusions: This study shows that neurocognitive impairment was found to be more when the age at onset of epilepsy was less, when the duration of the illness was more and when frequency of seizure was higher.
Conclusion: Neurocognitive impairment is noted in patients with epilepsy and must be treated in the long-term management of epilepsy.

Keywords: epilepsy, neurocognitive impairment, ACE-R, seizure frequency, seizure duration.

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INTRODUCTION

Epilepsy accounts for 0.5% of the global disease burden, about 35 million out of 50 million do not have adequate treatment available because the clinics do not exist or epilepsy is not seen as a psychiatric disorder or a treatable neurological disease [1]. Much focus has been paid to the quality of life of epilepsy patients over the last few decades, but the progress is slow, and the services are still poor [1-2].
Neuro-cognitive impairment means the gradual and chronic loss of mental abilities over time, not the reversible postictal cognitive deterioration that can be observed shortly after focal and generalized seizures. It is permanent in nature. Cognitive function is more frequently impaired in people with epilepsy than in the general population [3]. Multiple studies have suggested that epileptic seizures may be associated with cognitive problems in children and adolescent which are then carried into adulthood [4]. 10-20% of patients

of childhood epilepsy who have poorly controlled epilepsy are at an increased risk of developing intellectual impairment [4]. Epidemiological studies have reported that cognitive functions such as attention, language, verbal memory, executive functions, reaction time, visuo-spatial ability, visual memory, sensorimotor functions and emotional memory, are more frequently affected in patients with epilepsy than in the general population [3]. Also patients with epilepsy are more prone to develop specific learning disorders such as those affecting reading, writing or mathematical skills, than the general population even in children with normal intelligence [5-6]. Learning disabilities in turn undermine the social skills and educational attainment [7].

Cognitive changes in epilepsy have multifactorial etiology, including the epilepsy itself, age at onset, complications due to epilepsy, treatment of epilepsy (antiepileptic drugs (AEDs) or surgery), reaction to epilepsy (stigma, social marginalization, and familial dynamics), and any associated brain dysfunction and/or damage [3]. Epileptogenicity is known to cause changes of brain structure and function in many different ways [8]. Seizures induce progressive cellular and metabolic alterations correlated with (hippocampal) neuronal loss, neoneurogenesis and synaptic reorganization, increased susceptibility to evoked and spontaneous seizures, and behavioural and cognitive functions that worsen as a function of the cumulative number of seizures [9-10]. In infancy or in early childhood, abnormal recurrent synaptic bombardment of distant projection areas, caused by repeated ictal and interictal epileptiform discharges, can adversely affect the development of normal neuronal integration [11]. In the mature brain, this abnormal synaptic activity may induce plastic changes through kindling mechanisms, and impair the naturally occurring homeostatic seizure suppressing mechanisms which maintain the interictal state, with adverse consequences on the normal neuronal function [12]. Ten percent of the people with chronic epilepsy, some younger than 40 years of age, showed senile plaques. Plaques formation is more in people with chronic epilepsy than in the general population, especially in those patients expressing the epsilon 4 allele [13].

Cognitive functions, including psychomotor speed, vigilance, memory, attention, and mood, are affected by antiepileptic drugs. Children and old people are especially vulnerable [3]. Phenobarbital and benzodiazepines, for example, can have negative effect on cognition [14]. In general, newer antiepileptic drugs produce fewer cognitive effects, although topiramate may impair attention, memory and language [15]. Also some antiepileptic drugs can exacerbate vascular risk factors that, promote vascular dementia and Alzheimer's disease [16]. It is also seen across various studies, the longer one suffers from intractable epilepsy, the more prolonged the exposure to interictal discharges or anticonvulsant drugs, and greater the risk of seizure related brain damage. Seizure frequency itself also often related to increased or multiple antiepileptic drug dosage and uncontrolled seizures burden the psychological and psychosocial well being of the patient which also negatively affects the cognitive performance [17].

METHODOLOGY

This research was performed at the Epilepsy Clinic in the Out-Patient Department (OPD) of a tertiary care private hospital in Mumbai. Those patients who fulfilled the diagnostic criteria of epilepsy according to the International League Against Epilepsy (ILAE) definition of epilepsy, attending the epilepsy clinic in the OPD, were considered for the study. The study was a single centred, cross-sectional study and was performed after approval from the institutional ethics committee. According to the previous studies, the prevalence of neurocognitive impairment in patients of epilepsy was 32.5% [18]. $N = (Z^2 \times P(1 / P))/e$ was used for sample size calculation [19]. A sample size Total 84 cases would be sufficient to assess the objectives of study at 5% level of significance with 80% of Power. Considering 10% dropouts, a minimum of total 93 patients had to be enrolled in this study. Total duration of the study was one year. Initially 105 male and female patients between 18-65 years of age suffering from epilepsy disorder were included. Later, 12 patients were excluded as they either did not consent for the study, or had seizure in the last one month, or serious medical disorder which resulted in seizure, substance dependence , neurological disorder, head injury, acute psychosis, or pre-existing psychiatric illness, which could affect assessment. The participants were assured about the confidentiality of their data and asked to fill up a sociodemographic questionnaire which included domains of age, sex, religion, marital status, education, occupation, family and socioeconomic status.

Questions related to epilepsy like age of onset of illness, total duration of illness, frequency seizure in the last year were also asked.

Addenbrookes' Cognitive Examination- R (ACE-R) Hindi version was used for assessment of neurocognitive impairment. ACE-R is an inexpensive and sensitive tool to test for cognitive impairment. The Hindi version of ACE-R was developed at Nijam's Institute of medical sciences (NIMS), Hyderabad. The ACE-R takes between 12-20 min (average16) to administer and score in a clinical setting. This test has five subscales testing for attention and orientation (18 points), memory (26 points), fluency (14 points), language (26 points), and Visio-spatial (16 points) deficits. ACE-R maximum score is 100, composed by adding all the domains. Cut –off score of 82 was used to segregate patients into two groups of cognitive impairment or no impairment [20].

RESULTS

Table 1 shows the socio-demographic parameters of the study participants. The study included 96 participants with the age ranging from 18 – 65 years. 55.2% of the cases were males and 44.8% of the cases were females. Table 2 shows the phenomenological details of epilepsy in study population. 54.2% had duration of <5 years of seizures and 59.4% of them had onset after 20 years of age. Majoirty of them (55.2%) were seizure free in last 1 year.

When checked for neurocognitive impairment, 23 (23.96%) patients had ACER score of less than 82, suggestive of cognitive impairment, of which 14 were males and 9 were females. Table 3 shows correlation of various factors with ACER score in total population and in those having cognitive impairment. Overall there is significant correlation with age of patient, age of onset and duration of illness but not in patients having cognitive impairment. Even there is no association of cognitive impairment with number of antiepileptic drugs.

Table 1: Demographic details of study population:

Parameter (N = 96)		**Mean ± S.D./ Frequency (%)**
Age in Years		36.24 ± 12.99 (18-65)
Sex	Male	53 (55.2%)
	Female	43 (44.8%)
Religion	Hindu	33 (34.3%)
	Muslim	42 (43.7%)
	Others	21 (21.8%)
Education	Illiterate	6 (6.6%)
	Primary & Middle School	33 (34.3%)
	High School	19 (19.8%)
	Graduate	38 (39.5%)
Occupation	Employed	34 (35.4%)
	Unemployed	62 (64.6%)
Marital Status	Married	49 (51.0%)
	Single	36 (37.5%)
	Divorced/ Widowed	11(11.5%)

Table 2: Phenomenological details of epilepsy:

Parameters (N = 96)		**No. Of Cases (%)**
Age of Onset in Years	00 – 10	10 (10.4%)
	11 – 15	14 (14.6%)
	16 – 20	15 (15.6%)
	> 20	57 (59.4%)
Total Duration of Illness in Years	0-5	52 (54.2%)
	5-10	25 (26.1%)

	10-15	06 (6.3%)
	>15	13 (13.5%)
Frequency of Seizure in Last 1 Year	0	53 (55.2%)
	1	18 (18.7%)
	2	11 (11.5%)
	3	5 (5.2%)
	4	3 (3.1%)
	5	4 (4.2%)
	>5	2 (2.1%)

DISCUSSION

Epilepsy can occur at any age in life, most often in childhood (about two-thirds of seizures begin in the early years of life). According to statistics from the Epilepsy Foundation, the prevalence is 3% by the time a person reaches at the age of 75 [21]. In the present study, majority (30.2%) of the cases belong to the age group 26-35 years. There is a vast disparity in the studies conducted in the West and the Indian data regarding the marital status. The majority of the sample in our study were married (51%), whereas 37.5% were single, 5% were divorced, and 6% were widowed. Western data shows that a higher number of patients were either single or were divorced. In India, epilepsy is a ground for divorce or dissolution under the 1954 Special Marriage Act. Majority of participants were married, which might be due to cultural and social stigma associated with divorce in India. In the present study, the majority 34 (35.4%) employed are males whereas 11 (11.5%) reported being working women, 22 (23%) homemakers, 13 (13.5%) unemployed, 12 (12.5%) students, and 4 (4%) were retired. It has been found that work compromise due to epilepsy affects a significant number of patients 32 (33.3%). Epilepsy is associated with stigma, which makes it difficult for patients with epilepsy to find employment [22].

In this study, the majority 57 (59.4%) patients were with early onset of epilepsy over 20 years of age followed by 15 (15.6%) were 16-20 years of age, 14 (14.6%) were 11-15 years of age and ten (10.4%) were ≤ ten years of age. Therefore, the sample population consisted mainly of adult epilepsy patients. Patients in this study who had epilepsy for the last five years or less, 52 (54.2%) followed by 5-10 years 25 (26%), more than 15 years were 13 (13.5%), and 10-15 years were six (6.3%). A similar population was selected by stefanello et al. where 57% of patients had epilepsy for five years or less [23].

In this study profile, 53 (55.2%) patients did not have any seizure in the last one year, whereas 18 (18.7%) cases had one seizure, 11 (11.5%) cases had two seizures, five (5.2%) cases had three seizures, three (3.1%) cases had four seizures, four (4.2%) cases had five seizures and two (2.1%) cases had more than five seizure episodes. Though the frequency of seizures is a risk factor for the development of psychiatric comorbidities in patients of epilepsy [24]. Patients fear that they will lose their job if people find out about their illness, which results in less reporting of both epileptic symptoms and the psychiatric-comorbidities associated with them.

Present study shows that 23 (23.95%) out of 96 patients had neurocognitive impairment. A study by Helmstaedter et al. found that 26% of epilepsy patients presented with clinically relevant cognitive problems [25]. Mojs et al. found that 30% of patients had cognitive dysfunction which was connected to epilepsy [26]. In this study, 53.8% of the patients had Neuro-cognitive impairment belonged to 56 – 65 years of age. Most of the studies done on cognitive are in childhood epilepsy. No previous study reports that higher rate of cognitive impairment is seen in older age group. This result in our study might be due to the fact that, patients in the age group of 56-65 are more prone to develop dementia, which itself causes cognitive impairment. 26.4% of Males and 20.9% of the females had neurocognitive impairment, but the difference was not significant. In various previous studies, none report any sex predominance for development of neurocognitive impairment. In the present study, it was seen that 80 % of the patients were having neurocognitive impairment among patients in whom the age of onset of epilepsy was 00–10 years. The standard chronic synaptic bomb of discrete projection areas, accompanied by repetitive ictal and interictal epileptiform discharges, suspiciously influences the development of normal neuronal integration in infancy or childhood (Engel et al.) [27]. Berg et al. found that early age at onset of epilepsy is associated with

symptomatic causes and epileptic encephalopathy, which are both associate with neurocognitive impairment [28]. Krishnamoorthy et al. also reported that cognitive impairment is more when epilepsy starts at an early age [29]. This might be due to the fact that the brain and neuronal development takes place during infancy and early childhood.

84.6% of the cases had neurocognitive impairment amongst patients who suffered with epilepsy for > 15 years which was significantly more as compared to those having epilepsy for less than 15 years. This might be due to the fact that, as the duration of epilepsy increases, the brain of the patients has much more recurrent bombardment, leading to plastic changes through kindling mechanisms, which adversely affect the normal neuronal function [29].

Neurocognitive impairment was seen to be present when the age of onset of epilepsy was earlier and also when duration of the illness was more. Neurocognitive impairment was found to be more in the elderly population, but this might be due to the fact that they are more prone to develop dementia causing cognitive disturbances.

The study had some limitations in form that this was a single centered study of patients coming to private hospital so results cannot be applied to general population. Also it was a cross sectional study so course of illness was not studied.

CONCLUSION

This study shows that neurocognitive impairment was seen to be present in 23 (23.95%) patients of seizure disorders and neurocognitive impairment was more when the onset age of epilepsy was earlier and when duration of the illness was more.

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