

AGGRESSION IN INTRACTABLE EPILEPSY

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ABSTRACT: BACKGROUND: Increased rate of aggression in patients with epilepsy is well known. However this phenomenon is relatively less studied systematically. **AIMS:** To study the prevalence of aggression in medically intractable complex partial epilepsy and its association with Electroencephalograph (EEG), Magnetic Resonance Imaging (MRI) variables. **MATERIALS AND METHODS:** Forty random sample of patients with medically intractable epilepsy were assessed for frequency and severity of aggression on Overt aggression scale. The relationship between EEG, MRI variables and aggression were computed. **RESULTS:** Verbal aggression was present in 35(87.5%), physical aggression against other people was present in 13(32.5%), physical aggression against objects was present in 10(25%), physical aggression against self was present in 6(15%) patients. No significant correlation of aggression was found with age at onset, duration of seizures, frequency of seizures, presence of febrile seizures, presence & laterality of temporal focus, presence of generalized discharges on EEG and presence of MTS or other abnormalities on MRI. There was significant negative correlation between use of carbamazepine and physical aggression against self ($p=0.014$). **CONCLUSION:** High rates of aggression are present in patients with intractable epilepsy, and it is probably related to generalize subtle brain damage than any focal damage, interacting with the effects of seizures, interictal changes associated with epilepsy, effects of AED and adverse psychosocial events.

KEYWORDS: epilepsy, aggression, EEG, MRI.

INTRODUCTION: Patients with epilepsy have increased psychological problems, including, psychiatric disorders, personality problems, aggression, cognitive and psychosocial difficulties, more than that seen in general population^[1,2] and in other neurological disorders.^[3] Generally the rates of psychological problems are higher in complex partial epilepsy upto 30-50%,^[4,5] probably due to the important role of temporal lobe in psychiatric disorders, which further increase to up to 50-80% in patients with intractable epilepsy.^[6,7]

Aggressive behaviour in epilepsy can be categorized into three different types on the basis of their relationship to the seizures – Ictal, postictal and interictal aggression, the most common among these being the postictal aggression.^[8] Aggression can also occur as a part of prodromal symptoms, consisting mainly of irritability and verbal aggression.

Aggressive acts during complex partial seizures can occur both with and without provocation and consists of verbal or physical spontaneous, non-directed, stereotyped aggressive behaviour directed usually at inanimate objects. Though there are many reported cases of violent crimes in the ictal phase, further investigation with video EEG of suspected aggressive behaviour by epileptologists has shown that ictal aggression is extremely rare present in only 7 of 5400 patients with epilepsy.^[9]

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Postictal verbal/ physical aggression occurs during recovery from generalized tonic clonic seizures and less often complex partial seizures and is usually associated with confusion. Postictal aggression can also be a manifestation of postictal psychosis.^[10]

Increased rates of interictal aggressive behaviour have been reported in patients with temporal lobe epilepsy but the exact prevalence is not known. The problem with studying aggression is its phenomenological and probably neurobiological heterogeneity. Two different types i.e., predatory and defensive aggression are reported.^[11,12] Predatory aggression is characterized phenomenologically as a well structured and goal directed behavior performed in an emotionally calm and concentrated state of mind. Defensive aggression in contrast is less structured and is seen typically in the context of high emotional arousal associated with vocalizations and signs of fear or anger. Defensive aggression is the one commonly present in patients with epilepsy.

An interictal syndrome of episodic affective aggression independent of observable ictal activity, major psychiatric disorder, substance abuse or antisocial personality disorder is well described and has been referred to as episodic dyscontrol.^[13] Episodic dyscontrol is characterized by several discrete episodes of failure to resist aggressive impulses, and the behaviour is out of proportion to any psychosocial stressor. Such aggression is increasingly associated with temporal lobe epilepsy^[14] and male sex.^[10, 14]

Various brain structures have been implicated in the mediation of aggressive behaviour in animals and humans including periaqueductal gray, hypothalamus, amygdala and associated limbic structures and the frontal lobes.^[15] Pathology within the circuits affecting the amygdala might lead to mental states where misinterpretation of sensory input as threatening leads to aggressive outbursts and bilateral amygdalotomy has shown to improve aggressiveness.^[16] Involvement of one of these structures in TLE may explain the increased prevalence of aggression among patients with TLE. However investigators looking at relationship between specific EEG or CT pathology and aggression in patients with temporal lobe epilepsy could not find any such association.^[17]

Previous studies were mostly in patients who were candidates for epilepsy surgery and few studies have emphasized on personality or aggression, which can be major problems in the management of these patients. The role of seizure variables, psychosocial variables and antiepileptic drugs in aggression remains unclear. Further the anatomical basis for psychopathology in these patients has shown conflicting evidence. Imaging studies have indicated both presence and absence of any association between psychopathology and structural lesions like medial temporal sclerosis.^[18, 19]

The paucity of research in intractable epilepsy related to aggression, unclear etiological roles of various factors for aggression including seizure related and anatomical factors, importance of recognition and management of psychological problems in patients with intractable epilepsy in general and in candidates for surgery in particular, emphasizes the need for the present study.

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AIMS: To study the prevalence of aggression in medically intractable complex partial epilepsy.

To study the association of aggression with Electroencephalograph (EEG) findings of laterality of focus and other abnormalities and with Magnetic Resonance Imaging (MRI) findings of medial temporal sclerosis

METHODS: The random sample was selected from Refractory Epilepsy Clinic, a multispecialty integrated outpatient clinic held once in a fortnight, exclusively for patients diagnosed to have medically intractable epilepsy. The sample consisted of 40 patients.

Informed consent was taken for all patients.

INCLUSION CRITERIA: Patients in the age group 16-55 years, belonging to either gender, clinically diagnosed as having medically intractable complex partial seizures with or without secondary generalization. Medically intractable being defined as those individuals continuing to have seizures with an average frequency of at least twice every month, for a period of at least two years, in spite of therapy with at least two standard anticonvulsants in maximum tolerated doses.^[20]

EXCLUSION CRITERIA: Presence of a psychiatric disorder prior to the onset of seizure disorder.

Presence of other types of seizures, which are associated with intractability.

Presence of associated mental retardation.

TOOLS USED:

1. Pre-designed proforma to collect data, which included socio demographic, seizure related and antiepileptic drug related history.
2. Scalp EEG as per standard international 10-20-electrode placement technique was done and assessed for background and paroxysmal activity and for site and laterality of lesion. EEG was done for all patients around the time of psychiatric evaluation. All EEGs were assessed with the help of consultant neurologist. Sphenoidal EEG was done as part of work-up of refractory epilepsy in those patients where the scalp EEG did not yield good results.
3. MRI images were obtained in T₁, T₂ weighted and flair modes to demonstrate the medial temporal lobe structures and to exclude other structural lesions. An MRI done as part of the work-up for refractive epilepsy was considered. All MRIs were assessed with the help of radiologist and the consultant neurologist.
4. Clinical assessment – was done using relevant scales as follows:
 - a. **MMSE**^[21] Patients with a cut off score of >24 were included in the study.
 - b. **Overt Aggression Scale**^[22]

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This is an easily administrable scale used by mental health professionals, which rates severity of aggression under 4 categories.

- Verbal aggression
- Physical aggression against objects
- Physical aggression against self
- Physical aggression against others

Examples of representative behaviors are used to define the scale points and to guide in gauging severity of aggression. Each of the categories of aggression has 4 responses, which are marked if present. The responses in each category are rank ordered e.g. score of 0 is given if none of the responses are marked; a score of 3 is given if only the 3rd response is marked or if first, second and third responses are marked.

This scale has been earlier used in many studies to measure aggression in neuropsychiatric disorders^[23, 24, 25]

Analysis: Data was analyzed using SPSS statistical package version 10.

RESULTS:

Sociodemographic characteristics: Mean age of the subjects was 30.18 (SD 8.37). Other details of socio-demographic distribution are shown in Table 1.

Age	Mean – 30.18	SD – 8.37
	Min – 16	Max – 51
	Frequency (n=40)	Percentage
Sex		
Male	26	65
Female	14	35
Occupation		
Student	03	7.5
Manual labourer	11	27.5
Professional	09	22.5
Business	01	2.5
Others	10	25
Unemployed	6	15
Marital Status		
Never married	27	67.5
Married	11	27.5
Separated	2	5
Education		
<10 yrs	21	52.5
10-15 yrs	14	35
>15 yrs	5	12.5

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Residence		
Urban	32	80
Rural	8	20

Table 1: Socio-Demographic Details

Seizure related variables: As shown in Table 2, majority (85%) of patients had age at onset of seizures below 20 years and 37.5% of them below 10 years. The frequency of seizures in a majority of them was 1-4 per month. Most people had sought treatment within 6 months of the onset of seizures indicating that patients in this sample had developed intractability in spite of seeking early treatment. Duration in a majority was more than 10 yrs, 52.5% had a duration of 10-20 yrs, 25% had a duration of >20 yrs, 22.5% had a duration of <10 yrs. Complex partial seizures (CPS) with secondary generalization was the most common, simple partial seizures (SPS) with CPS and generalization was the next common and almost equal number had only CPS or SPS with CPS.

Past history of febrile seizures was present in 25%, and head injury in 5.4%. Family history of seizures in a first degree relative was present in 32.5% of patients. Head injury was present in 2(5%) patients. Five of our patients (12.5%) had undergone surgery.

EEG Variables: EEG was abnormal in 80% (n=32) of patients. Background was normal in 92.5% (n=37) of patients. The abnormalities were in the form of diffuse or hemispheric or focal slow waves. A temporal focus on EEG was present in 75% of patients, of whom 12 had right, 7 had a left and 11 had bilateral temporal focus. Generalized seizure discharge was present in 12.5% (n=5).

MRI Variables: MRI could not be done in 8 (20%) patients. Among the 32 (80%) people who had MRI, it was normal in 9 patients (28%) and abnormal in 23 (72%). Presence of hippocampal atrophy and hyper intensity on T2 was considered as medial temporal sclerosis (MTS). MTS was absent in 19 patients (57%), and present in 13 patients (39%) of whom 6 had right unilateral, 6 had left unilateral and 1 bilateral MTS. Ten patients had an abnormality other than MTS which included focal gliosis or infarct in a different area, cerebellar atrophy & temporal atrophy due to past infarct.

AED: Majority of the subjects were on more than three drugs (85%), of whom 55% (n=22) were on three drugs and 30% (n=12) on four drugs. Majority of patients (39 out of 40) were on rational polypharmacy reflecting difficulty in controlling their seizures.

Most people (87.5%, n=35) were on carbamazepine, majority in the dose of 600-1200 mg/day. Clobazam was the next commonly used drug in 65%. Thirty percent of people were on phenobarbitone and 55% on phenytoin. Compliance was good in 75% of patients and fair in 25%.

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A) Age at onset	Frequency (n=40)	Percentage
<10 yr	15	37.5
10-20	19	47.5
20-30	5	12.5
>30	1	2.5
Duration of seizures		
< 10	9	22.5
10-20	21	52.5
20-30	10	25.0
B) Frequency (per month) of seizures		
1-4	29	72.5
4-8	5	12.5
9-12	3	7.5
>12	3	7.5
Duration before treatment (months)		
1-6	31	77.5
7-12	3	7.5
13-36	5	12.5
>36	1	2.5
Type of seizure		
Complex Partial Seizure (CPS)	7	17.5
CPS –Generalization	17	42.5
Simple Partial Seizure (SPS)-CPS	6	15
SPS-CPS-Gen	10	25

Table 2: Seizure-related variables

Aggression: Overall 87.5% patients had some form of aggression. Aggression scores are shown in Table 3. Verbal aggression was present in 35(87.5%) patients of whom 21(52.5%) patients scored 1 indicating that they shouted angrily, 8(20%) scored 2 indicating that they made mild personal insults, 5(12.5%) scored 3 indicating that they cursed or used foul language and 1(2.5%) scored 4 indicating that they made clear threats of violence. Physical aggression against other people was present in 13(32.5%) patients, of whom 3(7.5%) scored 1 indicating that they made threatening gestures, 3(7.5%) scored 2 indicating that they kicked or pushed people. Physical aggression against objects was present in 10(25%) patients, of whom 2(5%) scored 1 indicating that they slammed doors or made a mess, 4(10%) scored 2 indicating that they threw objects or kicked furniture, 1(2.5%) scored 3 indicating that they broke objects, 3(7.5%) scored 4 indicating that they threw objects dangerously. Physical aggression against self was

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present in 6(15%) patients, of whom 3(7.5%) scored 1 indicating that they hit themselves, 3(7.5%) scored 2 indicating that they banged heads or hit fist into objects.

C) Verbal Aggression	Frequency (n=40)	Percentage
0	5	12.5
1	21	52.5
2	8	20
3	5	12.5
4	1	2.5
Physical aggression against objects		
0	30	75
1	2	5
2	4	10
3	1	2.5
4	3	7.5
Physical aggression against self		
0	34	85
1	3	7.5
2	3	7.5
3	0	0
4	0	0
Physical aggression against others		
0	27	67.5
1	7	17.5
2	5	12.5
3	1	2.5
4	0	0

Table 3: Aggression scores

Aggression and EEG Variables: The associations of aggression with temporal focus, generalized seizure discharges are shown in Table 4. There was no significant correlation between any of the aggression scores and age, gender, education, occupation, marital status and residence. No significant correlation was also found with age at onset, duration of seizures, frequency of seizures, presence of febrile seizures, presence & laterality of temporal focus, presence of generalized discharges on EEG.

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	Temporal focus	Mean	Std. Deviation	t/p	Generalized seizure Discharges	Mean	Std. Deviation	t/p
Verbal aggression	Rt	1.33	.98	-0.544	Present	2.00	1.41	1.527
	Lf	1.57	.79	p=.593	Absent	1.31	.87	P=.135
Physical aggression against objects	Rt	1.00	1.54	0.660	Present	1.40	1.95	1.527
	Lf	.57	.98	p=.518	Absent	.51	1.09	P=.135
Physical aggression against people	Rt	.50	.67	0.210	Present	.80	1.30	0.116
	Lf	.43	.79	p=.836	Absent	.46	.74	p=.387
Physical aggression against self	Rt	8.33E-02	.29	-0.387	Present	.00	.00	0.035
	Lf	.14	.38	p=.703	Absent	.26	.61	p=.358

Table 4: Aggression and temporal focus and generalized discharges

Aggression and MRI Variables: No significant correlation was found with presence of MTS or other abnormalities on MRI. The association of aggression with MRI variables is shown in Table 5.

	MRI abnormalities - mts vs others	Mean	Std. Deviation	T	P
Verbal aggression	Mts	1.31	.75	-0.769	.451
	Other abnormality	1.60	1.07		
Physical aggression against objects	Mts	.69	1.25	0.170	.867
	Other abnormality	.60	1.35		
Physical aggression against people	Mts	.46	.78	0.624	.687
	Other abnormality	.60	.84		
Physical aggression against self	Mts	.31	.63	0.053	.353
	Other abnormality	.10	.32		

Table 5: Aggression and MRI

Physical aggression against people was found to correlate positively with family history of epilepsy ($p=0.021$) and negatively with presentation of aura ($p=0.047$). There was significant negative correlation between use of carbamazepine and physical aggression against self ($p=0.014$).

DISCUSSION: Interictal aggressive behaviour has been reported in 5-50% of epilepsy population especially in temporal lobe epilepsy.^[10, 26, 27]

However, no prospective controlled studies of interictal aggression have been done in general epilepsy population. No study has used standardized rating scales or specified criteria for rating aggression. Several studies have compared the aggressive behaviour of patients with TLE, other epilepsies, neurological and psychiatric disorder; none have found an increase rate of aggression in TLE (reviewed by, Hermann & Whitman, 1984).^[28] However aggression scores have been found to be greater in TLE than in general population. To complicate issues further, risk

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factors for aggression often co-exist with epilepsy and may contribute to interictal aggression. These factors include male sex, lower socioeconomic status, exposure to violence as child, violent behaviour in childhood, focal/diffuse neurological lesions, cognitive impairment and medications.^[8]

The form of aggression studied has mostly been physical aggression or rage episodes. Less pathologic forms of aggressive behaviour such as irritability and anger have not been systematically studied, but when patients with partial or generalized seizures are systematically questioned, almost 30% report intense paroxysmal irritability and moodiness during the interictal period compared with 2% of normal or neurologic controls.^[8]

Our study revealed some interesting findings. Majority of patients (87.5%) had significant and distressing verbal aggression, they shouted loudly when angry, 35% of whom used personal insults in addition, 12.5% used foul language, and 2.5% made clear threats of violence. Thus patients with epilepsy can have varying degrees of verbal aggression, which is likely to be missed in studies measuring only rage episodes, wherein physical aggression predominates.

Physical aggression also can be of varying types. The subjects in this sample had physical aggression against others more commonly compared to physical aggression against objects and physical aggression against self.

Physical aggression can also vary in severity. Physical aggression against others ranged from making threatening gestures or swinging at people to striking, pushing or pulling by hair to attacking others causing mild physical injury.

Physical aggression against objects ranged from, slamming doors or making a mess (5%), to throwing objects or kicking furniture (10%), to breaking objects to throwing objects dangerously (7.5%).

Physical aggression against self-ranged from hitting self (7.5%) to banging head or throwing oneself to the floor without physical injury (7.5%).

The Overt Aggression Scale does not measure other forms of anger besides overt aggression. A substantial number of our patients also reported other forms of anger like sulking, refusing to eat food or refusing to talk, which was not measured.

Some studies have found an association between male sex and aggression.^[10, 14] This could also be related to the notion that physical aggression is more common in men. We did not find any association between aggression and gender, since we included verbal aggression also. We might have missed other forms of anger, including covert aggression, which could be more common in women.

Association of physical aggression against people with presence of family history of seizure was found in this study. However no firm conclusions can be drawn, as this study is a preliminary one. Negative correlation of physical aggression against self with the use of CBZ again indicates a general positive psychotropic effect of CBZ. Some have found increased rates of neuropsychiatric symptoms including aggression with levetiracetam,^[29] and decreased rates following treatment with lamotrigine.^[30]

Some studies have shown increased rates of aggression in patients with TLE.^[14] Medial temporal structures especially amygdala and associated limbic structures have been implicated in mediation of aggressive behavior.^[15] Involvement of these structures in TLE and especially in

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those with MTS could explain increased rates of aggression in TLE. Such an association has however not been found^[15] and it has been suggested that more widespread, but subtle, cerebral structural abnormalities were a probable etiological factor. A recent study reported increased rates of amygdala atrophy and left temporal lesions affecting either the amygdala or periamygdaloid structures in a subgroup of their patients with TLE.^[31]

Smaller amygdalar volumes have been found in normal people with high aggression.^[32]

A recent study by Woermann et al,^[33] found that there was decrease in left frontal grey matter in patients with TLE and aggression compared to control patients of TLE without aggression.

We however, did not find any association between presence or laterality of temporal focus on EEG, presence or laterality of MTS and presence of other MRI abnormalities with any form of aggression. This finding is consistent with the earlier suggestion that patients with TLE and aggression probably have more widespread and subtle structural pathology.

This study shows significant increase in rates of overt aggression in this population. Several questions however remain unanswered: do a fraction of patients with epilepsy who develop aggressive behavior do so due to the effects of seizures or interictal changes associated with epilepsy, or due to AED or due to the adverse psychosocial effects.

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