SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA

JUVENILE MYOCLONIC EPILEPSY: LONG TERM OUTCOME AND ITS PREDICTORS- A HOSPITAL BASED COHORT STUDY

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By

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DECLARATION

I, Dr. Harini Pavuluri, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Harini.P

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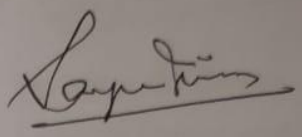
FORWARD BY GUIDE

FORWARDED:

The candidate, Dr Harini Pavuluri, has completed the thesis project under my guidance.



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Dr. Harini Pavuluri

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SYNOPSIS

PURPOSE: We aimed to elucidate the long-term outcome and its predictors of Juvenile myoclonic epilepsy (JME) beyond 20 years from onset

METHODS: We identified 341 persons (217 JME, 127 Non JME PGE) with JME/IGE by screening the outpatient and EEG registers in a tertiary epilepsy care center between 1991 and 1999. The initial clinical details of patients were extracted from the medical records. Their clinical status was updated in 2020 by telephone/postal contact (n=55 JME, 21 Non JME PGE) or clinic reviews (n=31 JME, 8 Non JME PGE). No updates could be done for remaining persons. Terminal 2 year remission was defined as seizure free period for a minimum of 2 years.

RESULTS: The main cohort consisted of 86 JME (44 females) and a subgroup of 29 Non JME PGE patients (7 females). In the main JME cohort, the focus of the study, median age at onset of epilepsy was 13 years (IQR=12-17). Median duration of epilepsy was 32 years (IQR=27 – 36). Family history was positive for 31.4%, and history of febrile seizure in 15.1%. The most common antiseizure medications (ASM) used were Valproate, Carbamazepine and Phenytoin. Newer ASMs like Levetiracetam and Lamotrigine, though were sparingly used initially, their use increased over time. At final follow up (in 2020), 5 (5.8%) persons in JME cohort and 3 (10.8%) in non JME PGE cohort had died, 69 (80.2%) were in remission (6 of them continued to have myoclonus); 23 (26.7%) were off ASM and in remission . Median period of remission was 12 years (IQR= 7-18.25). JME Patients

2remission tended to have lower age at onset (p=0.076), while female sex (p=0.034) and non GTCS onset JME (p=0.049) and off AED status (p-0.003) showed significant association with terminal 2 year remission. In the non JME PGE GTCS group 23/29 (85.2%) were in remission with 14/29 (48.3%) off ASM in the other group

CONCLUSION: After 30 years from onset of epilepsy, over 80% of persons with JME achieved remission of seizures and 26.7% could remain off ASMs. However, around 6% never achieved remission at any point of time and constitute the refractory group. Female sex and absence of GTCS at onset of JME and off AED status were associated with good prognosis. Non JME GTCS subgroup showed slightly higher rates of remission (85.2%) with a higher percentage being off AED (48%).

BACKGROUND AND INTRODUCTION

Juvenile myoclonic epilepsy (JME) is the most common and widely recognized epilepsy syndrome characterized by specific electroclinical characteristics and a genetic basis. Though initially described in the late 19 th century by Herpin(1) and Rabot(2) in single patients each, it was in 1957 that Janz and Christian had described a large series of patients with special clinical electrical characteristics and named it impulsive petit mal palsy(3). In 1989 ILAE (4)identified it as a specific epilepsy syndrome under the name Juvenile myoclonic epilepsy (JME) after the name given by Lund etal(5).

The age of onset is wide ranging from 8-36 years, with the recent consensus criteria extending the lower limit to 5 years.(6,7). It has a slightly more female preponderance. The incidence of JME has been estimated to be 1 per 100,000 persons, with a prevalence of0.1 to 0.2 per 100,000 (8). The prevalence of JME in large cohorts has been estimated to be 5% to 10% of all epilepsies and 18% of idiopathic generalized epilepsies(8).

The prognosis in JME is usually benign, with good response to appropriate antiepileptic drugs at appropriate doses. Seizure control is achieved in nearly 75% with appropriate management while drug refractoriness may be seen in 15% with pseudo resistance (due to poor drug compliance and other psychosocial factors in another 10% (9,10). The predictors of refractoriness as identified in the earlier short term follow up(5-10 year follow up) studies include presence of all the three seizure types, co existence of the psychiatric co morbidities, abnormal EEG at baseline, longer duration and Childhood absence epilepsy (CAE) preceding JME.

(9,11–15). A recent meta analysis (16) looked at the prevalence and risk factors of refractory JME and identified six variables across various studies- early age at onset, presence of absence seizures, all three seizure types, psychiatric co morbidity, history of childhood absence epilepsy and praxis induced seizures.

- In spite of good drug responsiveness, it often regarded as a lifelong disease requiring medications, with relapse being very common following drug withdrawal. However, the long-term outcome in Juvenile myoclonic patient remains an area of interest with very little information known to date. There are only 4-5 papers from various parts of the world which looked at the long-term outcome and its predictors after a long period of 2-3 decades after the onset of epilepsy.(17–21) The number of patients in these studies was relatively small with varying outcome criteria with disagreement between the majority papers and no definite consensus reached with regards to the long term outcome- i.e seizure related, psychosocial and antiepileptic drug related. These studies were majorly carried out in the Europe and America with no published study to date from Asia.
- Epilepsy affects nearly 50-70 million people worldwide with 80% of them living in the developing countries. Approximately 4 billion people (50% of the global population) live in Asia, of whom about 23 million people have epilepsy (upto 45% of total people with epilepsy)(22,23). The prevalence varies among Asian countries from 1.5 to 14.0 in 1000, with median lifetime prevalence of 6 in 1000, which is similar to western countries. In India, the

overall prevalence is 3.0-11.9 per 1,000 population and incidence is 0.2-0.6 per 1,000 population per year, comparable to the rates of high-income countries.(22,24)

In this background of contribution of Asia and India to the world epilepsy burden, data on Juvenile myoclonic epilepsy from India achieves prominence.

- Our study will be the first from South Asia to have looked at the long- term outcome and predictors in Juvenile myoclonic epilepsy nearly three decades since onset. With this background the main aims and objectives of this study were as listed below

REVIEW OF LITERATURE

The Idiopathic Generalized Epilepsy (IGE)/ Genetic generalised Epilepsy (GGE), as being known more commonly today comprises of four well-established epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic–Clonic Seizures Alone (ILAE position paper 2017(25))

Juvenile Myoclonic Epilepsy (JME) is the most common type of idiopathic generalised epilepsy (IGE) comprising 5-10% of all epilepsies and 26.7 %of IGE(6,8).Characterised by the presence of myoclonic seizures (100%), generalised tonic clonic seizures (90%) and absences in one third.(3)

EPIDEMIOLOGY:

The exact frequency of JME is often difficult to assess, in view of the diagnostic errors made and most often diagnosed in retrospect. The incidence of JME has been estimated at around 1 per 100,000 persons. The prevalence ranges from 0.1 per 1,000 persons to 0.2 per 1,000 persons. The frequency in large cohorts is estimated to range from 5% to 10%.(6,8) Other estimates of frequency tanged from 2-10% in most cases by various authors. In India, it was estimated to constitute around 5% of the IGE cases (26). On the other hand the rates of IGE with GTCS ranged from 22-36% .

Regarding gender distribution, considered equal in former studies, female predominance (61%, sex ratio = 1.56) has been reported in more recent series (6).

HISTORY:

In 1867 Theodore Herpin, a French neurologist was the first person to initially described the clinical characteristics of juvenile myoclonic epilepsy (JME) in a very intelligent 14-yearold boy, the son of a doctor, using the terms “secousses” and commotions to describe his cardinal symptoms, the jerks, which started at the age of 13, three months before his attacks and were violent enough to cause the objects to fall from the hands(1). While even before this in 1854, Delasiauve coined the term “motor petit mal” to describe these myoclonic jerks.

Another French neurologist, Rabot (1899),(2) in his thesis of 1899, entitled De la myoclonie épileptique, described five of his patients, with characteristic features of onset of sudden jerks on awakening in adolescence and generalized tonic-clonic (GTC) seizures. He was the first to use the term “myoclonic”, to describe the sudden onset of shock like jerks in his patient, which he referred to as “myoclonic shocks”, and this clinical description referred to similar events which were called by different names like Herpin's shocks and Delasiauve's “motor petit mal”. Aside from the myoclonic seizure phenotype, a more precise definition for the JME syndrome and the awakening morning myoclonias was not provided only towards the later half of the twentieth century when two separate groups, one by Janz and Christian from Germany and the other in Spanish reported cohorts of JME patients.

Janz and Christian, (3)were the first to report a large series of of 47 patients with a phenotype of JME, which they had named as “impulsiv petit mal.” Castells and Mendilaharsu, (2)writing in Spanish used the term “bilateral and conscious myoclonic epilepsy” as they described JME in 70 patients, initially mentioned in a doctoral thesis in 1954 and 1956 and subsequently when in 1958 , it was published in a Latin American journal.

Lund et al. (1976),(5) was the first one credited to name the disorder as JME, the name by which it is called now. It was 1984 when the first ictal video-EEG recordings of myoclonic seizures and clonic-tonic-clonic grand mal convulsions showed 3.5–6.0 Hz polyspike waves.(27)

In 1989, the International League Against Epilepsy (ILAE) asserted that Janz's “impulsiv petit mal” was equivalent to Lund's “JME,” and classified the disorder as a form of idiopathic generalized epilepsy, recognizing it as a specific electroclinical syndrome(4). In 2010, JME was classified by the ILAE as a genetic generalized epilepsy(28) .

DEFINITION OF JME:

The initial description of JME, by its founding fathers, Dr Janz, published in Acta Neurologica Scandinavica in 1985,(3) was “Juvenile myoclonic epilepsy is a special syndrome within the primary generalized epilepsies which is characterized by irregular jerks of shoulders and arms (so-called impulsive petit mal) on awakening clinically and electroencephalography wise, by bilateral synchronous

4–6/s spike, poly spike-wave complexes. The age of onset for this syndrome is predominantly between 12 and 18 years. It mostly starts with isolated jerks which as a rule are soon followed by generalized tonic-clonic seizures (GTCSs). Jerks and GTCSs are provoked by sleep deprivation and predominantly occur after awakening (awakening epilepsy). Sleep deprivation and photo stimulation are also very efficient in provoking specific EEG patterns"

Later on, as ILAE identified it as a specific electro clinical syndrome in 1989(4), and its original description is as follows "appears around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. The disorder may be inherited, and sex distribution is equal. Often, there are GTC seizures and, less often, infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEG have rapid, generalized, often irregular spike-waves and polyspike-waves; there is no close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good."

Thereafter there had been a lot of discussions among the experts as to what to be considered as obligatory criteria for Juvenile myoclonic epilepsy. Over the years, the strict criteria of the initial description are no longer adhered to, with broadening of the defining criteria as the understanding about the disease process, clinical and electrical features has evolved over the years.

Some clinicians believe that it is no longer necessary to have myoclonic jerks without loss of consciousness after awakening for diagnosis of JME. Likewise, there appears to be a loosening of the strict criteria for idiopathic generalized epilepsy (IGE) in general, i.e., abnormal consistent focal EEG features and abnormal MRI results are permissible.(10,29)

An international consensus workshop on juvenile myoclonic epilepsy (JME) was conducted in Avignon, France in May 2011, conceded by a group of 45 experts on JME, with Prof. Dr. Dieter Janz from Berlin, one of the founding fathers and pioneer in the field of JME research. This group discussed and formulated a set of diagnostic criteria as well as management guidelines for JME(7).

The international experts on JME proposed two sets of criteria, with an aim to broaden the criteria compared to the earlier strict versions to accommodate both clinical and scientific purposes(7).

Class I criteria encompass myoclonic jerks without loss of consciousness exclusively occurring on or after awakening and associated with typical generalized epileptiform EEG abnormalities, with an age of onset between 10 and 25. (7)

Class II criteria allow the inclusion of myoclonic jerks predominantly occurring after awakening, generalized epileptiform EEG abnormalities with or without concomitant myoclonic jerks, and a greater time window for age at onset (6–25 years).(7)

For both sets of criteria, patients should have a clear history of myoclonic jerks predominantly occurring after awakening and an EEG with generalized epileptiform discharges supporting a diagnosis of idiopathic generalized epilepsy.

CLINICAL FEATURES:

It usually manifests around puberty. Three seizure types are characteristic of idiopathic generalized epilepsies (IGEs), and all can be found in JME, namely, myoclonic jerks (MJs), generalized tonic-clonic seizures (GTCSs), and absence seizures (ASs). (11,12)

1. Myoclonic jerks /seizures: The characteristic symptoms of JME are spontaneous, brief, sudden, and grossly symmetric MJs of variable amplitude. Such MJs may be isolated or occur in brief arrhythmic clusters. They are not associated with any loss of consciousness except for brief lapses of attention as noticed by some. They typically after morning awakening, especially after a shorter than-usual sleep period, but can also occur following intermediary awakenings at night, on waking from short naps in the afternoon, or during relaxation periods during any part of the day. Less commonly, they occur sporadically over the day. Myoclonic status is uncommon (7.3% of patients in a series from Marseilles) and it is characterized by full preservation of consciousness and is often precipitated by acute drug withdrawal and by MJ enhancing antiepileptic medications. Myoclonic jerks predominate on the upper limbs, can be proximal or distal,

asymmetric or unilateral in some and can also involve the lower limbs causing them to fall on occasions.

2. Generalised tonic clonic seizures: most common type and are present in 80–95% of patients. They are often the reason for the first referral of patients to the doctor. They usually characteristically follow a longer-than-usual cluster of MJs, with increasing amplitude and frequency, until MJs melt into the tonic phase of the GTCS event often giving a clonic-tonic-clonic picture. In JME, similar to that in other IGE spectrum disorders, GTCS episodes are usually long and intense, unlike the secondary GTCS of focal epilepsies. Less typical variants with versive components have been described, even truly rotatory seizures. They occur usually once or twice per year at most in the natural course of JME but may, however, cluster over a few weeks at the onset. They are more frequent in inappropriately treated or noncompliant patients, more frequently seen in those with an erratic lifestyle characterised by irregular and poor sleep schedules, substance abuse and addictions, all of which can trigger seizures.
3. Absence seizures (ASs): When present, usually are infrequent and short, and are often ignored by patients and carers and are often found only on long-term EEG recordings. Their prevalence has thus been diversely quantified: 10% ofpatients for Janz(3); 14% for Tsuboi and 18% for Obeid and Panayiotopoulos [39]. ASs may be the initial seizure type in some patients who present CAE or JAE before they develop JME

The important triggering factors identified by more than 90% of the JME patients include severe stress (83%), lack of adequate sleep (77%), sustained focus/mental concentration (23%), performance of hand activities and complex finger movements (20%), visual stimuli like flashing lights and playing games (15%), speaking out in public (11%), alcohol intake (11%), reading (7%), calculating and writing (5%), playing musical instruments (4%), drawing (3%), and specific types of music (1%); the menstrual cycle is the third most important precipitant in women (33%). Certain environmental visual stimuli (television screen, stroboscopic flashes in discos, videogames, bright sunshine, etc.) are important factors that can trigger seizures. Patients with JME usually do not have any antecedents. Simple febrile seizures are found in upto 5–10% of patients. The evolution from one type of epilepsy to another type of epilepsy poses mainly nosological problems: there is a subset of patients who evolve into JME from childhood absence epilepsy (CAE).

Four reflex traits are common in JME:(10–12)

a) Photosensitivity: clinically quite unexpressed, seen in up to 50–90% of the cases depending on age, treatment, and modality of photic stimulation
b) Eye closure sensitivity: defined as appearance of spike and wave discharges and eyelid myoclonia, within two seconds after eye closure, occurs in 15–20% of cases

c) Praxis induction, the precipitation of epileptic seizures or epileptiform EEG discharges by complex, cognition-guided tasks often involving visuomotor coordination and decision-making, described in 30-50% of the patients.
d) Orofacial reflex myoclonic: lightning-like myoclonic in the perioral muscles, tongue, throat and jaw precipitated by language-related activities, mainly reading and talking, is present in 25–30% of JME patients and attributed to hyperexcitability of the network supporting linguistic communication

Common co morbidities associated with JME include Psychiatric and cognitive. There is a also a good association reported with headache- Migraine and other primary headache disorders. Essential tremor has also been escribed in a good number of patients. Certain medical conditions often interfere with the optimal management of JME patients like thyrotoxicosis. Similarly, conditions leading to severe sleep deprivation, e.g., obstructive sleep apnea syndrome, may cause an aggravation, relapse, or pseudo pharmacoresistance in JME

ENDOPHENOTYPING IN JME: Four subsyndromes are commonly know in JME

(1) classic JME, defined as adolescent onset of isolated awakening myoclonic seizures appearing as the first seizure type or following GTC seizures in 72%

(2) childhood absence epilepsy evolving to JME (18%)

(3) JME with adolescent onset of absences (7%);

(4) astatic seizures occurring independently of myoclonic jerks (3%)

ELECTROPHYSIOLOGICAL CHARACTERISTICS:(11,30–32)

The diagnostic EEG findings of JME include normal background activity with generalized 3–6 Hz SWs , very often with frontal predominance. Fragmentation of discharges is another characteristic finding, mostly encountered as irregular polyspike-waves, seen predominantly at sleep onset or on awakening. Ictal records of myoclonus showed fast, rhythmic generalized polyspikes around 20 Hz. However, there is high variability of EEG pictures of patients diagnosed with JME. Focal EEG findings and asymmetries of the "generalized" discharges are seen in 6–48% of the patients with JME. They can either be stable for years or constantly switch from one hemisphere to the other, even within the same recording, an entity known as Shifting asymmetry. They may present diagnostic difficulties for physicians not familiar with this possibility in JME. Even if the significance of focal EEG findings remains unclear, for the spectrum of JME their presence or absence should be noted. Giant somatosensory evoked potentials (SSEP) may be present in 35–50% of JME cases, in similar lines to patients with progressive myoclonus epilepsy. Trans cranial Magnetic Stimulation(TMS) provided new opportunities for electrophysiological research in recent years. TMS findings in JME are characterised by defective intracortical inhibition, due to impaired GABA-A mediated mechanisms, with preserved GABA-B-mediated inhibitory mechanisms.

GENETICS IN JME:(12,27,33)

Delgado Escueta et al were the first to credit for study of the role of genetics in JME patients. A handful of Mendelian genes, many related to ion channels were identified such as, CACNB4, GABRA1, and EFHC1 in some families with JME most of which were also in charge for other genetic generalized epilepsies. Besides, a few SNP alleles in BRD2, Cx-36, and ME2 were reported waiting still confirmation by other large cohorts. Recently the contribution of copy number variants was also disclosed in a minority of JME population. It was striking to note that the existing evidence supported a neurodevelopmental origin for common epilepsies like JME. JME genes are in fact, diverse suggesting that JME is more of a spectrum than a single disease entity.

MANAGEMENT:(7,10,12)

The management in Juvenile myoclonic epilepsy has to be comprehensive, focussing on lifestyle factors like adequate sleep hygiene in addition to appropriate and optimal antiseizure medication usage. The preferred usually are Valproate (VPA), Levetiracetam (LEV), Lamotrigine (LTG) and Topiramate (TPM), and VPA). Treatment of often started at the first clinic visit, when most patients present after the occurrence of a GTCS. Valproate though known to be the most effective, it is less commonly preferred in females of child bearing age due to side effects like polycystic ovarian disease and teratogenicity. Lamotrigine is also known to increase the occurrence of myoclonic jerks in some patients. Other drugs that have

been used successfully, especially in treating patients with pharmacoresistant epilepsy, are phenobarbitone/ primidone (PB/PRM), clonazepam (CLZ), and zonisamide (ZSM). Despite being well known for its unpleasant side effects, CLZ controls myoclonic jerks without affecting GTCSs.

In addition to good compliance to anti seizure medications, the other factors that are to be stressed upon include maintenance of a regular 7- to 8-hour sleep and limiting alcohol and caffeine, and the screen time especially in teenagers. Patients should also be aware of their triggers and avoid them as needed.

LONG TERM OUTCOME AND PROGNOSIS:

JME has been considered as generally responsive to adequate treatment, with 75% remission rates in most studies, while the rates of pharmaco resistance were found to be around 15% and that of pseudo resistance around 10% of consecutively diagnosed patients. The results from various short term studies, around 3-5 year follow up (9,10,13,34) have shown good remission rates of 70-80% with seizure free period of 3 or more years.

It has always been thought that JME is a lifelong disease, often requiring medications almost during the entire lifetime and is associated with a high risk of recurrence on withdrawal of AEDs. There are not many natural history studies that are available that throw light upon the seizure outcome and pattern of AED use in this group. Being one of the most common of the IGE/GGE subtypes, knowledge

on the long term prognosis is very useful, especially when deciding on when to stop antiseizure medications after attaining remission. This will throw a light on the overall prognosis and study of predictors will help in altering any modifiable entities in order to improve the overall outcome.

There is however a paucity on the long-term outcome data in patients with JME. There are less than 10 papers which have looked at the long-term outcomes, with overall data available from less than 300 patients world over.

There is no data available from the Indian subcontinent on the long term follow up in GGE/ JME patients and an attempt to bridge this knowledge gap was attempted in our paper.

A comprehensive review of the international data on long term follow up studies done to date is presented if the following section.

REVIEW OF LONG TERM FOLLOW UP STUDIES IN JUVENILE MYOCLONIC EPILEPSY:

- The first study on the long-term response to therapy in JME dates to 1989 by Penry et al (35)which looked at the long term response of JME patients after a follow up period ranging from 2 months to 9 years. A total of 50 patients were studied where in forty-three patients (86%) were seizure free for at

least 1 year. 25 patients (50%) relapsed at some point during follow-up. Common factors found to be precipitating relapse were found to be fatigue, noncompliance, stress, sleep deprivation, and alcohol consumption.

- E. Martı´nez-Jua´rez et al in 2006(14) made an attempt to study 252 patients of JME who were prospectively registered for JME genetic studies at multiple study sites over a period of 25 years (1978-2003). They have sub grouped JME into 4 separate groups according to the seizure phenotypes and studied their clinical course over a follow up period that ranged from 1 to 52 years (mean 11 ± 6 years). The four subgroups included (i) classic JME (72%), (ii) CAE (childhood absence epilepsy) evolving to JME (18%), (iii) JME with adolescent absence (7%), and (iv) JME with astatic seizures (3%). Overall the CAE evolving to JME subgroup had a difficult to treat epilepsy and unfavourable prognosis.Myoclonic seizures appeared as the first seizure type in 68%. Grand mal(GM) seizures preceded myoclonic seizures in 30% of probands.Myoclonic and GM seizures (15.9 years 95% CI 60.60; range 8–33 years) both appeared for the first time at 15 years of age. Absences, appeared a year later at the average age of 16.8 years 95% CI 61.19; range 11–30 years. Absence seizures, when present, rarely occurred in 33% of the patients. Absences were the first seizure type reported in only one case (onset at 16 years).

A total of 161 of these 186 classic JME patients for a mean period of 12.4 years (range 1–41 years). During follow-up, 58% (93/161) were free from all seizure

types tonic-clonic, myoclonic and absence seizures) during antiepileptic drug treatment. Of these patients without seizures, 65% were on valproate monotherapy, 11% on valproate plus one or more other antiepileptic drugs and 15% on antiepileptic drugs other than valproate either in monotherapy or polytherapy. Seizures continued in 68 of 161 (42%) patients despite antiepileptic drug treatment. Seizures in these 68 patients provide evidence of a chronic epilepsy syndrome that lasted up to at least 41 years of age. This study also showed that seizures continued to occur upto 41 years age often when followed up almost 11-40 years since onset. This further reiterated that JME was a life long disorde, but has a good prognosis with more than half of them achieving remission with appropriate anti epileptic medication and a significant percentage continued to remain in remission even when off AEDs for more than 5 years.

- Baykan et al in 2008 (17)carried out a single centre study in Istanbul Turkey with a primary focus on long term follow up of JME patients with an emphasis on the course of myoclonic seizures. Remission as per this study was defined as ever being seizure free for a period of at least 5 years during the course of the disease with or without AED treatment. This was carried out in a homogenous population group from a single centre that was prospectively recruited with a background of 7 years retrospective follow up. 48 patients were followed up for an average period of 19.6± 5.7 years. On the basis of the outcome, they had grouped the patients into three groups- i) benign group (patients with no GTCS and less than two

myoclonic jerks per month), ii) the resistant group (patients with one or more GTCS per year and iii) the pseudo resistant group (patients who continued to have seizures due to poor drug compliance and inappropriate lifestyle). They also looked at the seizure types, ages at onset of all seizure types, personal and family history, EEG and imaging findings, comorbid diseases, and AED treatment in the last five years. The treatment regimen used in the last 5 years was grouped as follows: 1) no treatment, 2) VPA monotherapy, 3) other monotherapy. On the whole 66.6% had a benign course, 16.7% had treatment resistance and 16.7% had pseudoresistance. 54.2% of the patients, myoclonia were in remission for a mean duration of 8.4 ▯ 7.7 years, after an average age of 32.9 ±9.6. Of these patients, 6 were on a lower dose of AED in comparison to the dosage needed to control the seizures in the beginning, and 5 patients had stopped AED treatment. None of the latter 11 patients except one relapsed during the follow-up. Furthermore, 21 other patients (43.8%) described substantial alleviation after age 31.3 ▯ 8.4 in the severity of myoclonia. They have concluded that although a great majority had continuing seizures after a 20 year follow-up , almost all had either 5-year remission or a substantial alleviation of the myoclonic seizures with myoclonic seizures abating with age.

- Camfield et al in 2008(18) carried out a population-based study in Nova scotia, Canada wherein all the children who developed JME before their 16th birthday during the years 1977 and 1985 were identified. This cohort was

then followed up in the years 2006-2008 providing at least 20 years of follow up. They looked at both the seizure and social outcome. 24 patients with JME were followed up after a mean period of 25.8 ± 2.4 years (range 20–30 years) at an average age of 36 ± 4.8 years. At the final follow up,11 (48%) had discontinued treatment: 6 were seizure-free (without AEDs for 5–23 years), 3 had myoclonic seizures only (without AEDs for ¬↴18 years), and 2 continued with rare seizures. About 70% reported good satisfaction with their health, work, friendships, and social life (Likert scales), however about 76% had at least one unfavourable social outcome. All seizure types in juvenile myoclonic epilepsy (JME) resolved in 17% and for 13%, only myoclonus persisted and hence for one-third of people disabling seizures vanished and antiepileptic drug treatment was no longer needed. Depression, social isolation, unemployment, and social impulsiveness complicate the lives of many patients. With respect to social outcome seventeen (74%) had at least 1 major unfavourable social outcome (failure to complete high school, unplanned pregnancy, depression, unemployment, living alone, never in a romantic relationship longer than 3 months). There was no significant association found between the seizure and social outcome. Though the sample size was modest in this study, the population-based design and long term follow up were the unique features which made it stand out from the earlier studies All the studies above however did not look at the longterm outcome predictors.

- Geithner et al in 2012, Germany(19) investigated the long-term seizure outcome in patients with JME after a follow-up of at least 25 years and attempted to identify the predictors for the seizure outcome. This study was carried out in Germany as a population based study in the catchment area of the University Hospital of Greifswald. All the patients diagnosed with JME before January 1986 and had at least 25 years of follow up were identified by retrospective chart review from the Epilepsy centre database. These patients did not have a regular follow up at the institute, as such a follow up practice did not exist and hence all of the identified patients were re evaluated by experienced epileptologists between May and September 2011 with a review of the medical records, telephonic or face to face interviews. A total of 31 patients were included, of which twenty-one patients (67.7%) became seizure-free under AED treatment. Mean duration of epilepsy was 34.2 years. The mean follow up was 39.1 years (SD ± 11.9, range 25–63). Ten patients (32.3%) continued to have seizures despite multiple different AEDs. Nearly half (51.6%) had a history of Myoclonic seizures and GTCS, while another one third (35.5%) additionally had absence seizures. In the majority of patients (51.6%) the epilepsy started with GTCS (with myoclonic seizures in 22.6%; with absences in 25.8%). The mean number of AEDs used was 3.1 (SD : 1.73, range 1–6). Around 61.3% received valproic acid and 14 of them in monotherapy. Neither the total number of AED trials during the entire course (chi-square test: $p = 0.34$) nor the duration of AED

treatment (p = 0.918) was significantly associated with the long-term outcome; however, a significant negative correlation was found between an increasing number of AEDs at follow-up and a seizure-free outcome (p = 0.023).With respect to predictors of seizure outcome, the occurrence of GTCS preceded by myoclonic seizures was significantly associated with a lower likelihood of attaining seizure freedom (chi-square test: p = 0.03).A shorter duration of epilepsy before seizure freedom was reached was associated with better outcomes. The occurrence of various seizure types and photo paroxysmal response did not influence the seizure outcome. While neither the number of AEDs, type nor duration of treatment showed an association with the long-term outcome, withdrawal of AEDs was found to be associated with recurrence.

- Senf et al (20)from Center for Epilepsy, Berlin, Germany have looked at the long term prognosis with respect to seizure control in a well defined cohort of JME patients along with the predictors – their positive and negative influence on the long term outcome. Their cohort consisted of 82 JME patients identified from 339 IGE patients, who had at least 20 years follow up as defined as time between JME onset and last patient contact, which was between January and June 2011, where in patients were contacted either personally or via the telephone.16 patients were excluded due to lack of insufficient data and the final cohort consisted of 66 patients. The mean follow-up time was 44.6 ± 13.7 years (range, 20–69 years). 39 of 66 patients

with JME (59.1%) had a 5-year terminal remission. Among these, 28 (71.8%) were still taking AEDs and 11 had been completely off medication (28.2%; or 16.7% of all patients) at least during the last 5 years. The mean terminal seizure-free time of the 39 seizure-free patients was 22.9 ± 10.9 years (range, 5–46 years). From the remaining 27 patients who were not seizure-free, 26 continued on AED except one who had rare non disabling myoclonic jerks who was off AED.

Of the 27 patients without remission, 4 (14.8%) continued to have only GTCS, 4 (14.8%) had only ongoing myoclonic jerks, and 19 (70.4%) still experienced both types of seizures. Absence seizures were however in remission for all of them. The patients with poor terminal outcome also had seizure-free intervals of up to 30 years (mean, 7.2 ± 8.7 years) during follow-up. Eleven of the 27 patients (40.7%) who were not in terminal remission, experienced intermittent remission period of more than 5 years. With respect to predictors of seizure outcome, presence of absence seizures at any point of time was associated with poor outcome i.e absence of terminal 5 year remission. While none of the other clinical variables like age at onset, sex, family history, EEG status and photosensitivity predicted the outcome. A significantly younger age at last seizure (29.3± 9.3 vs 39.8± 15; *p=0.037*) was found in those patients who have achieved remission while off AEDs when compared to those who were on AEDs. Fifty-four patients (81.8%) were still taking AEDs where in 38 patients(70.4%) were on

monotherapy and 16 on polytherapy (29.6%). The 2 most frequently used AEDs in mono- or polytherapy were primidone (48.1%) and valproate (51.9%). Newer AEDs were administered only in 3 patients (one in polytherapy), all of whom continue to have seizures. Primidone showed the most effective treatment results with a 5-year terminal remission rate of 73.3%, compared to 50% with valproate. AED withdrawal was attempted in 14 patients, and only one of those had seizure relapse.

- Marte R. Syvertsen et al(21) in 2012 carried out a similar hospital based long term follow up study in a cohort of 42 JME patients identified in the year 1992 as a part of another human leukocyte antigen based genetic study. These patients were then contacted again in the year 2012 to know the 20 year follow up data. 37 patients (88%) could be traced for a standardized semi structured telephone interview, focusing on seizure types, seizure frequency, medication, and psychosocial outcome. Medical records were reviewed for background information. Psychosocial outcome was assessed based on five elements: graduation from high school, disability or unemployment benefits, alcohol or illegal substance abuse causing social problems, need of psychiatric health care and self-reported social network. The psychosocial outcomes were simply graded as poor, sufficient or good rather than the use of complex scales. They looked at the seizure remission rates at 5 and 10 years for each of the myoclonic and generalised seizure

types and also for a combination of both of them. Mean duration of epilepsy was 31 years with mean age at final follow up being 47 years.

More than 50% had been completely seizure free for the last five years prior to assessment, and one-third for at least ten years. On the whole, around 19 patients, were not in remission , i.e had persistent seizures within the last five years; most common seizure types where MC only (10), both MC and GTCS (8), GTCS only (1). Of the 18 interviewed patients with persistent MC, all but two (age 39 and 41) reported a reduced frequency compared to younger years.

None of the three patients, all females, with absence epilepsy prior to MC onset had experienced seizure remission. The relationship between various clinical characteristics and five-year seizure remission was studied which showed that MC (myoclonic seizure) habitually or occasionally preceding GTC (generalised–tonic–clonic seizure) was associated with a poorer seizure outcome. Fifteen patients had a gap of little more than one year between MC onset and subsequent GTC. However, the longer interval between MC and GTC onsets, did not influence five year complete seizure remission. There was no difference in age at JME onset between patients with five-year seizure remission and patients with ongoing seizures (16 ± 3.9 years vs. 16 ± 2.3 years, $p = 0.494$). There was no significant difference between the two groups with respect to sex ($p = 0.165$).

Favourable psychosocial outcome by interview was found in a third, whereas another third had psychiatric comorbidity, seven with substance or alcohol abuse. No relationship could be established between the psychosocial status and seizure outcome ($p = 0.506$).

Seven patients (18%) had stopped AED treatment, 4 of them by their own initiative and two without medical supervision. Four of them had been completely seizure-free for more than ten years after withdrawal. Of the remaining 3, 1 relapsed with GTCS with the other two having only occasional myoclonic jerks.Of those remaining on treatment, 17 patients used monotherapy, and 18 a combination of AEDs. Among the 17 patients with five-year seizure remission still using AEDs, 10 had monotherapy, mainly valproate (seven). Valproate had been used by all, apart from three females. The second-generation broad-spectrum AEDs, (lamotrigine, levetiracetam and topiramate) were tried in 21 patients. Of the 19 patients who had received second generation AEDs for resistant seizures for at least five years, eight obtained seizure remission, with half of them attaining remission after introducing Levetiracetam. The remaining patients used lamotrigine in combination treatment. However, lamotrigine was withdrawn due to more frequent MC in five of them, while on the other hand, Levetiracetam was found to cause an apparent increase of GTCS, though there was reduction in myoclonic jerks. Topiramate was proven beneficial in the six patients, partly attributed to its property of counteracting valproate-

induced weight gain. Thirteen patients (33%) had not seen a neurologist for more than ten years. Only seven of them had been seizure-free for more than five years. Two had a GTC less than one year earlier. One had several unfavourable social factors, including substance abuse. Beyond that, we found no association between drop-out from follow-up and social outcome.

- Asadi Pooya et al (36)carried out a case control study in JME patients recruited over 4 years between 2008-2012. These patients were then followed up for 1.5 years and remission was considered as a seizure free period of 1 year. A total of 116 patients were studied. 68/116 (58%) patients were seizure free in the prior 12 months of their follow-up and 48 patients had at least one seizure of any type. The predictors of remission in this study were found to be longer duration of follow-up, valproate in their drug regimen and a better drug compliance, while those who experienced seizures had more frequent generalized tonic-clonic seizures (GTCS) before their first visit and more often reported alcohol and tobacco consumption. On multivariate analysis, long duration of follow up, good drug adherence and Valproate in the drug regimen were found to be significantly associated with seizure free state. This study however, followed up patients only for a short duration of 1.5 years, hence the long term outcomes with respect to seizure and antiepileptic drug status were not known.
- Julia Höfler and Iris Unterberger et al 2013 (15)retrospectively studied 242 patients with JME at the Department of Neurology, Medical University

Innsbruck, Austria. The cohort was identified during the time period of 1975-2006 i.e over a period of 31 years. Of these 242, patients with a treatment duration of less than 2 years at the hospital, missing clinical records and those who died were excluded from the study. The primary outcomes defined in this study were seizure outcome at the last visit in outpatient clinic. Three categories were defined: (1) seizure-free for more than one and less than or equal to 2 years, (2) seizure-free for more than 2 years and (3) not seizure-free. Median age at seizure onset was 15 years (range 3—46) and median age at the last follow up was 38 years (range 14—87) with a median observation period of 8 years (range 2—38). Mean epilepsy-duration was 24 ± 14.2 years, median 23 years (range 3—73). Seventy-one (41%) patients had a positive family history of epilepsy; seven (4%) had a history of febrile convulsions. Twenty-four patients (14%) showed photosensitivity on routine EEG recordings. Sixty-two percent (109/175) of patients were completely seizure-free more than one year under AED treatment, 53% (94/175) were seizure-free for more than 2 years, including 16 patients (9%) without taking any AED. Thirty-one percent (54/175) of patients were seizure free between 2 and 5 years, 15% (26/175) between 6 and 10 years and 8% (14/175) more than 10 years. Thirty-eight percent (66/175) were not seizure-free despite appropriate AED treatment. With respect to predictors of seizure remission, presence of all the three seizure types at onset were associated with absence of remission at the final

follow up (p=0.043). Seizure-free patients were significantly more likely to have MS and GTCS as their last seizure type before becoming seizure-free (37% vs. 15%, p = 0.003), whereas in the not seizure-free group MS only and GTCS only tend to persist.

The majority of patients (66% of seizure-free and 60% of those with persisting seizures) were on VPA monotherapy. Other drugs used in monotherapy were levetiracetam (LEV), topiramate (TPM), primidone (PRM) or lamotrigine (LTG). Patients taking LEV, TPM or PRM did not differ in seizure outcome. In contrast, patients receiving LTG became less frequently seizure-free (15%; p = 0.024). Three percent of patients (one patient of the seizure-free group and four of the not seizure-free group) received temporarily carbamazepine (CBZ) once in their medical history. At FU none of them had CBZ anymore. Eight percent of patients were on polytherapy. Nine percent (16 patients) of the patients were seizure free without any AED-therapy. The first documented seizure types of these 16 patients

were MS only in 46% of patients, AS only in 26%, GTCS only in 8%, AS and GTCS in 8%, AS and MS in 4% and all three seizure types in 8% of the patients.

PSYCHIATRIC CO MORIDITIES IN JUVENILE MYOCLONIC EPILEPSY:

Psychiatric disorders, especially mood disorders are well described in patients with Juvenile myoclonic epilepsy in addition to peculiar personality characteristics. There are a few studies which looked at the psychiatric co morbidities in this group of patients.

In patients with JME, mild but characteristic personality problems have been initially described by (3) and have later been reported by other authors (5), (37).

Perini et al in 1996 (38) evaluated the occurrence of psychiatric disorders in JME in comparison with temporal lobe epilepsy and found that 22% of JME patients qualified for a diagnosis of psychiatric disorders when compared to 80% of TLE patients. Mood disorders were found in 55% of the temporal lobe epilepsy patients while it was found in only 16% of the JME patients.

To our knowledge so far only three studies empirically assessed psychiatric diagnoses in patients with JME. Gelisse et al. (2001a)(9) found psychiatric diagnoses in 26.5% of their investigated JME cohort. Lund et al(1976) (5) investigated the personality of JME patients and diagnosed 36.4% as "character neurotic" (i.e., with personality disorders). The flip side of these studies is that there are several methodological shortcomings wherein most of the diagnoses were assigned without any clinical interview or psychometric assessment (9) or were not properly defined (5)and very small sample sizes were assessed (38).Trinka et al in 2006 (37)interviewed a larger number of JME patients with a high standard diagnostic procedure, the Structured Clinical Interview for *DSM-IV* and found the

occurrence of one or more psychiatric disorders (Axis I and Axis II) in thirty-five percent of the JME patients. It also found that Personality disorders were present in 23% and Axis I disorders (anxiety and depression) was found in 19%. Altogether, 47% had a psychiatric disorder at any time of their life.

A recent study of psychiatric disorders among 165 patients with Juvenile myoclonic epilepsy and association with clinical and social profiles was done by S Somayajula et al (39) from Hyderabad, India and showed that 46.6% were diagnosed with psychiatric disorders wherein 30% had anxiety and 16.6% had depressive disorders. Patients with PDs had lower overall QOLIE-31 score. Being married was the strongest predictor of depressive disorders ($p = 0.018$); whereas lower emotional well-being ($p = 0.002$) was the only variable associated with anxiety disorders. Depressive disorders were more prevalent among older patients with JME, and marriage was strongly associated with depressive disorders

AIMS AND OBJECTIVES

1) To elucidate the long-term outcome in patients with Juvenile myoclonic epilepsy (JME) / Idiopathic generalized epilepsy (IGE)
2) To study the predictors of long-term outcome

The long-term outcome measures consisted of primary outcomes, which included the seizure and antiepileptic drug outcomes and- these were the principal focus of the study. Secondary outcomes included survival, psychiatric co morbidities (depression and anxiety) and quality of life in epilepsy

METHODS

Study Setting:

The study was carried out as a single center, hospital-based cohort study with a Observational long term follow up design. Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India, a tertiary care referral center and one the premiere medical institutes of India, was the site of the study. It was principally carried out in Department of Neurology, including R Madhavan Nayar Centre for comprehensive epilepsy care, a well-known tertiary epilepsy care center from South Asia.

Study population and Recruitment process:

The study cohort primarily consisted of the people living with epilepsy diagnosed as Juvenile myoclonic epilepsy/Idiopathic generalized epilepsy registered with the department of Neurology between the years 1991-1999.

All the patients who were initially registered at the department of Neurology at Sree Chitra Tirunal Institute, with complaint of seizure, between 1991-1999 were identified through the Institute's Medical records department. This included the patients treated either in the outpatient department- both general neurology and epilepsy clinics or inpatient department. From this group, those patients with a confirmed diagnosis of Idiopathic generalized Epilepsy (IGE) or Juvenile myoclonic epilepsy (JME) were filtered with the help of ICD codes. In turn the clinicoelectrical data was screened to identify those patients who satisfy the

inclusion criteria of JME as per our study. In addition, the final EEG reports, each of which was written by a qualified epileptologist, containing the details like referral diagnosis, classification and final interpretation were screened to identify patients with typical EEG findings of IGE/JME (reference). The EEG recordings however could not be screened due to logistics issues. The clinical data of patients identified in this manner were screened in retrospect to confirm a diagnosis of PGE/JME, following which they were included in the cohort.

This cohort was then divided into two groups- i) JME , which included the patients who satisfied the clinicoelectrical criteria for JME, ii) Non JME -PGE group, which included the rest of the patients.

The inclusion criteria for the JME group included:

1. Age of onset above 5 years with presence of myoclonic jerks with generalized tonic clonic seizures with or without absences or myoclonic jerks alone
2. EEG evidence of generalized atypical fast spike and wave discharges with normal background in those patients without historical evidence of myoclonic jerks.
3. Normal psychomotor development

Exclusion criteria:

1. Static or progressive encephalopathy with intellectual subnormality

2. History of antecedents like meningoencephalitis, trauma, tumor etc.

The study period of 1991-1999, for recruitment of patients, was chosen so that patients would have had a minimum of 20 years or more follow up period to study the intended outcome measures by the time of the final follow up which was planned to be in 2020.

Follow up:

An attempt to trace the patients who were not under regular follow up was made in the final assessment year 2020. As no telephone numbers of these patients were available with the old records, an attempt to reach them through postal letters to the available address was made. These letters were in both English as well as the local language of Malayalam with an attached questionnaire pertaining to their seizure and antiepileptic drug status, survival, and follow up. Contact number of the principal investigator was provided, for them to contact and the patient's number was also requested if they were willing. A stamped and self addressed postal envelop was also included with the letter, for them to post the filled in questionnaire. 2 such rounds of letters were posted with the second round targeting those who have not responded in the first round keeping in view the background pandemic situation.

Data Collection:

The background clinical data of these patients were collected from the available medical records. Data was collected with regards to the age of onset, registration,

family history, history of febrile seizures, type of seizures and their onset and frequency during the course, natural history of each of the seizure type, various AEDs used during the period.

The final assessment was done through in person clinic visit for those who were under regular follow up and also for those who were willing to come for in person follow up. In view of the pandemic situation for those who could not come for the clinic visit, a telephonic interview was undertaken by the principal investigator, in those patients with an available telephone number. Follow up information from the rest was obtained through the answered semi structured questionnaires posted by mail.

The data collected at the final follow up included the seizure status- remission or not, use of AEDs, if yes mono or polytherapy, death. Assessment of secondary outcome measures like anxiety, depression, and quality of life in epilepsy was done only in those feasible in view of the pandemic situation. The total duration of follow up, defined as time period between the final assessment and the age of seizure onset was also assessed.

Outcomes:

The study mainly aimed to look at two principal primary outcome measures at the final follow up after more than a minimum of 20 year follow up.

PRIMARY OUTCOME MEASURES

1) Seizure outcome

2) Anti epileptic drug outcome

➢ Various seizure outcome measures looked into in this study:

- Terminal 2 year remission: Seizure free period of minimum 2 years, for disabling seizures at the final assessment.
- Terminal 5 year remission: Seizure free period of minimum 5 years, for disabling seizures at the final assessment.
- Brief Intermittent Remission at any point of time: Seizure free period of minimum 2 years at any point during the course irrespective of the final follow up seizure status.
- Resistant/ Refractory group:
    - Relative resistance/ refractory group: Presence of seizures in the preceding 2 years at final follow up
    - Absolute resistant/refractory group: Never had a minimum of 2 year seizure free period at any point during the entire natural history

➢ The natural history of seizures (all the types – myoclonic, generalized tonic clonic and absences) was further characterized as following:

- Never in remission: Includes patients who continue to have seizures with frequency remaining unchanged or decreased since the onset. This is suggestive of refractoriness.

- Short remission and relapse/ Early relapse: A seizure free period of 2-5 years followed by relapse at any point of time. This is suggestive of an early relapse.
- Long remission and relapse/Delayed relapse: A seizure free period of 5 years or more followed by relapse. This is suggestive of a delayed relapse.
- Terminal 5 year remission: A seizure free period of more than 5 years without any relapse at the final follow up.

2. Anti Epileptic drug outcome: At the final follow up number of patients who were off AED, on monotherapy and polytherapy were assessed. The spectrum of various antiepileptic drugs used was also studied, during the initial period of the study and also at the final follow up.

SECONDARY OUTCOME MEASURES:

The main secondary outcome measures looked at were presence of anxiety, depression and assessment of quality of life in epilepsy.

Assessment tools employed: (Attached in the annexure)

- Anxiety and depression were assessed through standardized Hospital Anxiety Depression Score (HADS) using English and its translated and validated Malayalam version (ref)HADS consists of 14 questions with 7 questions directed at assessing Anxiety and 7 at Depression. The scoring for

each question ranges from 0 to 3 with higher score suggestive of higher anxiety/ depression levels. A score of < 7 indicated no anxiety/depression; 7-10: borderline anxiety/depression; 10-21: significant anxiety/depression. In our study score of less than 7 was considered as no anxiety/depression and score between 7-21 as presence of anxiety/ depression

- Quality of life in epilepsy: (QOLIE-10) This is a simplified version of the original quality of life in epilepsy (QOLIE) score which consisted of 51 questions. QOLIE 10 consists of 10 questions, which can be easily administered in a short span of time and also feasible for administration over the phone. The 10 questions had scores ranging from 1 to 4, 5 or 6 varying from question to question. The maximum score was 51 and a higher score indicated a poorer quality of life. There are no specific standardizations available for the scoring system and hence, we have considered 25 as the cut off with patients with score <25→ good quality of life and those with > 25 as poor quality of life.
- HADS and QOLIE 10 were administered either through in person interview, telephone or google forms (in those who could not come for an in person assessment due to the COVID pandemic)

➢ Predictors of remission at final follow up were assessed by analyzing various factors like age at onset, sex, family history, history of febrile

seizures, type of seizure at onset, type of antiepileptic drug at follow up, monotherapy and poly therapy. The role of comorbidities like anxiety and depression assessed through standardized HADS scoring and quality of life in epilepsy in predicting the outcome was also assessed.

- A subgroup analysis of resistant JME cohort (both absolute and relative resistant groups) and Elderly JME cohort (defined as > 60 years in age) was done and clinical characteristics in these subgroups of patients was looked at.
- A comparison of clinical characteristics including the seizure and AED outcome between the JME and Non JME PGE subgroups was also made.
- Mortality assessment: Mortality was assessed in terms of no of deaths, no of deaths per 1000 years of follow up

Statistical analysis:

Data was analyzed using Microsoft Excel and latest SPSS statistical software (version 28). Descriptive variables were analyzed using mean with standard deviation, median with interquartile range. Categorical variables were presented in percentages and proportions. Predictors were analyzed using tests of significance like Chi square, Fisher's exact test as appropriate and parametric T test was used for comparing the means.

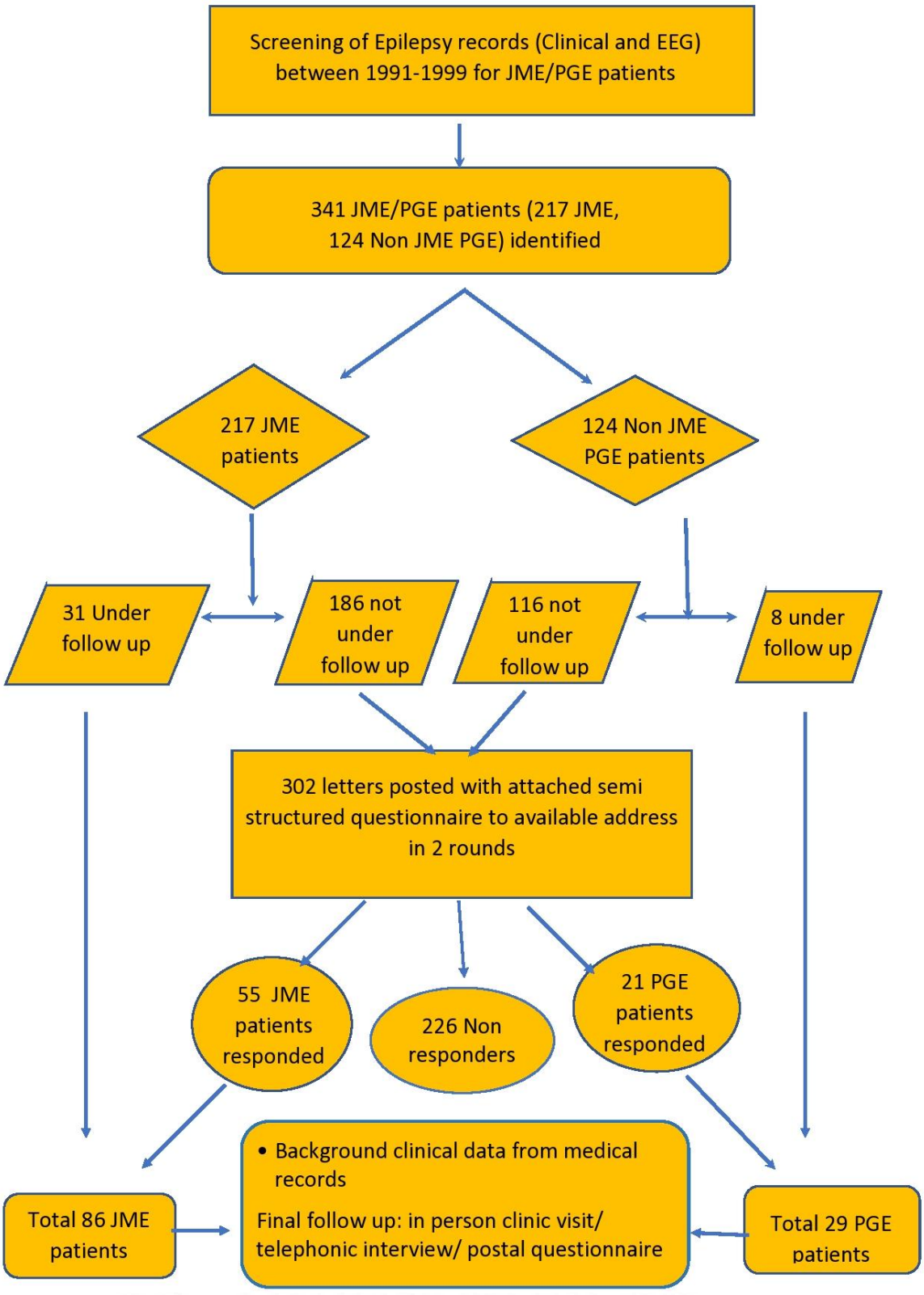

Fig 1: WORKFLOW OF RECRUITMENT AND FOLLOW UP OF STUDY POPULATION

RESULTS

A cohort consisting of a total 341 PGE patients (217 JME and 124 non JME PGE GTCS) were identified. 31 JME and 8 non JME PGE GTCS were under regular follow up. Of the 302 patients who were not under regular follow up 55 JME and 21 non JME PGE GTCS patients could be traced for final assessment in the year 2020. The final cohort consisted of 86 JME and 29 non JME PGE GTCS patients.

JME COHORT

Basic Demographics:

Of the 86 JME patients, males and females were in almost equal numbers. The mean age at onset was 14.6 years ±6.8 years, with minimum age of 5 and maximum 53. The age at onset did not vary between the various seizure types. The mean age at final follow up was 47 ± 7.8 years, ranging from 35-78 years. Family history of any type of epilepsy in first degree relatives was present in 31%, while 15% had febrile seizures in childhood. The mean duration of epilepsy (follow up period) was 32.3 years, with the minimum being 22 years and the maximum up to 62 years. In the final assessment year, 36% continued to be in regular follow up from the hospital, while 16.2% were under follow up from local doctor. Around 40% were not under any follow up.

Table 1: Demographic characteristics of JME cohort

Clinical character	Frequency (percentage) Total number n=86
Sex	
Female	44 (51.2%)
Male	42 (48.8%)
Age at onset of epilepsy	
Mean ± SD	14.6± 6.5
Median (IQR)	13 (12-17)
Minimum	5
Maximum	53
Age at onset of myoclonic seizure	
Mean ± SD	14.7±6.5
Median (IQR)	13 (11.75-17)
Age at onset of GTCS	
Mean± SD	14.7±6.5
Median (IQR)	13 (12-17)
Age at final follow up	
Mean ± SD	47.1± 8.7
Median (IQR)	46.5 (40-50.75)

Minimum **Maximum**	35 78
Epilepsy duration (years) **Mean** **Minimum** **Maximum**	 32.3±7.4 22 62
H/O Febrile seizures	13 (15.1%)
Family H/O epilepsy	27 (31.4%)
Follow up- present status **SCTIMST** **Local doctor** **Not on any follow up** **Status not known**	 31/86 (36%) 14/86 (16.2%) 34/86 (39.5%) 7/86
Death	5/86 (5.8%)

Spectrum of seizure types:

At onset the most common seizure types were generalized tonic clonic seizures (GTCS) and a combination of GTCS and Myoclonic jerks/seizures (MJ/MS). 4 patients had only absences at onset and later evolved into JME with appearance of myoclonic seizures and GTCS.

At any point during the entire course, absences were found in nearly quarter of the cohort. GTCS was the most common seizure type seen in 94% of the patients. A definite history of myoclonic jerks could be elicited in only 75% of the cohort. In the rest 25%, a definite history of myoclonus was not evident, but had electrical evidence of generalized atypical fast spike and wave discharges that was suggestive of Juvenile myoclonic epilepsy and hence were included in the JME cohort.

A combination of all the three seizure types was present in 14% of the cohort. 4 patients (4.7%) had only myoclonic seizures during the entire course.

Table 2: Seizure types in JME

Seizure types	Frequency	Percent
At onset		
Myoclonic sz alone	12	14
GTCS alone	37	43
Absence alone	4	4.7
Myo and GTCS	33	38.3
At any point		
Absence	21	24.4
MS	65	75.6
GTCS	81	94.2
MS alone	4	4.7
MJ+GTCS+Absence	12	14

Evolution of seizure types:

The evolution of the various seizure types, at onset and on follow up is depicted in the graph below.2/3 rd (14/21) of the patients with Absence seizures during the natural history had them at the onset of epilepsy while the rest developed it later during the illness.86% (70/81) of the patients who had GTCS had it at the onset

with rest developing it in due course. 70% (45/65) of the patients with myoclonic seizures, noticed it at the onset while the rest 30% noticed in follow up.

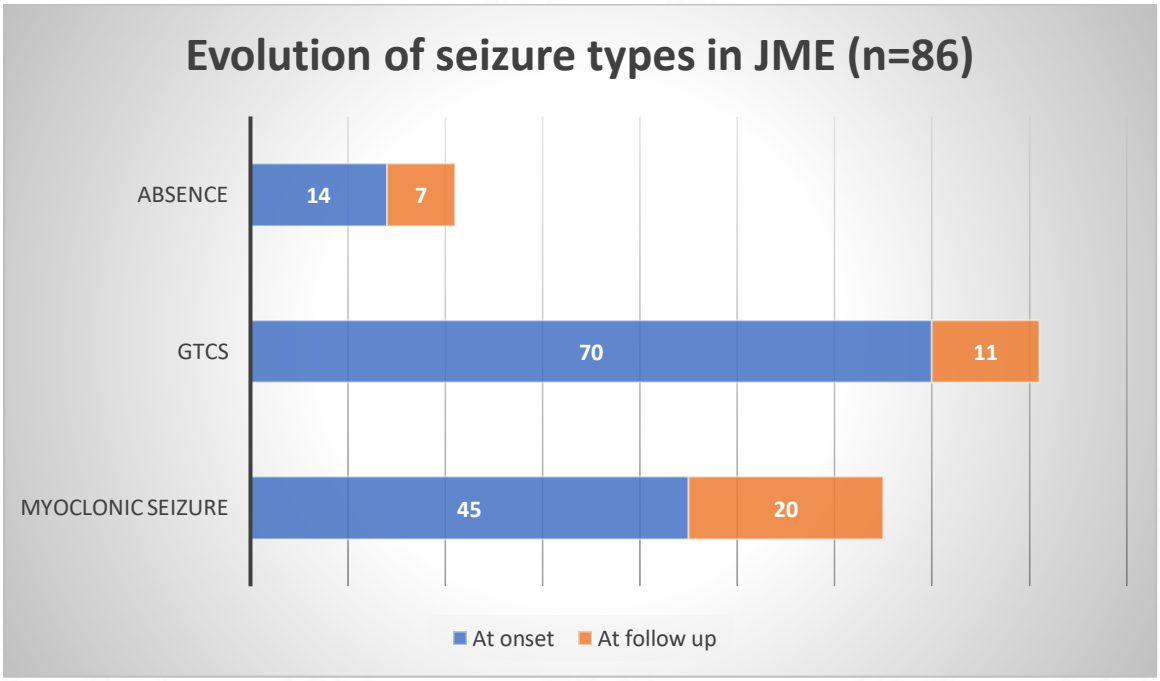

Fig 2: Evolution of seizure types in JME

Natural history of major seizure types: The natural history of the various seizure types was described in various defined patterns, in patients whom sufficient visits to elucidate it was carried out. as detailed in the methodology section.

Both MS and GTCS had good terminal remission rates of 60%. MS had a higher refractory (never in remission) rate compared to GTCS (18% vs 7% respectively). However, GTCS had a higher chance of either early or delayed relapse (long and short remission and relapse), inspite of achieving remission when compared to MS. (15% vs 7%; 18% vs 13% respectively). In those patients with absences, detailed

natural history was available in 13/21 of them, and all of them were in terminal remission without any relapse after achieving an initial remission state.

Sex differences in natural history patterns: There was no significant difference in the overall patterns of evolution of various seizure types during the natural history between males and females (p=0.957 for GTCS pattern, p=0.684 for MS pattern). However , the terminal remission percentage was higher in females compared to males.

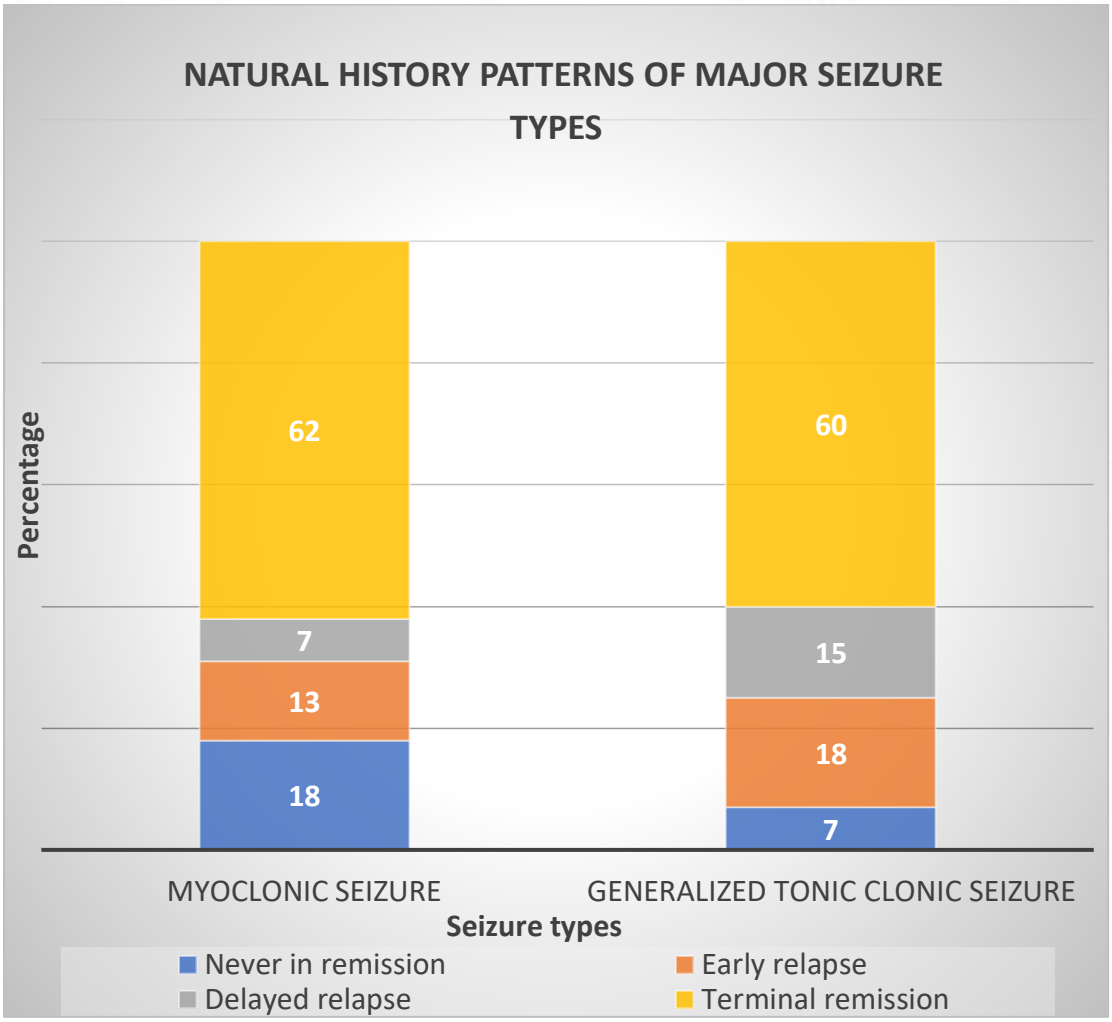

Fig 3: Natural history patterns of major seizure types in JME

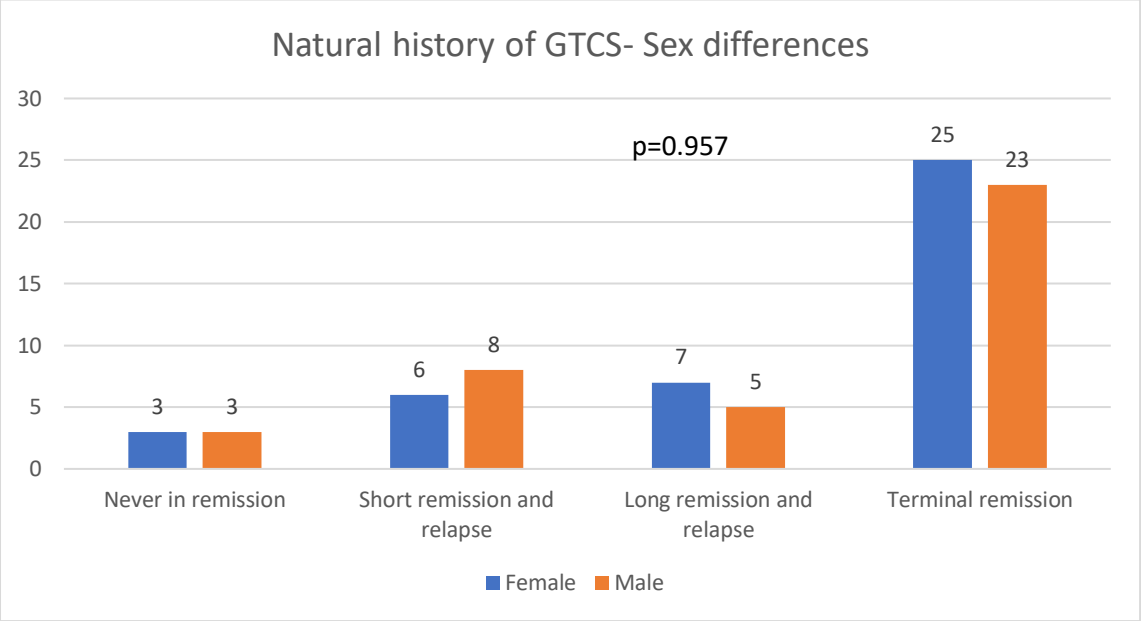

Fig 4: Sex differences in natural history of GTCS

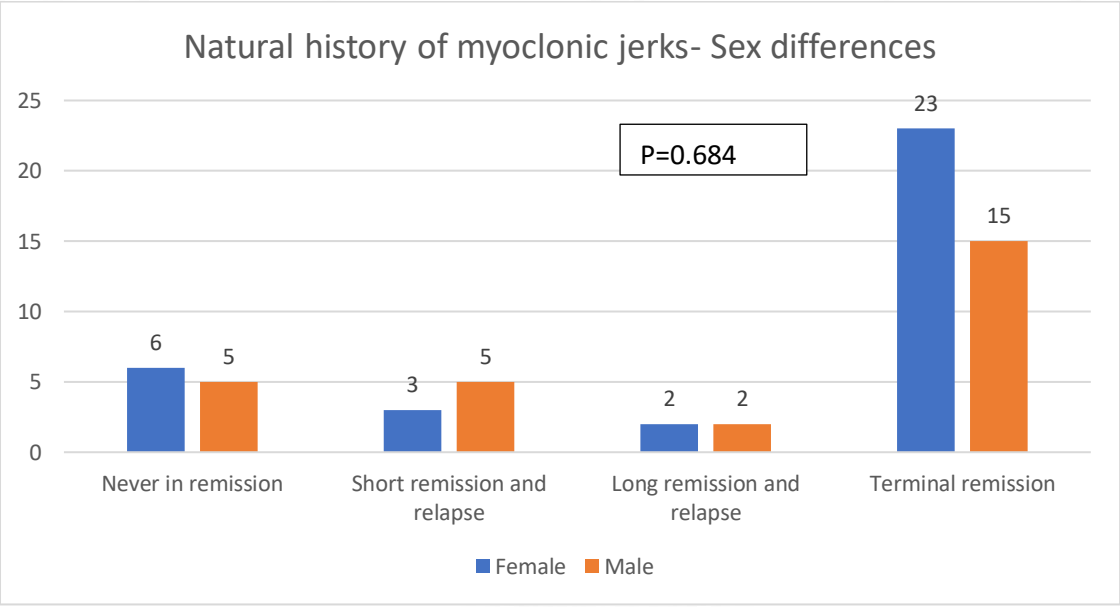

Fig 5: Sex differences in natural history of myoclonic jerks

PRIMARY OUTCOME MEASURES:

SEIZURE OUTCOME/REMISSION STATUS:

After a mean duration of 32.3 years since onset of epilepsy (Range 22-62 years), 69/86 (80.23%) were in remission for disabling seizures at the final follow up while 6 of them continued to have myoclonic jerks.79/86 (91.8%) attained remission at some point during their natural history irrespective of their status at the final follow up. Of the 69 in remission at final follow up 23 i.e 1/3 rd were off AEDs.

15/86 (17.4%) continued to have seizures at the final follow up. Of this group 5/86 (5.8%) never achieved remission at any point of time while the rest 10/86 (11.6%) were in remission at some of time during the natural course. Seizure status of 2 patients was not known at the final follow up.

Table 3: Primary outcome- Remission in JME

Primary Outcome measure- Remission	Number (percentage)
Terminal Remission (> 2 years) for GTCS	69/86 (80.2%)
Terminal Remission (> 2 years) for all types of seizures	63/86 (73.2%)

Brief intermittent remission (> 2 years) any time during natural history	79/86 (91.8%)
Terminal remission (>5 years) **On AED** **Off AED**	58/86 (67.4%) 35/86 (40.7%) 23/86 (26.7%)
Remission duration **Mean ± SD** **Median (IQR)**	 12.6±6.8 12 (7-18.25)
Death	5/86 (5.8%)

Mortality: Among the 86 patients of JME, at final follow up, 5 patients died (5.8%), the exact cause of death was not known. This amounts to 1.8 deaths per 1000 person years follow up.

Spectrum of usage of Antiepileptic drug / Anti seizure medication usage in JME:

The most commonly used antiepileptic drugs during the initial course of the disease were Valproate in 87.2% followed by carbamazepine (40.7%), phenytoin (30.2%) and phenobarbitone (27.9%). Newer antiepileptic drugs Levetiracetam (8.1%), Lamotrigine (5.8%) and Topiramate (3.5%) were only sparingly used. Topiramate (3.5%) and Clonazepam (3.5%) were used in very small proportion of the people.

Table 4: Anti seizure medications used in the initial period in JME

Initial drugs	Total	
	n	%
VPA	75	87.2
CBZ	35	40.7
PHT	26	30.2
PB	24	27.9
LTG	5	5.8
LEV	7	8.1
CLN	3	3.5
TOP	3	3.5

Antiepileptic drug status at final follow up:

23 patients (26.7%) were off AEDs at the final follow up and all were in remission. Average number of AEDs used in this group prior to stopping medications was 1.6 (mean: 1.6±0.9; median: 1 (IQR 1-2).

56 patients (65%) continued to use AEDs at final follow up, 16 were on polytherapy (18.6%), 40 (46.5%) were on monotherapy at final follow up. The final antiepileptic drug details were not available in 2 patients, in addition to the 5 patients who died.

The spectrum of various medications used in the initial period and at final follow up either in polytherapy or monotherapy is depicted in the table and figure above. When compared to the initial AED patterns, the percentage of people using newer AEDs like Levetiracetam and Lamotrigine has increased at the final follow up, while the proportion of people using Carbamazepine, phenytoin and phenobarbitone has decreased.

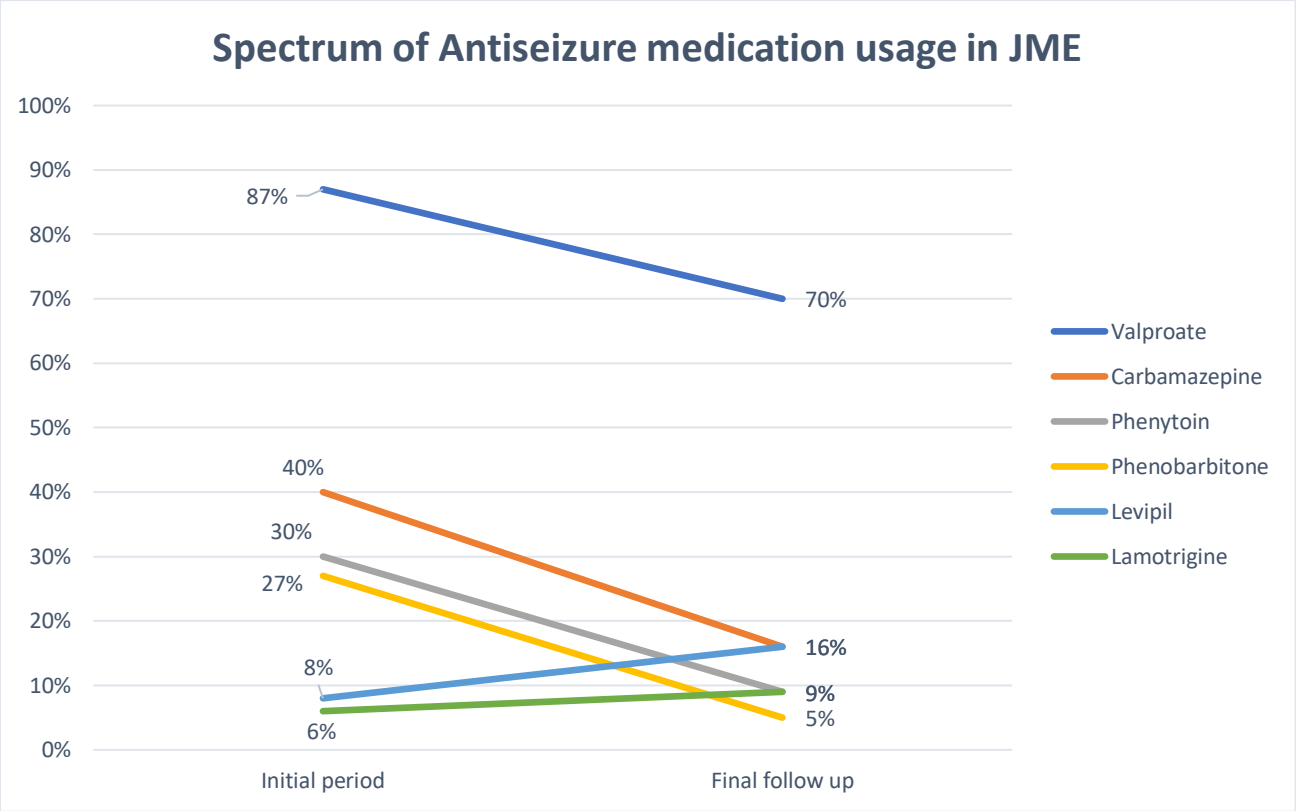

Fig 6: Spectrum of antiseizure medication usage in JME

Table 5: Anti seizure medication status at final follow up

Primary outcome: Anti seizure medication status at final follow up	Number (percentage)
On Anti seizure medication	56/86 (65.1%)
Monotherapy	40/86 (46.5%)
Polytherapy	16/86 (18.6%)
Off Anti seizure medication	23/86 (26.7%)

PREDICTORS OF TERMINAL 2 YEAR REMISSION:

Of the 86 patients, details (final remission status) of 2 patients who died was not known and hence not included in this analysis.

Predictors of terminal 2 year remission status were assessed.

Younger age at onset showed a tendency towards significant association (p=0.076) with remission at final follow up. Female sex was predictor of remission at final follow up (p=0.034). All the patients who continued to have seizures at final follow up had GTCS at onset, either alone or with myoclonic seizures(p=0.049). All the patients who were off AED were in remission at final follow up (p=0.005).40% of the patients who continued to have seizure at final follow up were on polytherapy (p=0.033). Use of carbamazepine and Levetiracetam at the final follow up were associated with refractoriness (p=0.049).

Table 6: Predictors of terminal 2 year remission in JME

Clinical variable	No terminal remission (n=15) Number (percentage)	Terminal 2 year remission (n=69) Number (percentage)	P value
Mean Age at onset	16.33± 6.6	13.8 ± 4.4	0.076
Female	4 (26.6%)	39 (56.5%)	0.034
First seizure type			
GTCS	15 (100%)	55 (80%)	0.049
Myoclonus/ Absence	0 (0%)	14 (20%)	
Effect of final AEDs			
on remission	6 (40%)	33 (48%)	0.397
VPA	4 (26.6%)	5 (7.2%)	0.049
CBZ	4 (26.6%)	5 (7.2%)	0.049
LEV			
Monotherapy	6 (40%)	34 (49.2%)	0.358
Polytherapy	6 (40%)	10 (14.5%)	0.033
Off AED	0	23 (33.3%)	0.005

On Multivariate analysis, only sex showed a significant association with terminal 2 year remission where in females were more likely to go into remission.

Table 7: Multivariate analysis of predictors of terminal 2 year remission in JME

Variable	P value
Age at onset	0.126
Female	0.036
Polytherapy	0.538
Carbamazepine	0.208
Levipil	0.187
Off AED	0.998

SECONDARY OUTCOMES:

HADS and QOLIE 10 scales were used for anxiety, depression and quality of life in epilepsy assessment in 29 patients of JME (35% of the cohort). Median score was 4 out of a maximum score of 21 for both anxiety and depression.

10 patients, (34.4%) had mood disorder- 5 had anxiety alone, 2 had depression alone while 3 of them had both anxiety and depression, with overall 27.5%(8/29)

having anxiety and 17% (5/29) having depression. However, neither anxiety (p=0.575) nor depression (p=0.358) influenced the outcome.

The median quality of life score was 18, while the maximum score was 51 , wherein higher score was associated with poorer quality of life. Any score above 25.5 (half the maximum score) was considered as poor quality of life. None of the patients in whom assessment was carried out had a score above 25.5. Hence, all the patients in whom assessment could be carried out had a good quality of life.

Table 8: Secondary outcomes in JME- Psychiatric and quality of life

Psychiatric outcome measure	Scores
Anxiety (assessed via HADS) score	
Mean± SD	5.6±4.3
Median (IQR)	4 (2-8)
Percentage with anxiety (score>7)	8 (27.5%)
Depression (assessed via HADS)	
Mean± SD	4.1±3.8
Median (IQR)	4 (1-6)
Percentage with depression (score >7)	5 (17.2%)
Quality of life in epilepsy-10 (QOLIE 10)	
Mean ± SD	17.8± 5.1
	18 (13-22)

Table 9: Psychosocial outcomes as predictors of terminal 2 year remission

	Not in remission (n=5)	In remission (n=24)	P value
Anxiety	1 (20%)	7 (29%)	0.575
Depression	0	5 (21%)	0.358

SUBGROUP ANALYSIS:

- **Elderly JME cohort:**

This included patients above 60 years age at final follow up. 8 such patients constituting 9.3% (8/86) of the cohort were identified. Median age of this group at final follow up is 68 (IQR = 66=69.25) (Minimum age=60, maximum age =78). The average age at onset in this group was 23 years, higher compared to that of the entire cohort as whole (14 years). Of these 8 patients, 2 died, and their final seizure status and AED status remains known. 4 are in remission with one of them off AED. 3 of them are in remission and continuing to take anti seizure medications. 2 of them are on poly therapy (2 or more drugs). One is on Carbamazepine and Phenytoin while the other is on Valproate and Lamotrigine. The other one is on monotherapy with Valproate.2 are not in remission at final follow up, of which one is under regular follow up from our center while the other one from another hospital. Former had a relapse after a long period of remission of more than 5 years

and is on monotherapy with Valproate while the latter is on polytherapy with Lacosamide and Levipil.

- **Resistant JME cohort:**

This group includes patients who continued to have seizures at final follow up including those who have never attained remission (seizure free period of 2 years) at any point during the natural history. 15 patients constitutes this cohort, where 10 (11.6%) of them attained brief remission at any point during their natural history and constitute the relative refractory group. Rest of them form the absolute refractory group i.e, have never attained remission at any point and constitutes 5 patients, i.e 5.8% of the cohort of 86 patients.4 of them are males and 1 female, but the sex difference was not significant(p=0.197). The average age at onset was higher compared those who could achieve remission at any point of time. (18 vs 14 p=0.041). 3 of the 5 i.e 60% were on polytherapy compared to 16% (13/79) in the remission group (p= 0.045). The mean age at final follow up was 50 years. 2 of them had family history of JME. All the patients had GTCS at onset with 3 of them having myoclonic seizures also in addition and 1 having absence seizure. 2 patients died and the reason was not known.

NON JME PGE GTCS COHORT:

Basic Demographics and key outcome comparison with JME cohort:

This cohort included those patients who did not satisfy the criteria for JME both clinically and as per electrophysiology. The basic demographics were assessed and compared with the main JME cohort. These results are presented in the table below. This non JME GTCS cohort differed from the JME cohort predominantly in the spheres of sex ratio (M:F= 1:1 in JME while 3:1 in non JME GTCS group) and with respect to history of febrile seizure, which was twice more common in the former.

The overall seizure remission rates and remission duration were higher in the non JME GTCS group compared to the main JME cohort with a relatively lower percentage of the resistant group.

Nearly half of the non JME GTCS patients were off AED while it was only one fourth in the JME cohort. In a similar manner the percentage of patients on AED were lower in the former group with those on poly therapy being less than half of the JME cohort. Though the non JME GTCS cohort fared better in most the outcome parameters, the mortality rate was high, nearly double that of the JME group. However, a statistical comparison could not be made due to smaller numbers.

Table 10: Comparison of demographics and key outcome measures between JME and non JME PGE GTCS cohorts

Variable	JME Cohort	Non JME GTCS group
Number	86	29
Age at onset	14.6± 6.5	14.7 ± 8.2
Age at final follow up	47.1± 8.7	45.3 ± 8.8
Sex **Males** **Females**	 42 (48.8%) 44 (51.2%)	 22 (75.9%) 7 (24.1%)
Family history	27 (31.4%)	7 (24.1%)
Febrile seizure H/O	13 (15.1%)	9 (32.1%)
Duration of epilepsy	32.3± 7.4	30.5±6.5
Seizure Remission **Terminal 2 year** **Terminal 5 year** **Any time remission**	 69 (80.23%) 58 (67%) 79 (91.8%)	 23 (85.2%) 18 (62%) 28 (96.5%)
Remission duration **Mean**	 12.6± (6.8)	 18.5±8.212

Resistant group (Absolute-never in remission)	5 (5.8%)	1 (3.4%)
Off AED	23 (26.7%)	14 (48.3%)
On AED **Monotherapy** **Poly therapy**	56 (65.1%) 40 (46.5%) 16 (18.6%)	11 (44.8%) 9 (37.9%) 2 (6.9%)
Death	5 (5.8%)	3 (10.3%)

Natural history of GTCS in Non JME GTCS Cohort: Similar to the JME cohort, nearly two thirds of them went into terminal remission. A very small percentage remained to be resistant. Overall, it portends a favorable outcome.

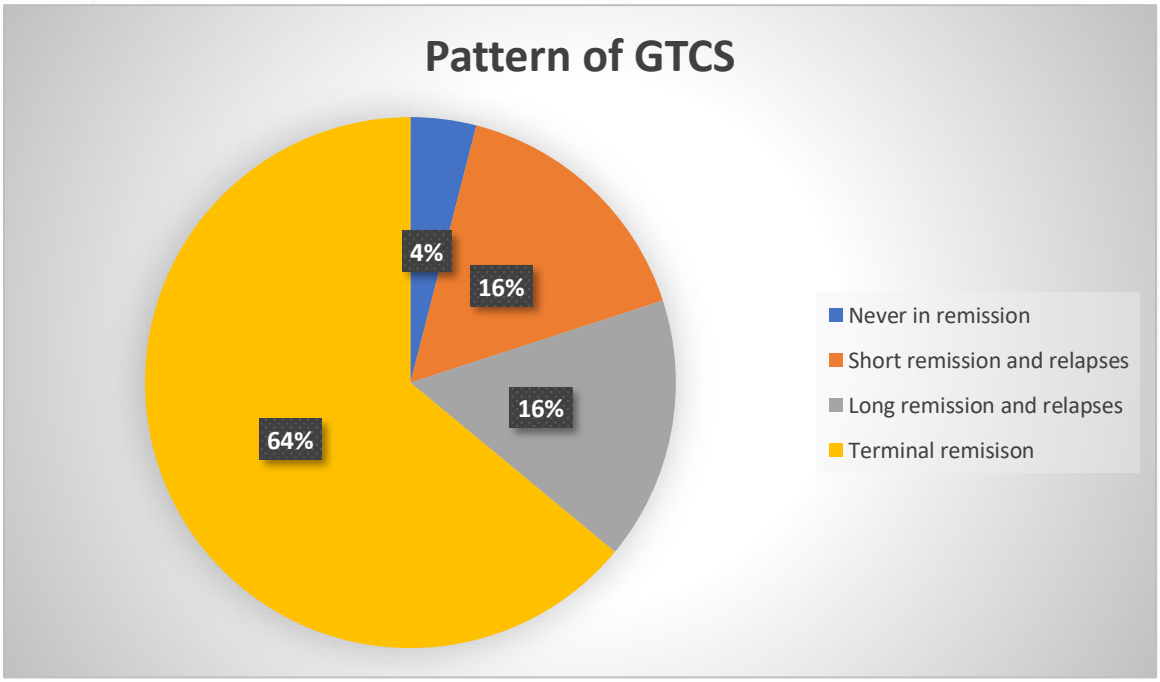

Fig 7: Natural history pattern of GTCS in non JME PGE GTCS cohort

- **AED Spectrum:**

At final follow up 14 were off AED, 11 continued to use AED, while AED status was not known in 4 patients. Of the 11 on AED, 9 were on monotherapy, 6 on Valproate and 3 on carbamazepine.

The drugs used in combination included Phenytoin and phenobarbitone in one patient and Carbamazepine, Levetiracetam and Clobazam in the other.

The spectrum of various AEDs used in the initial period is depicted in the table. Carbamazepine, followed by phenobarbitone and phenytoin were the most commonly used drugs.

The pattern of drug usage at the final follow up however differed from that of the initial period. A trend of the antiepileptic drug usage has been plotted in the graph below. This shows that there is a significant decline in the usage of drugs like phenytoin (decreased to 1/3 rd of prior usage), phenobarbitone (decreased to ¼ th of the prior usage) and Carbamazepine (decreased to half of the earlier usage). On the other hand, there was a considerable rise, almost three times in the usage of Valproate

Table 11: Antiseizure medications use in the initial period in Non JME PGE GTCS cohort

Antiepileptic drug (initial)	Number	Percentage
VPA	5	17.2
CBZ	19	65.5
PHT	8	27.6
PB	10	34.5
LEV	1	3.4
CLB	1	3.4

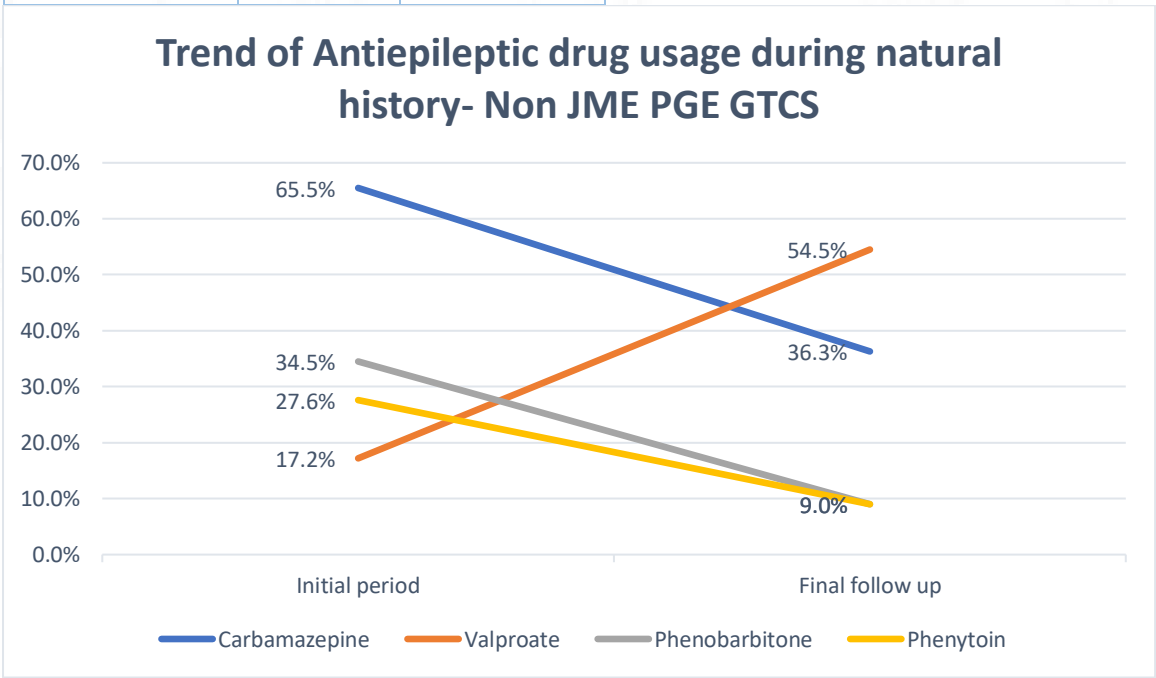

Fig 8: Trend of anti seizure medication usage in non JME PGE GTCS cohort

➢ OUTCOME: REMISISON RATES AND PREDICTORS:

As shown in the table, comparing with JME group the remission rates were higher in the non JME PGE GTCS group. Of the various parameters analyzed for association with remission, only lower frequency of GTCS at onset (p=0.02) and off AED status (p=0.008) were significantly associated with remission at the final follow up

Table 12: Predictors of remission in Non JME PGE GTCS cohort

	Remission				Total		p
	No (n=4)		Yes(n=23)				
	n	%	n	%	n	%	
Sex: Female	1	16.7	6	26.1	7	24.1	0.631
Family history	1	16.7	6	26.1	7	24.1	0.631
Febrile seizure	2	33.3	8	34.8	10	34.5	0.947
Off AED	0	0	14	60.9	14	48.3	0.008
VPA at remission	1	16.7	3	13	4	13.8	0.819
polytherapy	0	0	2	8.7	2	6.9	0.454

	Remission				p
	No (n=4)		Yes(n=23)		
	mean	SD	mean	SD	
Age in years	44.3	8.1	45.6	9.1	0.759
Age of onset in years	16.0	7.7	14.5	8.5	0.691
Duration of epilepsy in years	28.3	6.0	31.2	6.6	0.354
AR	20.3	8.4	20.2	8.5	0.977
Seizure frequency at onset	16.5	27.9	2.5	3.3	0.02

DISCUSSION

This study highlighted that in long term majority of the people with JME/IGE (80-85%) go into remission and a little more than quarter (27%) maintain remission even while off AEDs. A small proportion (20%) remain refractory with around 6% having absolute refractoriness, not having attained remission at any point of time. Though there is an attractive outcome of high remission there is also a small attendant risk of relapse after long periods of remission in 7-15% and patients should be aware of it and be more cautious. In addition, male sex, occurrence of GTCS as the initial seizure type and use of Carbamazepine, Levipil and polytherapy were associated with refractoriness at the final follow up.

The methodology followed is quite robust as a scrupulous review of the clinical and EEG records was done prior to identify and recruit the patients and a well organized, meticulous attempt was made to trace the patients who were not under follow up. Of the 302 patients whom we attempted to trace, response rate was 25% overall with 30% response rate in JME group (55/186) and 18% in non JME PGE group.

39/341 (11.4%) of the original cohort continued to be under follow up for more than 20 years since registration in the hospital, which is quite good, given the extremely long duration. This was partly achieved through Kerala registry for epilepsy in pregnancy, which worked in concert with the Epilepsy subsection of the department of Neurology at our institute and followed up women with epilepsy during their pregnancy. The well designed epilepsy clinics of the hospital that run twice a week were also instrumental in maintaining a good follow up of the

patients. The attrition rate in follow up could partly be because, patients who went into remission for a considerable period of time were advised only postal follow up for few years and thereafter, were advised follow up only when needed with a regular follow up from the local doctor. The overall number of JME patients might look small in comparison to the prevalent rates and 9 years duration of the recruitment (1991-1999) because, being a tertiary referral center, number of patients who are referred for a benign epilepsy syndrome like JME would naturally be low, a scenario similar to that in other tertiary epilepsy centers world over

The attrition rate in tracing the old patients could be because of long duration since their last follow up and lack of access to their updated contact addresses and telephone numbers. Some of them did not even have telephone numbers as a personal mobile number was a rarity in selected study period (1991-1999) making it difficult to trace them. The ongoing pandemic during the study period also posed considerable difficulties in reaching out to them. In spite of the above roadblocks, a 30% response rate was fairly good for an Indian setting, reflecting the meticulous planning and strategies employed to increase the response rate like postal questionnaires and self addressed envelopes in addition to an underlying gratitude and good will among the patients for the hospital from where they received treatment at least during a part of their disease course, even if they had stopped following up due to various reasons.

With respect to the various seizure types, a definite clinical history of myoclonic seizure was not evident in 21 patients but had EEG features typical of JME. Hence

these patients were also included in the JME cohort. However, many criteria world over make clinical presence of myoclonic seizure mandatory to label as JME(3,4,7). However, very often, the history of myoclonic seizure may not be forth coming as they can be subtle, and nondisabling and hence missed out unless specifically questioned. It is usually the more disabling GTCS that is often reported. Since the baseline data of our study was collected in retrospect, it is difficult to enquire about the history of myoclonus in whom it was not clinically documented. Therefore, we included even those patients without a historical evidence of myoclonic jerks but with a typical EEG pattern.

The most common first documented seizure type was GTCS in our study which was also found in few other studies(19), while some of them had myoclonic seizure as the most common first seizure type.(15) The proportion of absence seizure was 24% in our study similar to other long term outcome studies.(15,20) . Absence seizures went into complete remission in all of our patients, while myoclonic seizures and GTCS continued to occur, similar to one other study (15).A detailed analysis of the evolution of seizure types from onset through the course as done in our study was done in only few other studies(15,19,20).

Valproate was the most common antiseizure medication used during the initial period as well as the final follow up as expected, since it the drug of choice for JME for many years now. However, a decline in the usage of Valproate is observed over the years probably due to its side effect profile like teratogenicity, weight gain, polycystic ovarian disease especially in young females(40). On the

other hand, usage of other broad spectrum antiseizure medications like Levetiracetam and Lamotrigine, with fewer side effects compared to Valproate is rising, especially in the female JME patients.(40)

A recent meta-analysis (41)which looked at sex as a predictor showed female sex to be associated with larger time taken to attain remission, which is contrary to our finding. The higher remission rates in females as observed in out cohort could be due to the regular follow up, greater motivation and treatment adherence, as most of these patients were registered with Kerala Registry for Epilepsy in Pregnancy (KREP) maintained by our institute, which follows up them from time to time and advising them throughout their pregnancy. On the other hand, lifestyle factors like work related stress, sleep disturbances, alcoholism, and non-compliance to medications are important factors, more commonly seen in men which can prevent them from attaining remission. Carbamazepine is well noted to be associated with worsening of myoclonic jerks and refractoriness, concordant to its association with refractoriness in our study. One surprising finding in our study is the higher proportion of Levetiracetam usage among those who are refractory. However, there is no information with regard to the dosage of the medication and the duration of usage prior to our assessment and there is a possibility that the patient might not have been adequately tried on optimal dosage for a considerable period of time by the time of final assessment.

A comparison of the remission rates, follow up durations and various predictors of our study were compared with various other major long term follow up studies done to date world over in the table. Ours is the first study which looked at long term outcomes from the South Asian region. There are only 3 studies, apart from our study which looked at the outcomes beyond 30 years of epilepsy duration and our study has the highest number (86). The 5year remission rate is comparable to that of Geithner et al from Germany (67% vs 68%) and higher than the other studies. The percentage of patients off AEDs (26.7%) is the highest among these studies, except for a single study by Camfield et al with a very small number of 23 patients, where 48% were off AEDs.

Table 13: Comparison of our study with other major long term follow up studies

Variable	Our study 2021, India	Hofler et al 2014, Austria (15)	Syversten et al 2014, Norway (21)	Senf et al 2013, Germany (20)	Geithner et al 2012, Germany (19)	Baykan et al 2008, Turkey (17)	Camfield et al 2008, Canada(18)
Sample size	86	175	40	66	31	48	23
Mean age at onset	14.6	15	16	14.3	13	14.4	10.4
Mean age at final follow up	47.1	38	47	58.8	52.2	40	36
Epilepsy duration in years (mean)	32	8	31	45	39	26	26
Terminal 5 year remission rate	58 (67%)	40(36.6%)	21 (53%)	39 (59%)	21 (68%)	13 (27%)	7 (30%)
% off AED	23 (26.7%)	19 (10.8%)	7 (18%)	12 (18%)	6 (19%)	9 (19%)	11 (48%)
Predictors of refractoriness	Male sex GTCS at onset of epilepsy Polytherapy	All 3 seizure types (MJ, GTCS and absence) in the first year of onset	Myoclonic sz evolving to GTCS	Additional presence of absence seizure	Bilateral myoclonic seizures preceding GTCS, longer	N/A	N/A

					duration, AED polytherapy and PPR		
Psychosocial outcome	Anxiety- 27.5% Depression- 17.2% Good quality of life in all	N/A	1/3 rd psychiatric co morbidity 1/3rd favorable psychosocial profile #	N/A	N/A	N/A	70% good satisfaction on Likert scale Unfavorable social outcome in 76%

#- No structured methodology was used

An attempt to identify the predictors of outcome was made which was carried out only in a few of the earlier long term follow up studies (15,19–21).

In contrast to other studies, occurrence of GTCS at onset was associated with refractoriness while in most other studies it was occurrence of myoclonic seizures preceding the GTCS. Presence of absence seizures or all the three seizure types were not associated with refractoriness in our study, unlike that in other studies. (15,16,20)

The study looked in detail at the evolution of the seizure patterns and well as the patterns followed by each of the seizures over the long course, which was not attempted in other studies, as much in detail as we have done. The percentage of

different types of seizure types at the onset of epilepsy was comparable to the study done by Hofler et al, 2014.

The overall natural course predicted a benign outcome of terminal remission as in other studies, but the important point highlighted in our study was that even after a achieving a long remission period of 5 years, there is a chance for relapse, of both the GTCS (15%) and myoclonic jerks (8%) and the patients have to be aware and cautious about it. The exact reasons for a relapse after a longer period of remission however cannot be explained with certainty as is likely to be the result of complex interplay of various factors including genetics.

Secondary outcomes:

Psychosocial:

Our study is the first long term study which attempted to look at the psychosocial outcomes using structured scales- HADS and QOLIE 10, which were less time taking and easier to administer even on the telephone. Two of the earlier done long term follow up studies(18,21) have also looked at the psychosocial outcomes, which were however abstract variables and subjective in nature without any standardization in assessment unlike the well structured and validated scales used in our study. We also tried to look at the relationship between presence of anxiety and depression and the final seizure outcomes. The overall prevalence was marginally lower compared to a recent study done in an Indian cohort (39)with 165

patients (34% vs 46%). The individual rates of anxiety and depression (27.5% vs 30% anxiety and 17% vs 16% depression) were however similar.

However, this assessment was feasible only in 35% percentage of the cohort. Various factors like level of education, willingness, approachability and lack of appropriate contact details, death and the prevailing pandemic situation precluded carrying out of the assessment in the rest of the people.

STRENGHTS:

All the clinical and EEG data was meticulously screened to identify the patients fitting into the definition of JME and the background clinical data was carefully extracted from the old medical records in the absence of any electronic documentation available at that time.

This is the first natural history/ long term follow up study from the Indian subcontinent in patients with JME/PGE. The sample is larger compared to the other long term follow up studies when adjusted to the recruitment period of the various studies and also the duration of follow up was either comparable or higher than other studies as depicted in the table above.

We could trace nearly 30% JME cohort who were not under regular follow up which is remarkable keeping in view the long duration i.e nearly 3 decades follow up and also carrying out the study in the midst of a pandemic overcoming various technical hindrances, a reflection of scrupulous planning and teamwork

The uniqueness of our study compared to other studies is that it comprehensively reflected on the natural history patterns of various seizure types, the seizure and AED outcomes along with predictors and psychosocial factors, all of which were looked in one single study, unlike the other long term follow up studies. A subgroup comparison between the pure JME and non JME PGE cohort was made with respect to the defined primary outcome measures. In addition analysis of elderly JME and resistant JME cohorts was made.

Standardized and validated tools for psychosocial assessment like HADS and QOLIE 10 were used, administered via telephone and google forms in addition to in person assessment unlike non standardized assessment in the other long term follow up studies.

LIMITATIONS:

Background clinical data of some patients could not be traced due to loss of old data from the medical records. Many patients could not be traced as updated contact addresses and phone numbers of these patients were not available. EEG data and use of PPR/photosensitivity for prediction of outcome could not be used as we did not have access to review the records because digital EEGs were not available, and we had access only to EEG reports. Potential confounders in assessing the treatment outcomes like medication adherence, dosage of each of the medications and duration of usage and regular follow up were not addressed while looking at the final seizure outcomes.

HADS and QOLIE in person assessment was abandoned in view of the covid pandemic, but nevertheless was carried out over phone to the extent feasible.

Subgroup analysis of JME patients- classic JME, CAE evolving to JME, JME with astatic epilepsy could not be done due lack of information on the accurate sub classification of the retrospectively collected data. In view of the relatively smaller sample size compared to the prevalence rate, generalizability of certain aspects like predictors and high mortality rate is questionable.

CONCLUSIONS

- This study highlights an attractive long term outcome in JME patients with nearly 80% terminal seizure remission
- More than 90% of the people with JME had remission for more than two years at some point during their natural course
- A quarter of those who were in remission were off antiepileptic drugs.
- There is however an attendant 7-15% risk of relapse of seizure in spite of long remission period of more than 5 years.
- A small percentage 5.8 % constitute the absolute refractory group without attaining remission at any point of the natural history.
- Female sex, absence of GTCS at onset, off AED status predict a good outcome while use of Carbamazepine, Levetiracetam and polytherapy is associated with refractoriness in the JME cohort. Non JME PGE GTCS cohort had better remission rates with a higher percentage off antiseizure medications.34% of the JME patients have mood disorders- anxiety, depression or both. All the patients were found to have good quality of life in epilepsy score,
- Mortality in 5 persons, 5.8% of the JME cohort compared to 10% in the non JME PGE GTCS cohort.

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ANNEXURES

LIST OF ABBREVIATIONS:

JME- Juvenile myoclonic epilepsy

IGE- Idiopathic generalised epilepsy

GGE- Genetic generalised epilepsy

CAE- Childhood absence epilepsy

EEG- Electroencephalography

MJ/MS- Myoclonic jerks/ seizures

GTCS- Generalised tonic clonic seizures

ABS- Absence seizures

AED/ASM- Anti Epileptic Drug/ Anti Seizure Medication

VPA- Valproate

PHT- Phenytoin

CBZ- Carbamazepine

PB- Phenobarbitone

LEV- Levetiracetam

LTG- Lamotrigine

CLN- Clonazepam

TOP- Topiramate

HADS- Hospital Anxiety Depression Scale

QOLIE -10- Quality of Life In Epilepsy- 10 component

ILAE- International League Against Epilepsy

PROFORMA

PROFORMA					
Serial No					
Date of Assessment					
Name				Age	
Hospital Number				Sex	
Date of registration				Age at registration	
Family history					
Antecedents					
Age at onset of Epilepsy					
Seizure type					
-At onset -At registration					
Seizure frequency at registration					
SEIZURE CONTROL					
Seizure Type	Initial Seizure Frequency (ISF)	Follow up Seizure Frequency (FSF)	Last attack date	Pattern Unchanged/ Increased/ Decreased/ Short remission and relapses/ Continuous remission	
1.					
2.					
3.					
AED USAGE					
Name of AED		From Date	To Date	Continuous/ Interrupted	
1.					

2.			
3.			
4.			
5.			
6.			
PSYCHIATRIC OUTCOME			
HADS (Hospital Anxiety Depression Scale-10 question test)			
QOLIE scale (Quality Of Life in Epilepsy- 10 question version)			

Remission is defined as seizure free period for a minimum of 2 years in this study.

Current Status

Last follow up

Sz:

AED:

Co morbidities:

Seizure timeline:

Obstetric and Family history:

Hospital Anxiety and Depression Scale (HADS) - English version

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Quality Of Life In Epilepsy (QOLIE-10) – 10 component version

Patient Weighted Quality Of Life In Epilepsy:
QOLIE-10-P (Version 2.0, US English)

Patient's Name:	Today's Date:
	⌊⌋⌊⌋ ⌊⌋⌊⌋ ⌊⌋⌊⌋ D M Y

If you experienced a simple or complex partial seizure within the previous four hours, or a generalized tonic-clonic seizure within the previous 24 hours, please delay completing this questionnaire

INSTRUCTIONS:

This questionnaire asks about your health and daily activities. **Answer each question** by circling the appropriate number (1, 2, 3…).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin. Please feel free to ask someone to help you if you have difficulty reading or completing the form.

Part A.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
1. Did you have a lot of energy?	1	2	3	4	5	6
2. Have you felt downhearted and low?	1	2	3	4	5	6

The following questions ask about problems you may have with certain ACTIVITIES.

How much of the time during the past 4 weeks your epilepsy or antiepileptic drugs have caused trouble with…

(Circle one number)

	A great deal	A lot	Somewhat	Only a little	Not at all
3. Driving (or other transportation)	1	2	3	4	5

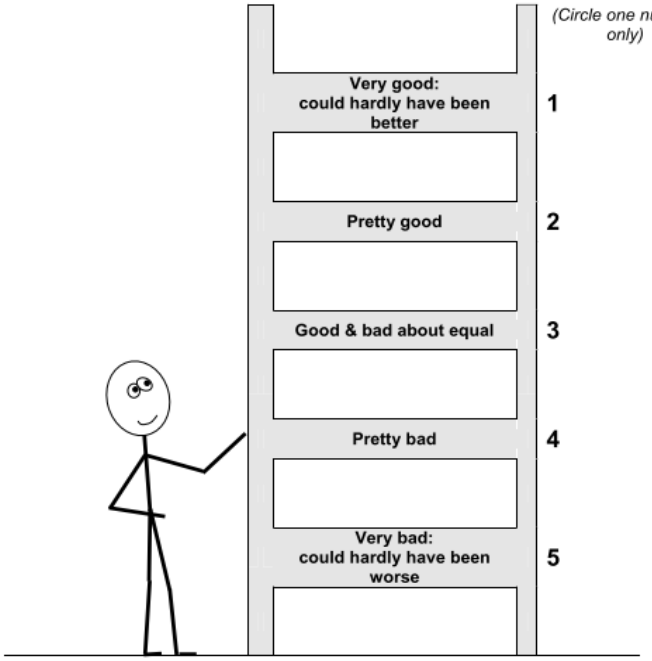
During the past 4 weeks…

	Not at all bothersome				Extremely bothersome
4. How much do your work limitations bother you?	1	2	3	4	5
5. How much do your social limitations bother you?	1	2	3	4	5
6. How much do your memory difficulties bother you?	1	2	3	4	5
7. How much do physical effects of antiepileptic drugs bother you?	1	2	3	4	5
8. How much do psychological effects of antiepileptic drugs bother you?	1	2	3	4	5

	Very afraid	Somewhat afraid	Not very afraid	Not afraid at all
9. How afraid are you of having a seizure during the next 4 weeks?	1	2	3	4

QOLIE-10-P (US English)

10. How has your **QUALITY OF LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?



QOLIE-10-P (US English)

HOSPITAL ANXIETY AND DEPRESSION SCALE

ഈ ചോദ്യാവലി നിങ്ങളുടെ മാനസികാവസ്ഥയേയും മാനസികാരോഗ്യത്തെയും സംബന്ധിച്ചുള്ളതാണ്. അനുയോജ്യമായ ഉത്തരത്തിന്റെ നമ്പർ ഒരു '3' വരച്ച് അടയാളപ്പെടുത്തുക.

1. എനിക്ക് വല്ലാത്ത പിരിമുറുക്കം അനുഭവപ്പെടാറുണ്ട്
   ☐ മിക്ക സമയവും ☐ കുറേ സമയം ☐ സമയാസമയം, അവസരോചിതമായി
   ☐ തീർത്തുമില്ല

2. എനിക്ക് ഇപ്പോഴും എന്റെ ഇഷ്ടപ്പെട്ട കാര്യങ്ങൾ ആസ്വദിക്കാൻ കഴിയുന്നുണ്ട്
   ☐ തീർച്ചയായും, പഴയതുപോലെ ☐ അത്രയേറെ ഇല്ല
   ☐ വളരെ കുറച്ച് ☐ തീർത്തുമില്ല

3. എന്തോ വിപത്ത് സംഭവിക്കാൻ പോകുന്നു എന്നുള്ള തോന്നൽ എനിക്ക് ഉണ്ടാകാറുണ്ട്
   ☐ തീർച്ചയായും, വളരെ വിഷമകരമായി ☐ ഉണ്ടാകാറുണ്ട്, അത്രക്ക് വിഷമകരമല്ല
   ☐ വളരെ കുറച്ച് പക്ഷെ വിഷമിപ്പിക്കാറില്ല ☐ തീർത്തുമില്ല

4. എനിക്ക് വസ്തുതകളുടെ രസകരമായ വശങ്ങൾ മനസ്സിലാക്കുവാനും ആസ്വദിക്കാനും (ചിരിയ്ക്കുവാനും) കഴിയുന്നുണ്ട്.
   ☐ പഴയത് പോലെ കഴിയുന്നുണ്ട് ☐ അത്രത്തോളം കഴിയുന്നില്ല
   ☐ വളരെ കുറച്ചുമാത്രം ☐ തീർത്തുമില്ല

5. അസ്വസ്ഥതകരവും, വിഷമിപ്പിക്കുന്നതുമായ ചിന്തകൾ എന്റെ മനസ്സിലൂടെ കടന്നുപോകാറുണ്ട്.
   ☐ മിക്ക സമയവും ☐ ഏറെ സമയവും ☐ എല്ലായ്പ്പോഴുമില്ല ☐ വളരെ കുറച്ചുമാത്രം

6. ഞാൻ ഉല്ലാസവാനാണ്
   ☐ ഒരിക്കലുമില്ല ☐ എല്ലായ്പ്പോഴുമില്ല ☐ ചിലപ്പോഴൊക്കെ ☐ ഏറെ സമയവും

7. എനിക്ക് സ്വസ്ഥമായും സമാധാനപരമായും ഇരിയ്ക്കുവാൻ കഴിയും
   ☐ തീർച്ചയായും ☐ മിക്ക സമയവും ☐ എല്ലായ്പ്പോഴുമില്ല ☐ തീർത്തുമില്ല

8. എനിക്ക് മന്ദത അനുഭവപ്പെടുന്നതായി തോന്നാറുണ്ട്
   ☐ ഏകദേശം എല്ലാസമയവും ☐ മിക്ക സമയവും
   ☐ ചിലപ്പോഴൊക്കെ ☐ തീർത്തുമില്ല

9. വയറ്റിൽ അസ്വസ്ഥതയുളവാക്കുന്ന പ്രതീതി എനിക്ക് അനുഭവപ്പെടാറുണ്ട്
   ☐ തീർത്തുമില്ല ☐ അവസരോചിതമായി
   ☐ ചിലപ്പോഴൊക്കെ ☐ മിക്ക സമയവും

10. എന്റെ വേഷത്തിലും രൂപത്തിലും എനിക്ക് താത്പര്യം നഷ്ടപ്പെട്ടിരിക്കുന്നു
    ☐ തീർച്ചയായും ☐ അത്രയേറെയൊന്നും ശ്രദ്ധിക്കാറില്ല
    ☐ വലിയ ശ്രദ്ധ നല്കാറില്ല ☐ മുന്നതേതുപോലെ ശ്രദ്ധ നല്കാറുണ്ട്.

11. ഒരിടത്ത് അടങ്ങിയിരിക്കുവാൻ എനിക്ക് ബുദ്ധിമുട്ടുണ്ട്
    ☐ തീർച്ചയായും, ഒരുപാട് ☐ ഒരുപാട് ☐ അത്രയേറെ ഇല്ല ☐ തീർത്തുമില്ല

12. കാര്യങ്ങൾ ചെയ്യുവാൻ എനിക്ക് നല്ല ഉത്സാഹമുണ്ട്
    ☐ മുമ്പേ ഉണ്ടായിരുന്നത് പോലെ ☐ സാധാരണയിൽ നിന്ന് കുറച്ച്
    ☐ തീരെ കുറച്ച് ☐ തീർത്തുമില്ല

13. എനിക്ക് പെട്ടെന്ന് സംഭ്രമടെുത്തുന്നതുപോലുള്ള തോന്നൽ ഉണ്ടാകാറുണ്ട്
    ☐ തീർച്ചയായും, ഒരുപാട് ☐ ഒരുപാട്
    ☐ എല്ലായ്പ്പോഴുമില്ല ☐ തീർത്തുമില്ല

14. എനിക്ക് ഒരു നല്ല പുസ്തകമോ ടി വി പരിപാടിയോ, റേഡിയോ പരിപാടിയോ ആസ്വദിക്കാൻ കഴിയാറുണ്ട്
    ☐ മിക്ക സമയവും ☐ ചിലപ്പോഴൊക്കെ ☐ എല്ലായ്പ്പോഴുമില്ല ☐ വളരെ കുറച്ചു മാത്രം

അപസ്മാരം മൂലം ജീവിതഗുണനിലവാരത്തിലുള്ള മാറ്റങ്ങൾ അറിയുവാനുള്ള ചോദ്യാവലി

(Quality of life in Epilepsy Inventory QOLIE 10)

ഈ ചോദ്യാവലി നിങ്ങളുടെ ജീവിത ഗുണനിലവാരത്തെപ്പറ്റി അറിയുവാനുള്ളതാണ്. അനുയോജ്യമായ ഉത്തരവിന്റെ നമ്പർ ഒരു '3' വരച്ച് നിങ്ങളുടെ അഭിപ്രായം രേഖപ്പെടുത്തുക.

കഴിഞ്ഞ നാലാഴ്ചകളായി എത്ര സമയം

1. നിങ്ങൾ ഉന്മേഷനായിരുന്നു?

എല്ലായ്പ്പോഴും	മിക്കപ്പോഴും	കൂടെക്കൂടെ	ചിലപ്പോഴൊക്കെ	വല്ലപ്പോഴും	ഒരിക്കലുമില്ല

2. നിങ്ങൾ നിരാശയുടെ പടുകുഴിയിൽ ആണോ? ഒന്നിനും നിങ്ങളെ പ്രസന്നനാക്കാൻ കഴിയില്ലേ?

എല്ലായ്പ്പോഴും	മിക്കപ്പോഴും	കൂടെക്കൂടെ	ചിലപ്പോഴൊക്കെ	വല്ലപ്പോഴും	ഒരിക്കലുമില്ല

3. നിങ്ങളുടെ അപസ്മാരമോ അപസ്മാര ചികിത്സ മരുന്നുകളോ ഡ്രൈവിംഗിന് ബുദ്ധിമുട്ടാക്കിയിട്ടുണ്ടോ?

ഒട്ടുമില്ല	വളരെകുറച്ച്	ഏറെക്കുറെ	ധാരാളം	വലിയതോതിൽ

താഴെക്കൊടുത്തിരിക്കുന്ന പ്രശ്നങ്ങൾ കഴിഞ്ഞ നാലാഴ്ചക്കുള്ളിൽ നിങ്ങളെ എത്രമാത്രം ബുദ്ധിമുട്ടിലാക്കിയിട്ടുണ്ട്.....

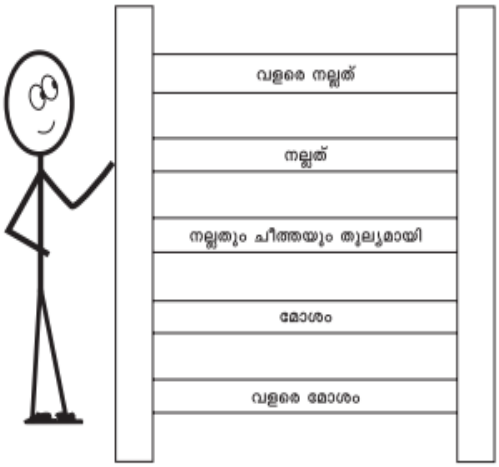
		അശേഷം അലട്ടുന്നില്ല	വളരെക്കുറച്ച്	ഏറെക്കുറെ	ധാരാളം	വളരെയധികം
4.	ഓർമ്മക്കുറവ്					
5.	ജോലിക്കുള്ള തടസ്സം					
6.	സാമൂഹിക തടസ്സം					
7.	മരുന്നിന്റെ ശാരീരിക പാർശ്വഫലം					
8.	മരുന്നിന്റെ മാനസിക പാർശ്വഫലം					

9. അടുത്ത ഒരു മാസത്തിനുള്ളിൽ വീണ്ടും സന്നിയുണ്ടാകും എന്ന ചിന്ത നിങ്ങളെ എത്രത്തോളം അലട്ടുന്നുണ്ട്?

അശേഷം ഭയമില്ല	മിതമായ തോതിൽ ഭയമുണ്ട്	മദ്ധ്യമമായ തോതിൽ ഭയമുണ്ട്	വളരെ ഭയമുണ്ട്	അങ്ങേയറ്റം ഭയമുണ്ട്

11

10. കഴിഞ്ഞ നാലാഴ്ചയായി നിങ്ങളുടെ ജീവിതത്തിന്റെ പൊതുവായ മേന്മ എത്രമാത്രമുണ്ട്? (അതായത്, കാര്യങ്ങൾ നിങ്ങളെ സംബന്ധിച്ച് എങ്ങനെ



ജീവിതമേന്മ അളക്കുവാനുള്ള സൂചിക

(ലോകാരോഗ്യസംഘടന, 1998 ആഖ്യാനം)

(WHO (five) Well Being Index, 1998 Version)

താഴെക്കൊടുത്തിരിക്കുന്ന അഞ്ചു പ്രസ്താവനകളിൽ കഴിഞ്ഞ രണ്ടാഴ്ചക്കുമേൽ നിങ്ങളുടെ ജീവിത മേന്മയോട് ഏറ്റവും അടുത്തു നില്ക്കുന്നു എന്നു തോന്നുന്ന പ്രസ്താവന തെരഞ്ഞെടുത്ത് '3' രേഖപ്പെടുത്തുക

കഴിഞ്ഞ രണ്ടാഴ്ചക്കുമേൽ പകുതിയിലധികം സമയം നിങ്ങൾക്കുണ്ടായ അനുഭവമായിരിക്കണം രേഖപ്പെടുത്തേണ്ടത്

	കഴിഞ്ഞ രണ്ടാഴ്ചക്കു മേൽ	മുഴുവൻ സമയവും	കൂടുതൽ സമയവും	പകുതിയിൽ കൂടുതൽ സമയവും	പകുതിയിൽ കുറഞ്ഞ സമയം	ചുരുക്കം സമയം	ഒരു സമയത്തുമില്ല
1.	എനിക്ക് ആഹ്ലാദവും മനഃസ്സമാധാനവും അനുഭവപ്പെട്ടിരുന്നു						
2.	എനിക്ക് ശാന്തതയും സ്വസ്ഥതയും അനുഭവപ്പെട്ടിരുന്നു						
3.	ഞാൻ സജീവവും ഊർജ്ജസ്വലവും ആയതായി എനിക്ക് അനുഭവപ്പെട്ടിരുന്നു						
4.	ഞാൻ അക്ഷീണനും ഉന്മേഷവാനുമായി ഉണർന്നെഴുന്നേറ്റിരുന്നു						
5.	എനിക്ക് താത്പര്യമുള്ള കാര്യങ്ങൾകൊണ്ട് എന്റെ ദൈനംദിന ജീവിതം നിറയ്ക്കപ്പെട്ടിരുന്നു						

QOLIE- Scoring

Quality Of Life In Epilepsy: QOLIE-10 and QOLIE-10-P SCORING INSTRUCTIONS

The QOLIE-10 screening questionnaire includes 10 questions. Three questions have opposite response sets, requiring reverse-scoring. The scoring should be calculated so that all positive responses are lower numbers and all negative responses are higher numbers.
[The QOLIE-10-P includes 11 questions, with items 1-10 identical to the QOLIE-10.]

Items scored with "1" as best should be scored as indicated: items 1, 4, 5, 6, 7, 8, 10
Items scored with "1" as worst should be scored in "reverse": items 2, 3, 9

The conversion for item 2 is:
1=6
2=5
3=4
4=3
5=2
6=1

The conversion for item 3 is:
1=5
2=4
3=3
4=2
5=1

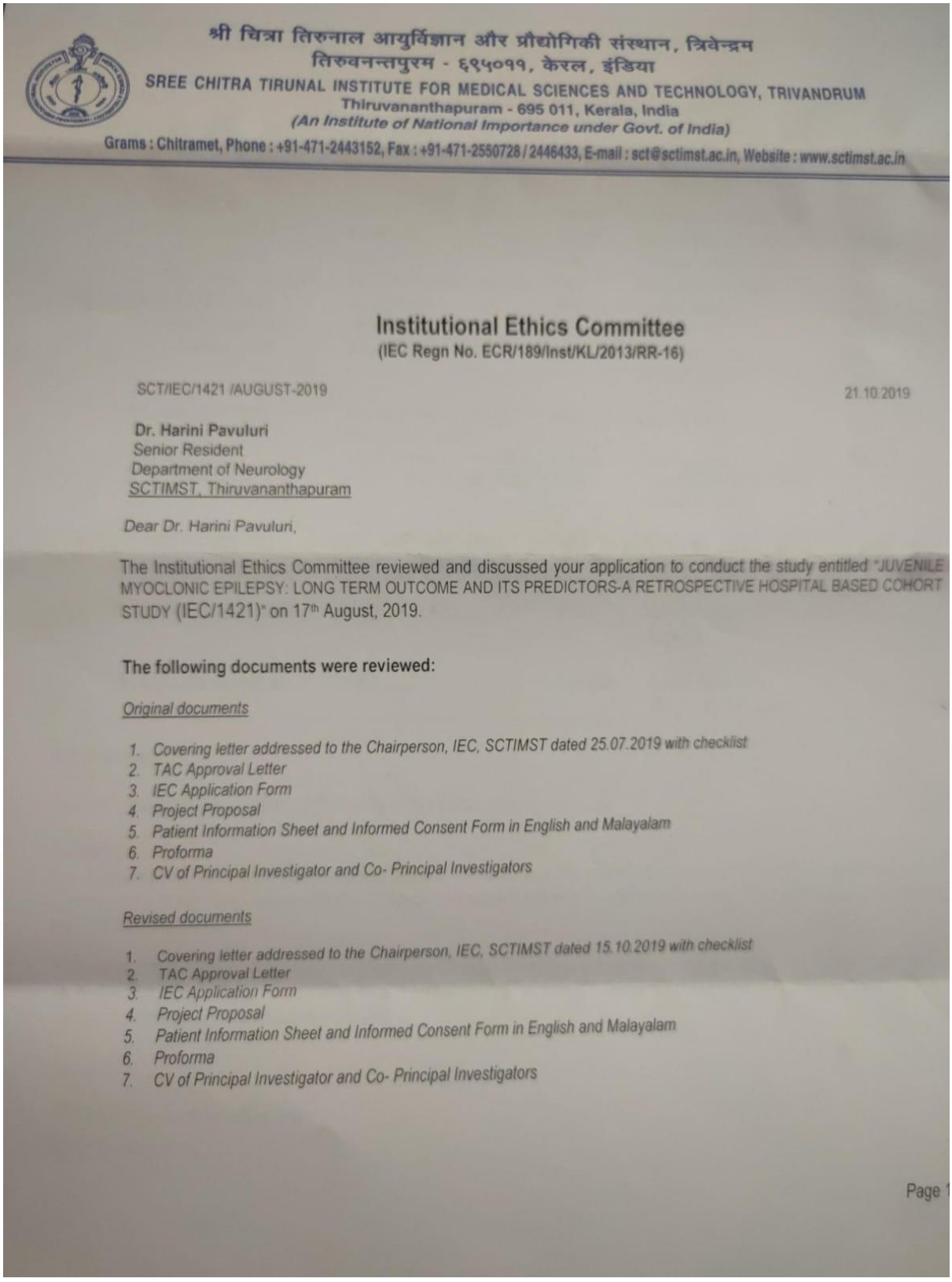
The conversion for item 9 is:

1=4
2=3
3=2
4=1

The total score is the sum of scores for all questions divided by the number of items answered. Thus, if a patient skipped an item, it is not reflected in the total score. Patients with lowest scores have the least problems.

Scoring for the **QOLIE-10-P** includes item #11 that is scored as indicated. The total score is the sum of scores for all questions divided by the number of items answered. Question 12 is not scored, but may be used to weight other items.

Institutional Ethics Committee (IEC) Clearance



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1421 /AUGUST-2019 21.10.2019

Dr. Harini Pavuluri
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Harini Pavuluri,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "JUVENILE MYOCLONIC EPILEPSY: LONG TERM OUTCOME AND ITS PREDICTORS-A RETROSPECTIVE HOSPITAL BASED COHORT STUDY (IEC/1421)" on 17th August, 2019.

The following documents were reviewed:

Original documents

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 25.07.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
6. *Proforma*
7. *CV of Principal Investigator and Co- Principal Investigators*

Revised documents

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.10.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
6. *Proforma*
7. *CV of Principal Investigator and Co- Principal Investigators*

Page 1

The following members of the Ethics Committee were present at the meeting held on 17th August, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
8.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
9.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
10.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
11.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
12.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
13.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
14.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

PLAGIARISM CHECK

Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **10%**

Date: Aug 8, 2021
Statistics: 1433 words Plagiarized / 14469 Total words
Remarks: Low similarity detected, check your supervisor if changes are required.

Sources

1	https://www.researchgate.net/publication/237843420_Consensus_on_diagnosis_and_management_of_JME_From_founder's_observations_to_current_trends INTERNET	1%
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