"INTER-ICTAL PSYCHOSIS OF EPILEPSY-CLINICAL PROFILE AND PREDICTIVE VARIABLES"

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CHENNAI – 600 032

AUGUST 2008

CERTIFICATE

This is to certify that this dissertation entitled **"INTER-ICTAL PSYCHOSIS OF EPILEPSY- CLINICAL PROFILE AND PREDICTIVE VARIABLES"** submitted by **Dr. R. PRIYA** appearing for **D.M., Neurology** Degree examination in **August 2008** is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled **"INTER-ICTAL PSYCHOSIS OF EPILEPSY - CLINICAL PROFILE AND PREDICTIVE VARIABLES"** is done by me at Institute of Neurology, Madras Medical College & Govt. General Hospital, Chennai, during 2005-2008 under the guidance and supervision of Assistant Professor of Neurology, **Dr. K. BHANU, D.M Neurology.,**

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of **D.M., Degree in Neurology.**

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CONTENTS

INTRODUCTION

Psychosis is widely accepted as a complication of epilepsy. With regard to phenomenology, etiology and prognosis both psychosis and epilepsy are complex disorders. Studying their association is therefore challenging. Some aspects of this association are now better established than they were at the time of Slater's[1] classic report on psychosis of epilepsy.

Over the past four decades a consensus has begun to take shape that certain forms of epilepsy may act as risk factors for subsequent development of chronic interictal psychosis, a syndrome sometimes referred to as the schizophrenia-like psychosis of epilepsy. This psychosis does resemble schizophrenia in its phenomenological manifestations, pursues a similar course and is responsive to antipsychotic medications.

Considering that epilepsy may be a risk factor for development of psychosis, it is important to identify if there are epileptic characteristics that predict such a development. This study is to analyse the association of interictal psychosis and epilepsy and to identify the predictive variables for interictal psychosis in epilepsy.

REVIEW OF LITERATURE

HISTORY

The association between epilepsy and psychosis has attracted attention since nineteenth century but many aspects of this relationship still remain controversial. Fredrich Hoffman[2] introduced the term epileptic equivalents for mental disorders in epilepsy and recognized that epilepsy and mental disorders often develop into one another. Kraeplin, identified most of psychiatric disorders of epilepsy that can be presently recognized. He had observed that preictal and postictal psychiatric changes may also occur interictally independent of convulsive events. Heinrich Londoft[3] identified the relationship of transient psychotic episodes, seizures and electro encephalogram. Slater and Beard[1] in their paper on schizophrenia like psychosis of epilepsy proposed the presence of association between seizures and psychosis.

Prevalence of psychosis in epilepsy

The overall evidence from various studies on prevalence of psychosis in epilepsy clinic groups has shown 3 to 9% prevelance (Schmitz et al [4] and Onuma et al [5]) and in

community based studies 2 to 8% prevalence (Kroh et al [6] & Gudmandsson et al [7]). The overall evidence suggests that schizophrenia like psychosis is 6-12 times more likely to occur in epileptic patients than in general population.

Aetiology of epileptic psychosis

Epilepsy and psychosis may arise out of some form of cerebral dysfunction common to both; or psychosis may be a consequence of seizure activity. Most forms of epileptic psychosis occur more commonly in partial epilepsies.

In contrast to patients with schizophrenia, hippocampal volumes were preserved, cerebral volume loss more pronounced along with amygdala enlargement in patients with epilepsy.

Psychiatric symptoms from a aetiopathogenic perspective can be due to 4 important processes.

1) An intrinsic epileptic process resulting from neurochemical and neurophysiological changes in the limbic circuit.

2) Due to iatrogenic potential of Anti epileptic drugs (AEDs).

3) An expression of a reactive process to a chronic disorder that demands multiple adjustment.

4) Bidirectional relationship between epilepsy and psychiatric disorders.

Pathophysiology of psychosis associated with epilepsy

Discussion has centered broadly on two mechanism.

I. Psychosis is a direct consequence of the epileptiform disturbance

Kindling has been proposed as one possible mechanism. Studies of behavioural and pharmacological kindling in animals and the development of mirror foci, suggests that the potential exists for repetitive epileptiform discharges to facilitate interictal psychosis. The long duration of epilepsy, the increased frequency of partial seizures and limbic origin of seizures seen in psychosis associated with epilepsy provide evidence for this hypothesis. But it is uncertain if kindling can be permanent.

Another mechanism by which frequent seizures bring about chronic psychosis is the production of plastic regenerative changes affecting in particular the medial temporal lobes.

II. Both psychosis and epilepsy are symptomatic of underlying neuropathological

or physiological dysfunction

Twothirds of the patients with temporal lobe epilepsy show hippocampal cell loss and sclerosis and a substantial proportion have heterotopias.Heterotopias and disorganization of pyramidal cell layer have been demonstrated in the brains of schizophrenic persons.If similar developmental abnormalities underlie both disorders, it is not surprising that some patients with epilepsy develop psychosis.

III. Composite Model

Epileptic patients who develop chronic schizophrenia- like psychosis have a brain lesion which may be due to cortical dysgenesis, trauma, hypoxia etc that makes them vulnerable to psychosis. The abnormality may be wide spread but is likely to involve limbic structures. This abnormality is likely to cause electrical storms in limbic cortex, with occurrence of seizures. Recurrent seizures exacerbates the abnormality owing to kindling mechanism or the regenerative changes involving axonal sprouting and synaptic reorganization. In due course these result in schizophrenia- like psychosis. Seizures either by continuous subictal activity or by modulation of pre and post synaptic glutamatergic and Gamma Amino Butric acid (GABA)ergic activity modulate the expression of psychosis [8].

The picture is further complicated by long-term drug therapy, psychological factors and chronically disabling and stigmatizing illness.

Categorization of psychosis associated with epilepsy

A consensus on the classification of psychotic syndromes associated with epilepsy is lacking and neither DSM-IV nor ICD-10 has addressed this issue specifically. Most often, separate diagnosis of epilepsy and the particular psychotic syndrome are appropriate. Since clinical seizures are the outstanding feature of epilepsy, psychotic syndromes have traditionally been classified according to their temporal relationship to these events as Ictal, postictal (or peri-ictal) and interictal. Interictal psychosis can be brief or chronic. Clinical features of psychosis of epilepsy is variable in its description.

Proposed five-axis classification scheme for patients with epilepsy and psychosis[9].

Axis 1: Epilepsy variables (type of epilepsy and laterality of focus)

Axis 2: Psychosis variables (type of psychosis and clinical course)

Axis 3: Ictus/EEG variables (temporal relationship with seizure occurrence and EEG charges during psychosis)

Axis 4: Precipitating factors for developing psychosis (co morbidity of

psychiatric disorders, specific personality traits, charges in anticonvulsive drug regimen, psychosocial factors)

Axis 5: Organic background (intelligence disturbance, abnormalities by brain, imaging techniques)

Clinically, psychosis may be divided as follows [2]:

1) Psychosis with confusion and impairment of consciousness predominating with minimal or absent affective and schizophrenic features. This type has a clear relationship with cerebral dysrhythmia of epilepsy and may reflect ictal or postictal disturbances of cerebral function. They represent ictal automatisms, absence status or post ictal confusional states.

2) Psychosis with both organic and affective – schizophreniform features. This group shows both impaired consciousness and functional psychotic features. A combination of visual and auditory hallucinations, confusional states, paranoid delusions and depression amounting to stupor can occur in these patients. Temporal lobe epilepsy may be associated with such symptoms.

3) Psychosis characterized by predominantly affective – schizophreniform features occurring in clear consciousness. This third group constitutes psychotic illness,

which manifest with clear consciousness and occur either as transient self limiting episodes or chronic severely disabling forms. These may be affective, schizophrenic or schizoaffective

Based on the temporal relationship of psychosis to seizures psychosis associated with epilepsy is classified into the following four types

Ictal psychosis

Postictal psychosis

Brief interictal psychosis

Chronic interictal psychosis.

Clinical Features of psychosis associated with epilepsy :

1.Ictal psychosis

Nonconvulsive status epilepticus can result in symptoms resembling psychosis. Psychosis usually lasts for hours to days. The most common association is with complex partial status and patients present with behavioural, cognitive and affective symptoms in association with automatisms and amnesia for the episode.

Simple partial status may produce affective, autonomic and psychic symptoms

with preserved insight.

Petitmal status results in altered consciousness and motor symptoms like eyelid fluttering and myoclonic jerks and may superficially resemble psychosis, but delusions and hallucinations are lacking.

By definition, ictal psychosis is concurrently associated with epileptic discharges in the brain. The majority of discharges have a focus in the limbic and temporal lobe but in 30% can be extratemporal in frontal or cingulate cortex.

2.Postictal psychosis

They usually follow seizure clusters or a recent exacerbation in seizure frequency. If the psychosis develops gradually and in parallel with increasing seizure frequency, it may be referred to as peri-ictal. Some clouding of consiousness is often present in this period and it may extend to the initial period of psychosis.Psychotic symptoms are pleomorphic and affective symptoms are prominent. The majority of patients suffer from complex partial seizures that are secondarily generalized.

Postictal psychosis resolves with in a few days with the mean duration in the study by Kanner et al[10] being about 70 hours and maximum duration of one month in the study by savard et al [11].

EEG abnormalities persist in the majority during the psychosis. So et al[12] reported that patient with postictal psychosis had frequent bitemporal independent epileptiform discharges on depth recording that were maximal in the mesial limbic regions.The finding of chronic frequent subictal discharges suggests that ictal activity in temporal lobe is directly related to this kind of psychosis.

Postictal psychosis has also been conceptualized as a phenomenon akin to Todd's paralysis, indicating the postictal inactivation of cortical regions involved in the ictal event, which usually include bilateral medial temporal structures

3.Brief interictal psychosis

Brief psychotic episodes can also develop when seizures are infrequent or fully controlled. These psychosis last from days to weeks, they are usually self limiting and their separation from postictal psychosis may be difficult. The phenomenology is characterized by paranoid delusions and auditory hallucinations, but multiple other features including affective symptoms, may occur. Patients with brief interictal psychosis have been reported to suffer from either complex partial epilepsy or primary generalized epilepsy.

4.Chronic interictal psychosis

In patients with chronic interictal psychosis Slater et al had found that symptoms were largely paranoid – hallucinatory, commonly associated with affective blunting and volitional symptoms. Phenomenologically, the disorder was indistinguishable from schizophrenia although there was better preservation of affect, mood swings, mystical experiences and visual hallucination. Slater et al [1] have illustrated that religious delusions commonly occurred and passivity feelings of being controlled and ideas of persecution were prominent .

Mendez et al [13] has shown that epilepsy with schizophrenia group did not differ from the non-epileptic schizophrenic comparison subjects on any psychosis item except increased suicidal behaviour. There are many reports of lack of negative symptoms and benign course for epileptic schizophrenia but controlled studies are lacking.

Auditory hallucinations are predominant, although visual, somatic. olfactory and gustatory hallucinations also occurs in this group. Thought disorder, neologisms and thought blocking are also seen. The commonest emotional disturbances were aggressiveness, irritability and severe depression. Toone et al [14] have observed that catatonic syndromes were less common in patients with schizophrenia affected by epilepsy than in their non epileptic counterparts.

With acute onset, the prognosis was better. Recovery and improvement were seen in a third. However preservation, retardation and impairment of memory was seen in many. Many of these patients showed little intellectual deterioration and lived well with the community.

Risk factors for psychosis associated with epilepsy

1. Seizure type in relation to interictal psychosis.

Psychosis in epilepsy might be preferentially associated with temporal lobe epilepsy. Mendez et al[13] reported a higher rate of partial complex seizures of temporal lobe foci in their group with schizophrenia like psychosis plus epilepsy than in their non-schizophrenic epilepsy group. The major challenge has come from Stevens[15] who argued that proportion of temporal lobe epilepsy in epilepsy - psychosis patients is no different from that in adult epileptic population in general. This debate has not resolved but continues to be in favour of a special but not exclusive relationship between schizophrenia – like psychosis and temporal lobe epilepsy.

The next question is whether the mediobasal or neocortical, temporal lobe epilepsy is associated with psychosis. Kristensen and Sindrup[16] reported that psychotic patients had a preponderance of temporal mediobasal spike foci, recorded on sphenoidal electrodes and an excess of epigastric auras . Hermann et al[17] reported higher frequency

of schizophrenia in patients with an aura of fear. Mendez et al[13] reported more psychic and autonomic auras in the psychotic patients. The majority of evidence points to a mediobasal rather than neocortical temporal lobe abnormality. The neuropathological literature has supported a predominant abnormality in the medial temporal structures.

Adachi et al[18] have shown that occurrence of generalized tonic clonic sezures (GTCS) is predictive of psychosis. GTCS is supposed to be a result of severe cerebral disturbance and a cause of secondary brain damage besides complete impairment of consciousness. However no control study has scrutinized whether existence of GTCS is linked to psychosis. Schmitz and wolf[4] also showed that impairment of consciousness seemed to be more important than the presence and localization of an epileptogenic focus.

2. Lateralization of epileptogenic focus

Since the suggestion of Flor-Henry[19] of a preponderance of left sided pathology in patients with schizophrenia – like psychosis, many studies have examined this issue. In the EEG studies, the majority opinion favours an excess of left temporal foci in patients with temporal lobe epilepsy and psychosis. There are many arguments against this hypothesis. First, the vigor with which laterality was established differs in different studies and the use of surface EEG to establish the laterality is open to question. Second ,the presence of an epileptic focus on one side does not mean that pathology is

restricted to that side. Third ,left sided preponderance of temporal lobe foci may not be restricted to psychotic individuals, as the evidence supports a left sided bias in general. Fourth , there is emerging evidence that epilepsy patients with schizophrenia have generalized seizures even when they have temporal focus. Fifth , the instruments and diagnostic criteria for psychosis are language dependent , thus introducing a left side bias.

The neuroimaging studies that examined laterality were again inconclusive. The CT and MRI studies failed to demonstrate lateralized lesions. Two small functional imaging studies provided preliminary evidence of greater left medial temporal lobe dysfunction in schizophrenia like psychosis with epilepsy. A proton magnetic resonance spectroscopy study showed metabolic abnormalities in left temporal lobe.

The laterality issue remains undecided , but the importance of a left sided focus is not striking. It is possible that the structural abnormality is not lateralized but the functional abnormality is predominantly left sided. However right sided abnormality seems to be sufficient, and generalization of epileptic disturbance is commonly present.

3. Age of onset of epilepsy

The onset of seizures in early childhood is associated with higher risk of intellectual impairment[18]. Psychotic phenomena may have a biological basis similar to intellectual decline as a consequence of early brain damage. It has been shown in an experimental model, seizures in prepubertal animals caused a reduction of cell number and size in the brain. It is probable that such cerebral disturbances impede normal neural development and precipitate psychiatric consequences.

4. Severity of Epilepsy

It is often noted that patients who develop psychosis have a severe form of epilepsy involving multiple seizure types, history of status epilepticus and resistance to drug treatment. The frequency of seizures at the time of development of psychosis is variable. Some authors report an improvement and others report a worsening. Most often, it is not possible to relate the onset of psychosis to any change in seizure frequency.

5. Family history of psychosis

Adachi et al, Ping et al have shown that patients with a positive family history of

psychosis were extremely susceptible to psychosis [18,20]. The risk of psychosis is nearly 40 times higher than that of patients with a negative family history. This may be contrasted with the family history of epilepsy, which was equally, distributed between patients with or without psychosis. Genetic vulnerability to psychosis may have facilitated the development of psychosis in patient with epilepsy.

Forced normalization and alternative psychosis.

EEG findings:

The phenomenon of forced normalization and its clinical counterpart, alternative psychosis, has been in the literatures for half a century. It was Landolt[21] who brought a specific scientific approach by defining the EEG changes during psychotic episodes of epilepsy and noted three different types of changes .

First was the post paroxysmal twilight state, this is essentially the post ictal psychosis.

Second was the petitmal status of Lennox, essentially non-convulsive status.

Third type, was the most innovative and these were the psychotic episodes with forced normalization in the EEG.

He went on to say “forced normalization is the phenomenon characterized by the fact that, with the occurrence of psychotic states, the EEG becomes more normal, or entirely normal, as compared with previous and subsequent EEG findings”. Forced normalization and its counterpart, alternative psychosis, so termed by Tellenbach to avoid the necessity of doing an EEG to define these states, occurs with both generalized and focal epilepsies, although in recent years more patients with temporal lobe epilepsy have been the defined population.

There are several problems in making a diagnosis.

1. Should the EEG necessarily be completely normal or should relative normalization also be included.

2. Is alternative psychosis the expression of forced normalization or its variant?

3. Should the term be included only for psychotic symptoms or is it a term to describe behaviour disorder with normalization of EEG.

These questions were actually posed by Landolt, Jarz and Tellenbach with no

clear consensus. Trimble and Krishnamoorthy et al [22] have proposed a criteria for forced normalization . It has been proposed that a broader approach with inclusion of cases who show a decrease of seizure frequency with both relative and complete normalization of EEG is useful in clinical practice.

Mechanisms of forced Normalization

The neurobiological processes that underlie forced normalization and alternative psychosis are poorly understood. Knowledge of these mechanisms will greatly help in understanding the interesting relationship between epilepsy and behaviour and has the potential to influence the treatment of both epilepsy and mental illness.

Several mechanisms have been proposed. These include a true inverse relation between seizure and psychosis, continuing epileptic status in the limbic system, propagation of epileptiform discharges along unusual pathways, a role of AEDs in influencing metabolic processes .

It is also proposed that alternative psychosis is due to epilepsy being still active but subcortical and restricted and at same time, inhibitory processes are active leading to impending psychosis in the form of insomnia, hypervigilance and dysphoria. The

development of frank psychosis depends on the appropriate setting of psychotic experiences, social competence , family history of psychosis etc.

Experimental models suggest that the neuroanatomic and neurophysiologic mechanism of electrically kindled seizures and pharmacologically kindled seizures are antagonistic to kindled behaviour disorder. The expression of electrically kindled seizures is modified by neurochemicals which themselves can kindle behavioural changes and as antagonistic effect can inhibit the expression of seizures.

Neurotransmitters and forced normalization

Neurotransmitters may play an important role in mediating an antagonistic relationship between seizures and psychosis[23]. Dopamine, glutamate and GABA are clearly the most important neurotransmitters in this regard.

Dopamine is an obvious candidate and has been linked with development of psychosis for many years. Antipsychotics are dopamine antagonists but are known to provoke seizures. On the other hand, dopamine agonists increase the intensity of psychotic symptoms. It can therefore be postulated that Dopamine may have a significant role in mediating forced normalization.

Enhanced glutaminergic excitation is a potential epileptogenic mechanisms by its action on N-methyl- D- Aspartate glutamate (NMDA) receptor. In schizophrenia, on the other hand, an endogenous NMDA receptor antagonist appears to enhance activity in the frontal cortex and hippocampal formation[24]. This hopothesized dysfunction of glutaminergic transmission interdigitates with dopamine hypothesis of schizophremia.

Loss of GABA inhibition is a potential epileptogenic factor. Interestingly, AEDs that increase GABA levels are associated with the development of a psychopathoglogic state in upto 10% of patients, characterized by mood changes, agitation and psychotic symptoms.

Therefore at the levels of neurotransmitters, there appears to be an antagonism between epilepsy and functional psychosis. Alterations in the balance of glutaminergic and GABAergic activity may cause seizures or psychosis to predominate at different times and dopamine, with its complex interactions, may play an important role in modulating this mechanism.

Relationship between seizures and psychosis [8]:

Neurotransmitter	***Seizure***	***Psychosis***	***Relationship***
Dopanine	Anticonvulsant	Propsychotic	Antagonistic
Glutamate	Proconvulsant	Antipsychotic	Antagonistic
Peptides	Unclear	Unclear	Unclear
Norepinephrine	Unclear	Unclear	Unclear
Serotonin	?Pro convulsant	?Pro psychotic	Unclear
GABA	Anticonvulsant	Pro Psychotic	Antagonistic

The role of AEDS in forced normalization

The commonest AED reported in the literature has been ethosuximide, although almost all AEDs have at some time been anecdotally reported to provoke these effects.

The number of patients in whom a forced normalization is related to AEDs is unclear because most patients are not having continuous EEG monitoring. Alternative psychosis however are clearly described. Thomas et al have shown a group of patients on vigabatrin who developed psychosis as treatment emergent effect and 64% of this population group was seizure free. It is not yet clear if any particular class of drugs is

interlinked with this, although studies suggest that GABergic drugs may be particularly involved. Most of the cases reported have been when the drugs have been given as polytherapy.

Postlobectomy psychosis

Schizophrenia – like psychosis may develop denovo many months or years after temporal lobectomy for the treatment of intractable epilepsy. The condition was noted in early surgical series, but has recently received greater attention. It is difficult to know whether this represents a true increase in incidence, better recognition or a fall in age of surgery.

Clinical features of denovo psychosis after lobectomy are diverse, some are depressive, some schizophrenic, some are episodic and some pursue a chronic course [25]. In some the development of psychosis may be predetermined by earlier events. In a few cases seizure control may lead to forced normalization and an alternating psychosis. One feature that stands out is the presence of preoperative psychosis is associated with left temporal focus and 85% of denovo psychosis follows right temporal surgery . The reasons for this association are unclear.

The presence of major psychiatric disturbance has generally been thought to be a relative contraindication but recently it has been accepted that it would be unwise to reject a patient simply because of existence of psychosis. It might be considered better to be psychotic without seizures than to be psychotic with them.

Neuroimaging in psychosis associated with epilepsy

Conlon et al have shown that magnetic resonance imaging of patients with epileptic psychosis did not show any difference in T1 relaxation times between epilepsy with psychosis patients and schizophrenic comparison subjects. Some of the morphological abnormalities like large ventricles, small hippocampus are common to schizophrenia and temporal lobe epilepsy.

Van Elst et al[26] have found that patients with Temporal lobe epilepsy (TLE) and psychosis differed from patients with TLE alone and healthy volunteers in that the total brain volumes were significantly smaller while there were no differences in hippocampal volumes between the three study groups. There was a significant 16-18% enlargement of the amygdala on both sides in patients with psychosis of epilepsy,

Wuerfel et al[27] in their study compared the amygdala and hippocompal volumes in

high and low scores on the religiosity, writing and sexuality subscales of neuro behavioural inventory . Patients with high ratings on the religiosity scale had significantly smaller right hippocampus.

A small study using Single Photon Emission Tomography (SPECT) showed lower left medial temporal blood flow in psychotic than nonpsychotic epileptic patients [28].

A position emission tomography (PET) study demonstrated lower oxygen extraction ratios in the frontal, temporal, and basal ganglia regions of psychotic patients with epilepsy than in nonpsychotic epileptic patients.

The PET study of patients with psychosis by Reith et al which included two patients with chronic and two with postictal schizophremia – like psychosis, showed higher than normal levels of dopa decarboxylase activity in schizophrenia like psychosis and schizopherenia. It was suggested to be due to suppressed tonic release of dopamine in striatum because of low corticostriatal glutamatergic input.

Treatment of interictal psychosis

Sulpiride in particular has significant anxiolytic effects and is very suitable for the interictal psychosis often seen in epilepsy, with subtle psychotic features, but manifest irritability, anxiety, and dysphoria. It may be used in low doses to reduce the

anxiety, agitation and emotional lability that are manifest in the stage of evolution. However, this may be too benign a drug to employ during acute exacerbations of psychotic behavior, and risperidone, olanzapine, or quetiapine may become necessary. Sometimes, exacerbations of interictal psychosis are prolonged and nonresponsive to treatment. In this situation, clozapine may need to be introduced. Close monitoring of blood counts, and withdrawal of other offending agents such as carbamazepine, which can also independently have similar effects on white cell counts, is necessary. The combination of carbamazepine and clozapine must therefore be avoided.

AIMS OF THE STUDY

1. To study the clinical profile of interictal psychosis associated with epilepsy
2. To evaluate different variables which predict interictal psychosis in epilepsy

    1) Age of onset of seizure
    2) Duration of epilepsy
    3) Frequency of seizures
    4) Lateralization of seizures
    5) Type of seizure
    6) EEG changes
    7) Neuro imaging

3. To look for the phenomenon of alternative psychosis in epilepsy.

MATERIALS & METHODS

CASE SELECTION

The cases for this study were collected from the out patient department of Institute of Neurology of Madras Medical College, Chennai. 35. Patients with Epilepsy who developed interictal psychosis were collected over a period of 3 years (2005-2008)

Definition of interictal Psychosis:

Psychosis was defined as the presence of hallucinations, delusions or a limited number of severe abnormalities of behaviour in accordance with the international classification of diseases (ICD-10). In a state of retained consciousness, patients exhibited psychotic episodes lasting more than 2 weeks with no distinct preceeding seizures. Hence ictal and postictal psychotic phenomena during seizures were excluded.

Inclusion criteria:

1. Epileptic patients with interictal psychosis above 12 years of age
2. Psychotic symptoms occured after onset of epilepsy.
3. Psychotic phenomena occurred in clear consciousness
4. Psychosis was atleast 2 weeks in duration.

Exclusion criteria:

1. Mental retardation
2. Psychosis prior to onset of epilepsy/premorbid psychosis antedating the development of epilepsy.
3. EEG suggestive of status epilepticus
4. Acute symptomatic seizures.

Methods

Patients who fulfilled the above mentioned criteria were taken for the study.

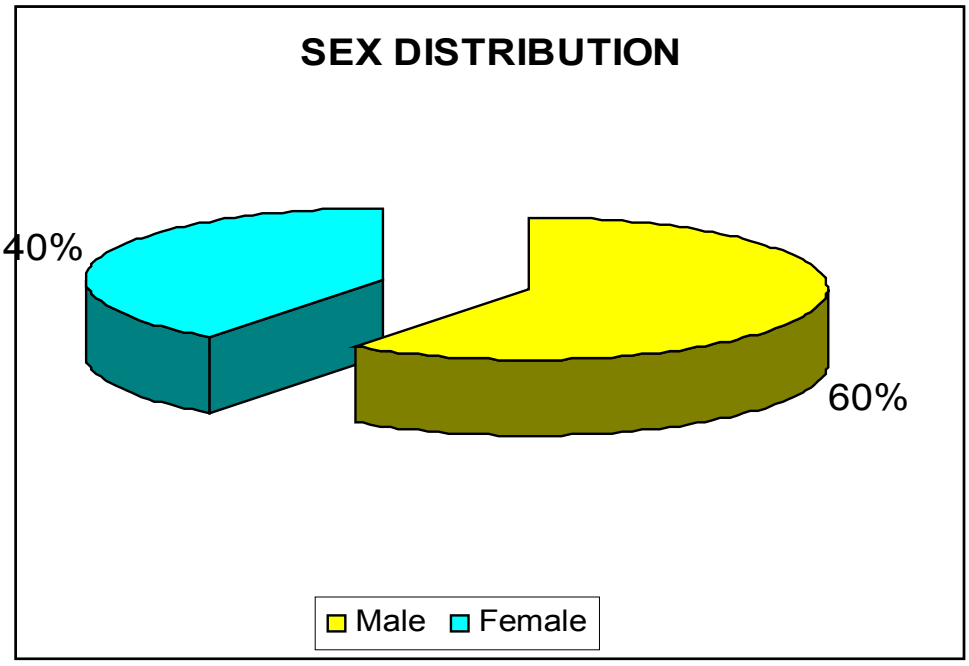
These patients were systematically studied for:

1. Age at onset of seizures
2. Age at onset of psychosis
3. Family History of epilepsy and of psychosis
4. Semiology of seizures and type of epilepsy
5. Frequency of seizures
6. Lateralization of epilepsy if possible by semiology, EEG or Neuro imaging
7. Features of psychosis
8. Alteration in frequency of seizures with onset of psychosis
9. Neuro Imaging - CT Scan (MRI Scan when available)

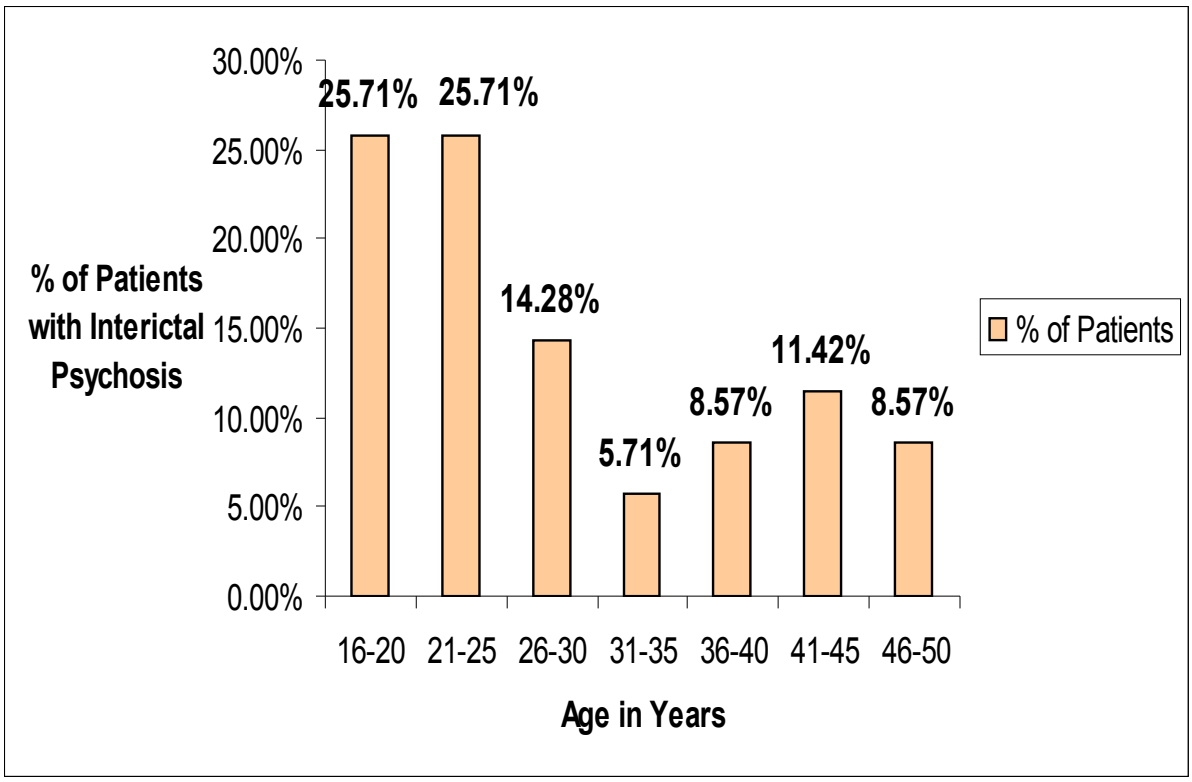
RESULTS

TOTAL NUMBER OF PATIENTS : 35

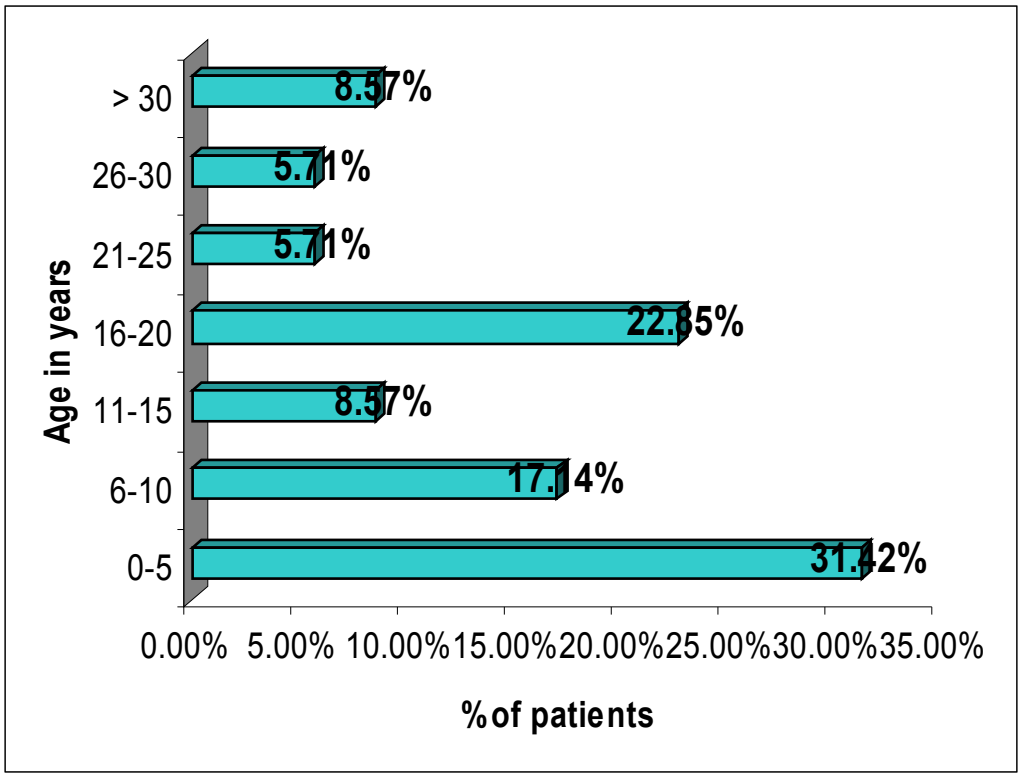
SEX DISTRIBUTION IN EPILEPSY PATIENTS WITH PSYCHOSIS



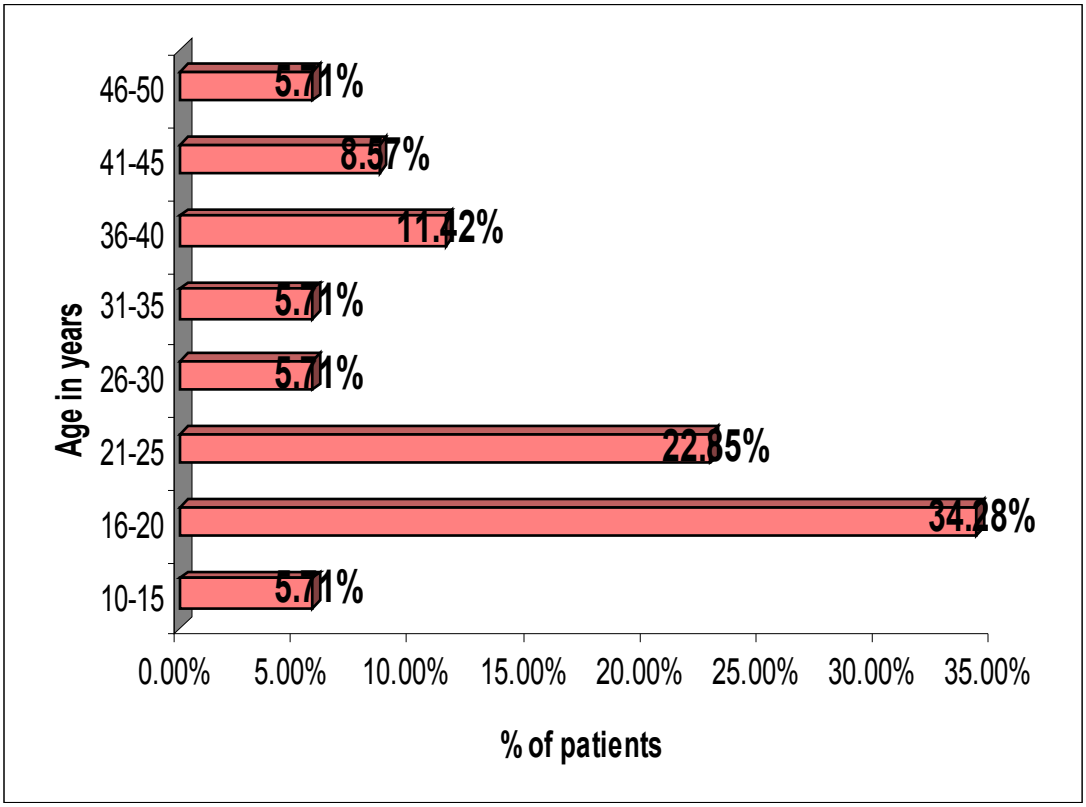
AGE DISTRIBUTION



AGE IN YEARS AT ONSET OF EPILEPSY



AGE IN YEARS AT ONSET OF PSYCHOSIS



INTERVAL BETWEEN ONSET OF EPILEPSY & PSYCHOSIS

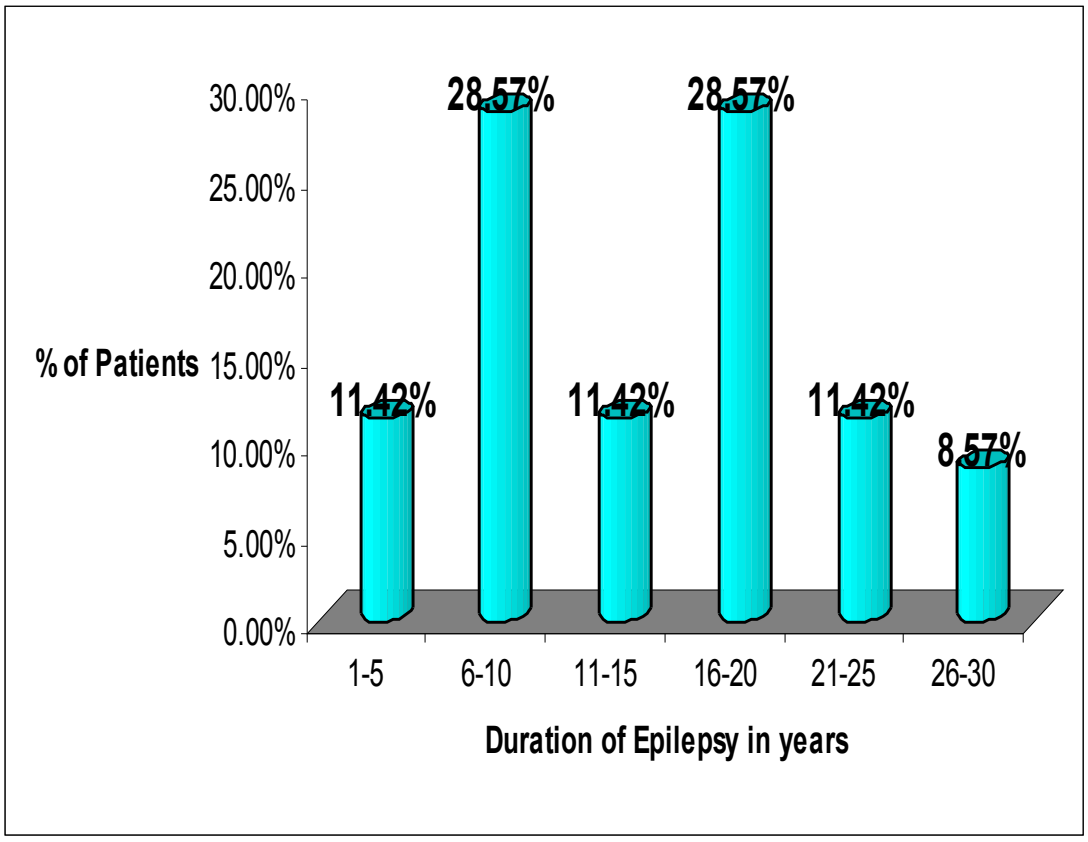
No. of Years	No. of Patients	% of Patients
0-3	4	11.42%
4-6	5	14.28%
7-9	6	17.14%
10-12	3	8.57%
13-15	8	22.85%
16-18	1	2.85%
19-21	6	17.14%
21-24	1	2.85%
25-27	1	2.85%

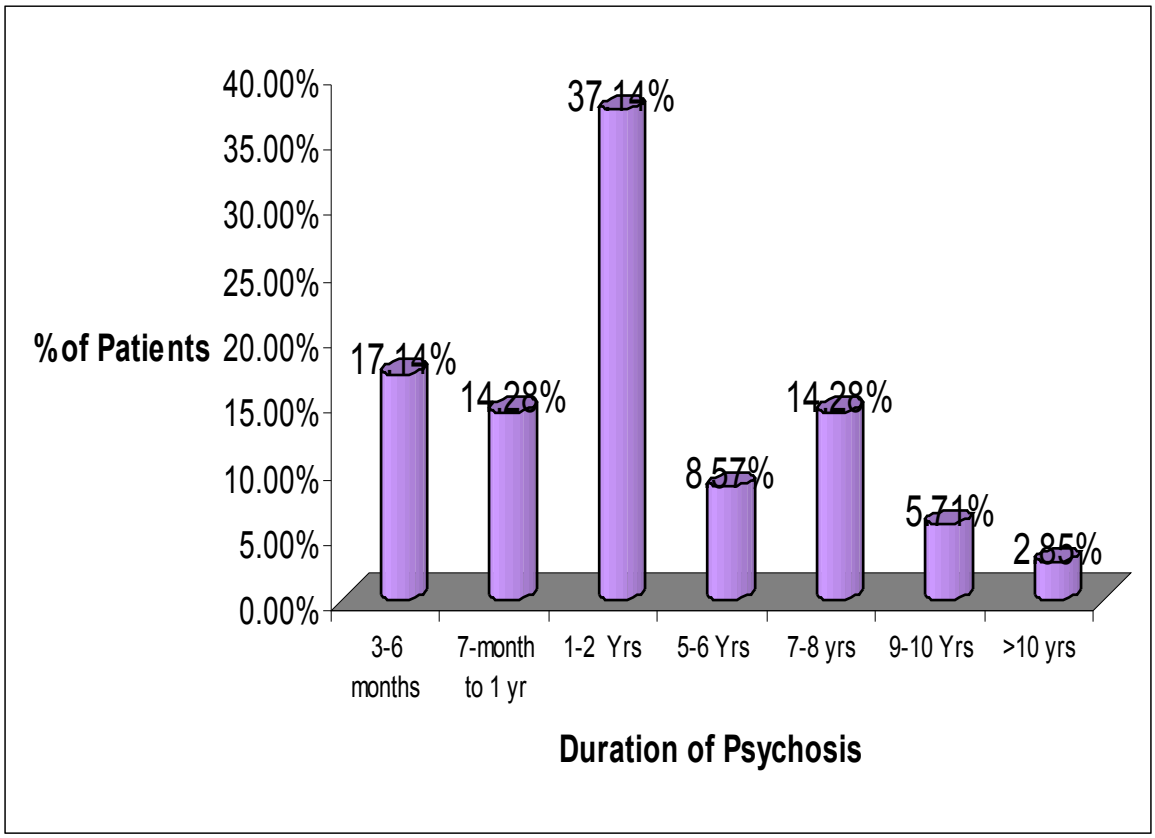
FREQUENCY OF SEIZURES AT ONSET

Frequency	No. of Patients	% of Patients
> 4/week	15	42.85%
1-4/month	16	45.71%
>1/3 months	1	2.85%
>1/6 months	2	5.71%
>1/year	1	2.85%

FREQUENCY OF SEIZURES AT PRESENT

Frequency	No. of Patients	% of Patients
> 4/month	12	34.28%
1-3/month	11	31.42%
>1/3 months	4	11.42%
>1/6 months	3	8.57%
>1/year	3	8.57%
< 1 /year	2	5.71%

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15.00%
10.00%
5.00%
0.00%
%of Patients
17.14%
14.28%
37.14%
8.57%
14.28%
5.71%
2.85%
3-6 months
7-month to 1 yr
1-2 Yrs
5-6 Yrs
7-8 yrs
9-10 Yrs
>10 yrs
Duration of Psychosis

FAMILY HISTORY OF EPILEPSY

Family History of Epilepsy	Positive	Negative
No. of Patients	5	30
Percentage of Patients	14.28%	85.72%

Family history of Psychosis was absent in all patients.

7 patients had history of born of consanguinous parentage.

SEIZURE TYPE

Seizure Type	**No. of Patients**	Percentage of Patients
CPS/secondary generalization	20	57.14%
Simple partial seizure/ secondary generalization	3	8.57%
GTCS	12	34.28%
Myoclonus /absence	0	0%

SEIZURE TYPE BASED ON GENERALISATION

SEIZURE TYPE	**No of patients**	**% of patients**
Partial without generalisation	14	40%
Seizures with primary or secondary generalisaton	21	60%

LATERALITY OF SEIZURES BASED ON SEMIOLOGY

Laterality	**Right**	**Left**
No. of Patients	6	4
Percentage of Patients	17.14%	11.42%

TYPE OF AURA

Aura	**No. of Patients**	**Percentage of Patients With CPS**
Epigastric	7	35%
Vertigo	1	5%
Visual	1	5%
Auditory	1	5%
Sensory	2	10%
Affective	1	5%
Cephalic	1	5%
Dysmnestic	1	5%

History of Postictal Psychosis was present in 15 of the 35 patients (42.85%) .

Clustering of seizures was present in 14 of the 35 patients (40%) and was often associated with post ictal Psychosis

TIME SINCE LAST SEIZURE

Time Since last seizure	No. of Patients	Percentage of Patients
2weeks -1 month	11	31.42%
1-3 months	14	42.85%
3-6 months	6	17.14%
> 6 months	4	11.42%

PERSONALITY CHANGES IN PSYCHOSIS WITH EPILEPSY

Personality changes	No. of Patients	Percentage of Patients
Aggression	17	48.57%
Hypersexuality	3	8.57%
Paranoid	2	5.71%
Religiosity	4	11.42%
Suicidal Ideas	2	5.71%
Withdrawn	4	11.42%

PSYCHOTIC FEATURES

Psychotic Features	No. of Patients	Percentage of Patients
Auditory hallucinations	26	74.28%
Visual Hallucinations	14	40%
Affective symptoms	7	20%
Paranoid Ideations	5	14.28%
Catatonia	1	2.85%

EEG was done in all patients. 27 Patients (77.14%) had more than 1EEG.

EEG

EEG	Normal	Abnormal
No. of Patients	13	22
Percentage of patients	37.14%	62.85%

Lateralization in EEG

Lateralization in EEG	Right	Left	Not definite

No. of Patients	1	5	29
Percentage of patients	2.85%	14.28%	82.85%

Left temporal spikes and right temporal spikes were seen in one patient each.

Left sharp waves in anterior and mid temporal region was seen in 1 patient.

Left Temporal Phase reversal in T3 was seen in 1 patient.

Left Temporal slowing was seen in 1 patient.

Left Hemisphere sharp and slow waves was seen in 1 patient

Forced Normalization

Forced Normalization was seen only in three of the 27 patients who had more than one EEG recording.

Alternate Psychosis

11 of the 35 patients had history of decreased frequency of seizures after onset of Psychosis.

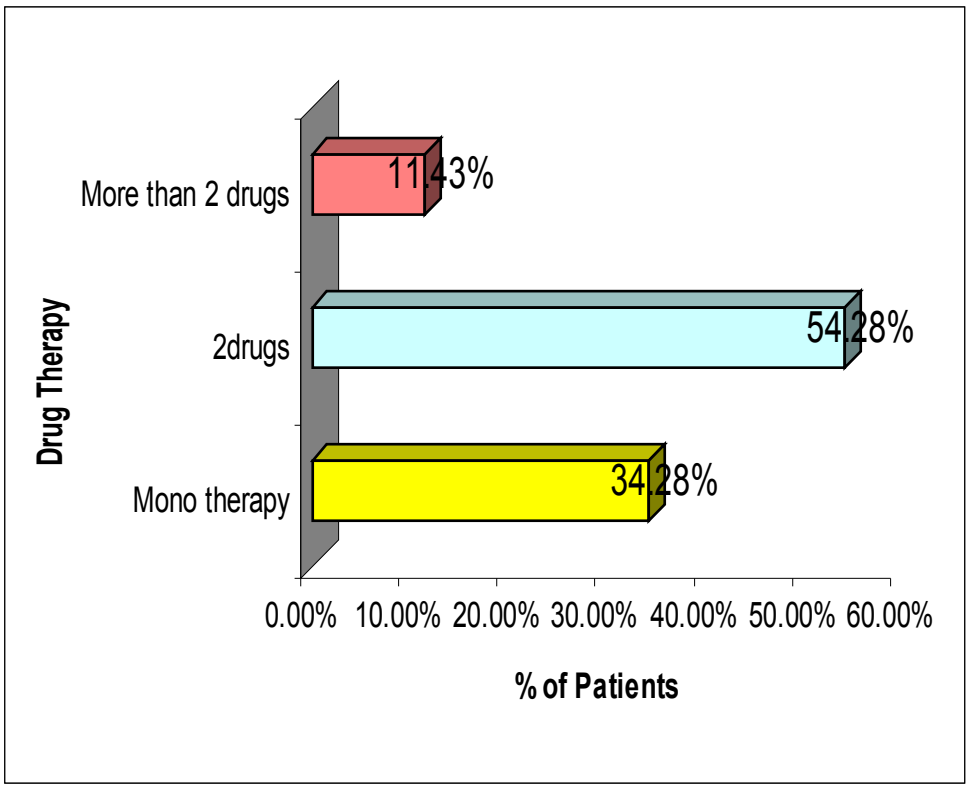
Neuroimaging

All patients had CT Scan of brain.

7 / 35 patients (20%) had abnormal CT Scan.

Abnormal CT Scan	No. of Patients
Dilated Temporal horn	3
Calcification	2
Hypodensity in parietal region	2

MRI Scan was done in 10 /35 patients. MRI was abnormal in 2 patients in whom it showed mesial temporal sclerosis on the left side.



DISCUSSION

Interictal psychosis is widely accepted as a complication of epilepsy. In this study 35 patients with interictal psychosis and epilepsy were analyzed to identify the predictive variables associated with interictal psychosis in epilepsy.

The study group comprised of 21 males and 14 females. A male female ratio of 2:1 was observed in this study. Most of the earlier studies report a slight preponderance of men in their studies on inter-ictal psychosis in epilepsy (Adachi et al, Ping et al) [18,20].

Mean age of onset of epilepsy in this study is 13.85 years with a range of 2 years to 40 years. 57.3% had onset of epilepsy at less than 15 years of age.

Slater et al[1] have shown a mean age of onset of epilepsy of 15 years. Trimble et al[29] have shown a mean age of onset of epilepsy of 11 years. Patients with interictal psychosis showed a significantly earlier onset of epilepsy.

The mean duration between onset of epilepsy and psychosis in this study is

15.14 years. 22.85% had a duration of 13-15 years between onset of seizures and psychosis. Ping et al[20] in their study have shown that the mean duration between epilepsy and schizophrenia was 8.2 years . In Slater's series[1], the mean interval was 14 years between onset of epilepsy and schizophrenia .

88.58% of patients had a duration of epilepsy more than 5 years indicating the occurrence of psychosis is more commonly associated with chronic long standing epilepsy.

42.85% of patients in this study had more than 4 seizures per week at onset of epilepsy and 45.71% had 1-3 seizures per month indicating that a increased frequency of seizures at onset was associated with higher risk of interictal psychosis.

Family history of epilepsy was present is 14.28% of patients. 2.85% had family history of psychosis. Adachi et al[18] have shown family history of epilepsy is 6.95% and of psychosis in 5.57% of patients.

In a population based cohort study Ping et al[20] have shown that a family

history of psychosis and a family history of epilepsy were significant risk factor for schizophrenia and schizophrenia - like psychosis.

In this study 57.14% of patients had complex partial seizure with or without secondary generalization. CPS is the predominant seizure type in patients with interictal psychosis. 34.28% had GTCS and 8.57% had simple partial seizures with or without secondary generalization.

Complex partial seizures were the predominant seizure type associated with inter-ictal psychosis in several other studies also. Adachi et al[8] have shown that 66.25% of patients and slater[1] et al have shown that 79.71% of patients had CPS.

In the present study 60% of patients had GTCS either primary or secondary and 40% had partial seizures without generalisation. In the study by Adachi et al[18] 72.6% of patients with interictal psychosis had GTCS either primary or secondary. The occurrence of GTCS also is predictive of psychosis. GTCS is supposed to be a result of severe cerebral disturbance and a cause of secondary brain damage thus increasing the risk of psychosis.

In the present study only 42.44% of patients had features of lateralization by semiology of seizure. 17.14% had Left hemisphere seizure focus and 11.42% had Right hemisphere seizure focus . This indicates a slight

preponderance of left sided pathology in interictal psychosis. But many of these patients did not have definitive lateralization features in the corresponding EEG studies. EEG studies showed definite evidence of lateralization in 17.14% (Left - 14.28 and right - 2.85%).

Laterality and inter ictal psychosis

Study	Left hemisphere	Right hemisphere
Adachi et al[18]	30.86%	32.17%
Flor- Henry et al[19]	38%	18%
Onuma et al[5]	41.46%	12.19%
Kristensen et al[16]	27.84%	32.91%

Meller et al[30] suggest an important role for dominant temporal lobe abnormality. The laterality issue remains undecided and the importance of a left sided focus is not striking.

35% of patients with complex patient seizures had epigastric aura. Kristensen and Sindrup[16] reported that interictal psychosis patients had preponderance of temporal mediobasal spike foci, recorded on sphenoidal electrodes and an excess of epigastric auras.

42.85% of patients also had history of postictal psychosis in the form of

worsening of psychosis following seizures and were often associated with clustering of seizures.

Personality charges were commonly associated with psychosis. 48.5% had aggressive behavioural, 11.42% had Religiosity, 8.57% had Hypersexuality in the present study. Religiosity was present only in patients with CPS. Dewhurst and beard[31] described six cases of religiosity all of whom had temporal lobe epilepsy. Slater et al[1] have commented that mystical delusions were common in their series on psychosis in epilepsy and occurred in 38% of cases .

Psychosis were most often schizophrenic in nature with thought disturbances. 74.28% had auditory hallucinations and 40% had visual hallucinations and delusions of passivity, 14.28% had paranoid ideations control and 2.85% had catatonia. 20% of patients had affective symptoms in the form of depression and mania.

Bruens et al[32] have shown that hallucinations occurred in 78% and were mainly auditory. Toone et al[33] have observed that catatonia syndrome are less common in patients with schizophrenia affected by epilepsy than their non-epileptic counterparts and delusions and hallucinations were more common.

Of the 27 patients who had more than 1 EEG only 3 had forced normalization. Kido et al[34] have shown aggravation of EEG changes in psychosis. Oana et al[34] have shown normalization of EEG in 40%.

31.42% of patients had features suggestive of alternative psychosis with decreased frequency of seizures with onset of psychosis. A multicenter study by Matsura et al[34] reported that the incidence of alternative psychosis was 6.3%.

CT Scan brain was abnormal in 20% of patients with 3 patients having dilated temporal horns, 2 patients with calcification and 2 patients with hypodensity in right parietal region. Of the 10 patients who underwent MRI, 2 patients had mesial temporal sclerosis.

Most of the patients had chronic seizures and were on more than one AEDS. 34.38% of patients were on monotherapy, 54.28% were on 2 AEDs and 11.43% were on 3 drugs. The higher incidence of polytherapy indicates the severity and intractable nature of seizures in these patients.

SUMMARY

- Patients with interictal psychosis showed a significantly earlier age of onset of epilepsy.

- 88.58% of patients had a duration of epilepsy more than 5 years indicating the occurrence of psychosis is more commonly associated with chronic long standing epilepsy.

- Increased frequency of seizures at onset was associated with higher risk of interictal psychosis.

- CPS is the predominant seizure type in patients with interictal psychosis. In this study 57.14% of patients had complex partial seizures with or without secondary generalization.

- The occurrence of GTCS also is predictive of psychosis. In the present study 60% of patients had GTCS either primary or secondary.

- The laterality issue remains undecided and the importance of a left sided focus is not striking.

- Personality changes were commonly associated with psychosis.

- Psychosis were most often schizophrenic in nature with thought disturbances, auditory and visual hallucinations. Catatonic symptoms were uncommon.

- 31.42% of patients had features suggestive of alternative psychosis with decreased frequency of seizures with onset of psychosis.

- CT Scan brain was abnormal in 20% of patients .

- Most of the patients with interictal psychosis had chronic seizures and were on more than one AEDS.

CONCLUSIONS

- The most important predictors for development of interictal psychosis associated with epilepsy were
    - Earlier age of onset of epilepsy
    - Chronic long standing epilepsy
    - Increased frequency of seizures
    - Complex partial seizures
- Psychosis was most often schizophrenic in nature with thought disturbances, auditory and visual hallucinations .

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ABBREVIATIONS AND ACRONYMS

- EEG : Electro Encephalo Gram.
- CPS : Complex partial seizure
- CT : Computerized Tomogram.
- MRI : Magnetic Resonance Imaging.
- GTCS : Generalized Tonic-Clonic Seizure
- AED : Antiepileptic Drug
- TLE : Temporal lobe epilepsy

PROFORMA

NAME: MIN NO:

AGE : SERIAL NO:

SEX : EEG NO:

ADDRESS:

Occupation :

Date of registration :

Age of onset of seizures :

Age of onset of psychosis:

Duration of epilepsy :

Duration of psychosis :

Seizure type :

Prodrome :

Aura :

Automatisms :

Post ictal psychosis :

Frequency of seizures at onset:

Frequency of seizures at present :

Clustering of attacks :

Last episode of seizure :

Family history :

Personality changes :

Psychotic features :

Affective symptoms :

H/o Alternative psychosis :

EEG- No of EEGs-

Report of EEGs-

1.

2.

CT Scan :

MRI Scan :

Blood sugar :

Blood urea : serum creatnine:

Hb% :

TC: DC:

Treatment history

AEDs

1.

2.

3.

Anti- psychotics

1.

2.

MASTER CHART

S.No.	Sex	Age	Age at onset of Epilepsy in Yrs	Age at onset of Psychosis in Yrs	Frequency of Seizures at onset	Frequency of Seizures at Present	Duration of Epilepsy In Years	Duration of Psychosis in Years	Family History of Epilepsy
1	F	22	3	17	1-3/m	1/m	18	5	-
2	M	35	5	25	1-3/m	1-3m	30	10	-
3	F	22	2	16	1/3m	1/m	20	6	-
4	F	35	6	32	>4/wk	1/6m	29	3	-
5	M	30	20	29	1-3/m	1/3m	10	1	+

6	M	48	28	40	1-3/m	3/m	20	8	+
7	F	37	20	35	1-3/m	1/yr	17	2	-
8	F	30	17	25	1-3/m	1/m	13	5	-
9	M	19	10	18	>4/wk	10/m	9	1	-
10	M	20	18	20	>4/wk	3/m	2	7m	-
11	M	17	10	16	1/6m	1/yr	7	1	-
12	M	25	21	23	1/m	1/6m	4	2	-
13	M	21	2	19	1-3/m	4/m	19	2	-
14	F	16	6	16	1-3/m	1/m	10	6m	-
15	F	17	1	15	>4/wk	1-4/m	16	1	-
16	M	27	1	21	>4/wk	1/m	26	6	-
17	F	42	20	41	1/6m	1/yr	22	1	-
18	F	28	15	22	1 yr	1/m	7	6	-
19	M	22	12	20	>4/wk	10/m	10	2	-
20	M	47	40	44	1-4/m	4/m	7	3	+
21	F	25	24	3	1-4/m	2/m	5	6m	-
22	F	40	20	49	>4/ wk	1/yr	20	4m	-
23	M	21	6	20	1-4m	1/m	14	1	-
24	M	18	2 yrs	16	1-4/m	1m	16	2	-
25	M	18	10	16	1-4/m	4/m	8	2	-
26	F	23	21	23	>4/wk	3-4/m	2	3m	+
27	M	16	3	13	4m	4/m	12	2	-
28	M	30	5	30	1m	1/3m	25	3m	+
29	M	23	2 yrs	21	5m	4/m	21	2	-
30	M	44	26	40	1-4/m	1-2/yr	18	4	-
31	M	45	40	44.5	1-4/m	1/6m	5	6m	-
32	M	16	3 yrs	14 yrs	1m	1/m	13	2 yrs	-
33	F	49	40	48	2m	1/m	9	1	-
34	F	38	15	36	5-6m	3/m	23	2	-
35	M	44	24	37	3-4m	5-6/m	20	7	-

S.No.	**Family History of Psychosis**	**H/o Consanguity**	**Aura**	**Seizure Type**	**Laterality**	**Postictal Psychosis**	**Clust-ering**	**Time Since Last Seizure**
1	-	-	Epigastric	R CPS	R	+	+	3 wk
2	-	-	-	GTCS		+	+	4 m
3	-	+	-	GTCS		+	+	2 m
4	-	-	-	GTCS		+	+	6 m
5	-	+	-	SPS Rt. 20	R	-	-	1 m
6	-	+	-	GTCS		+	+	1 m

7	-	-	Epigastric	L CPS 2^0	L	+	+	8 m
8	-	+	-	CPS 2^0		+	+	2 m
9	-	-	Vertigo	CPS		+	+	1 m
10	-	-	-	CPS		-	-	1 yr
11	-	-	Epigastric	CPS Lt	L	+	+	7 m
12	-	-	Visual	CPS 2^0		+	+	1 m
13	-	-	-	CPS 2^0		+	+	2 m
14	-	-	Epigastric	L CPS	L	-	-	1m
15	-	-	-	GTCS		-	-	4m
16	-	+	-	GTCS		-	-	3 wk
17	-	-	-	GTCS		-	-	4 wk
18	-	-	Aud/Numb.	L CPS	L	-	-	5 m
19	-	-	Numb.	SPS Rt. 2^0	R	+	+	1 m
20	-	+	Fear	CPS		-	-	15 d
21	-	-	-	CPS		+	+	1m
22	-	-	-	GTCS		-	-	6m
23	-	-	-	GTCS		-	-	1 m
24	-	-	-	GTCS		-	-	1 m
25	-	-	Dejavu	CPS 2^0		-	-	15 d
26	-	-	-	CPS		-	-	1 m
27	-	-	-	SPS Rt. 2^0	R	-	-	15 d
28	-	-	Epigastric	CPS		-	-	3 m
29	-	+	Cephalic	CPS 2^0		-	-	4 m
30	-	-	-	GTCS		-	-	3 yr
31	-	-	Epigastric	CPS		-	-	6 m
32	-	-	-	R CPS	R	-	-	5 m
33	-	-	-	R CPS	R	-	-	1 m
34	-	-	Epigastric	CPS		-	-	3 wk
35	-	-	-	GTCS		+	+	15 d

S.No.	**Psychosis S/SA**	**Personality Change**	**Halluci-nation**	**No. of EEGS**	**EEG**	**Forced Normalisation**	**Alternate Psychosis**	**CT**
1	S	A	A	2	L T S			N
2	S	A R	A / V	2	BEA		P	N
3	S	A	A	1	N		P	N
4	SA	W	A	1	N		P	N
5	S	A	V / A	2	BEA		P	N
6	SA	A R	A	2	R TS			N
7	S		A	2	BEA		P	N
8	SA	A	V	2	BEA			N
9	S	A P	A / P	1	BCD			N
10	SA	A HS	V	2	BEA			N

11	S	P	P	2	BEA		P	N
12	SA	A W	A	2	BCD		P	N
13	S		V / A	2	L T SH			DILTH Lt
14	S	A	A	2	BCD			N
15	S		A	1	BCD			N
16	SA	S P R	A / P	2	BEA			N
17	S	A	V	2	BEA		P	N
18	S	W	A	2	N			CAL P Lt
19	S		A	2	BCD	P		Hypo P Rt
20	S	A P	P	2	BEA			N
21	S		V / A	2	N			DILTH Lt
22	S	A	A	2	LT S		P	N
23	S	A	A	2	N			N
24	S	W	A / V	1	BEA	P		N
25	S		V/ C	2	BEA			N
26	SA	A S	A / V	2	N		P	N
27	S		A / V	1	N			N
28	S		A	2	L TSL			N
29	S	A R	A	2	N		P	N
30	S	P	P	2	N			N
31	S		A	2	BEA	P		N
32	S	A	V	2	L H SH SL			CAL P Lt
33	S		V / A	1	N			N
34	S		V	2	N			N
35	S	HS	A	1	N			Hypo P Lt

S.No.	MRI	Drugs AED	Drugs ANTIPSYCHOTICS
1		P	R
2		P, PB	H
3		P, PB	R
4		P, PB	R, A
5		C	R
6		C	Cl
7		C, PB	H, R
8	N	C	H
9	MTS LT	C	R
10		C, P	R
11	N	C	R
12		P, SVP, PB	R
13		C, SVP	H
14	N	C, SVP	H
15	N	P	R
16		P, PB	R
17		SVP	R
18		SVP	R
19		C, PB	H
20	N	C, SVP	R
21		C	O
22	MTS LT	E, C	R
23	N	SVP,C	R
24	N	PB,C	H
25		C,PB	R
26		C,SVP	R
27		SVP	R
28		C,SVP,PB	H
29		C,SVP	R
30	N	C	O
31		C,SVP	R
32		SVP, C, P	R
33		C	R
34		C,P,SVP	H
35		PB,P	H

KEY TO MASTER CHART

CPS : Complex Partial Seizure
GTCS : Generalised tonic clonic seizure
SPS : Simple partial seizure
2^0 : secondary generalization
R : right

L	:	left
S	:	shizophrenic
SA	:	schizoaffective
A	:	auditory hallucinations
V	:	visual hallucinations
P	:	paranoid ideations
LTS	:	left temporal spikes
RTS	:	right temporal spikes
LTSH	:	left temporal sharp waves
LTSL	:	left temporal slow waves
BCD	:	bilateral cortical dysfunction
BEA	:	bilateral epileptiform activity
LH SH SL	:	left hemisphere sharp and slow waves
P	:	present
DILTH	:	dilated temporal horn
CAL P	:	calcification parietal lobe
Hypo P	:	hypodensity parietal lobe
MTS	:	Mesial temporal sclerosis
Psy	:	Psychosis
Rt	:	right
Lt	:	left
SVP	:	Sodium valproate
C	:	Carbamazepine
P	:	Phenytoin
PB	:	Phenobarbitone
R	:	Risperidone
O	:	Olanzepine
H	:	Haloperidol
Cl	:	Chlopromazine