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Modulation of epileptiform EEG discharges in patients with JME

Kamakshi Dhamija*, Neera Chaudhry, Vinod Puri

Department of Neurology, GIPMER, New Delhi, India

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ABSTRACT

Purpose: To study modulation of epileptiform EEG discharges in patients with JME.
Method: 50 subjects with JME underwent a sleep deprived EEG recording along with conventional provocative methods and testing with cognitive tasks (CTs). Both categories of tests were evaluated for their effect on occurrence of IEDs. Number of IEDs per unit time was calculated at baseline as well as with each task. Statistical and arbitrary methods were used to assess modulation. By arbitrary method if frequency of IEDs was more than twice that of baseline, it was considered as provocation and if less than half, it was considered as inhibition. To account for spontaneous fluctuation of IEDs, 95% CI was calculated for baseline IEDs in each patient and provocation/inhibition was considered if frequency of IEDs exceeded/remained below limits of CI respectively.
Results: There was no significant difference in rates of provocation of IEDs by conventional or CTs. However there was exclusive provocation of IEDs by CTs in 4 patients, 3 of whom were already on AEDs. There was a significant inhibitory effect of CTs as mean baseline discharge frequency was 0.4 ± 1.16 IEDS/min and during CTs was 0.1 ± 0.38 IEDs/min. However when spontaneous fluctuation was accounted for, inhibition was seen in only 22.23% patients by statistical method as compared to 90.91% by arbitrary method.
Conclusions: Inclusion of CTs may assist in provocation of IEDs, thereby increasing yield of routine EEG. Spontaneous fluctuation of IEDs accounts for much observed inhibition by CTs in JME patients.

1. Introduction

Juvenile myoclonic epilepsy (JME) is the most common age related idiopathic generalized epilepsy corresponding to 5–11% of all epilepsies [1]. The myoclonic jerks of the arms, which occur especially after awakening, are the hallmark of this syndrome. Generalized tonic–clonic seizures (GTCS) occur in most patients, and one third of individuals also have absences. Patients frequently come to medical attention only after a generalized convulsion, and the history of earlier myoclonic jerks is often obtained retrospectively. JME, though being a classical epileptic syndrome with an age related onset, is not always diagnosed with ease. The typical interictal EEG features including bilateral spike or polyspike-wave complexes of 4–6 Hz on a normal background are not always found. Various authors have concluded that in around 25% of cases, the diagnosis is missed on a routine EEG [2]. Hence various provocative methods as sleep deprivation, hyperventilation and photic stimulation are conventionally employed to increase the yield of interictal epileptiform discharges (IEDs). Since some patients also report sensitivity of their seizures to mental activation, various authors have also worked on the role of higher mental function in seizure precipitation [3]. This form of neuropsychological activation has already been used by various research groups to identify specific seizure patterns in various epileptic syndromes [4]. Studies have suggested that JME would be the most sensitive epileptic syndrome to this form of cognitive activation [5]. The aim of the present study was to assess the effect of a video EEG neuropsychological protocol, whether precipitant or inhibitory on IEDs and seizures in patients with JME and to assess the correlation between self-perceived and actual trigger factors for seizures if any. There are only few studies available in the literature regarding the influence of higher brain functions on epileptiform activity in JME. Moreover spontaneous fluctuation of epileptiform discharges in JME has been considered in only one such study so far [6]. Since the diagnosis of 'JME' carries an important therapeutic connotation, we further assessed whether extending the routine EEG protocol to include various cognitive tasks could additionally help in provocation of IEDs in JME patients or not.

2. Material and methods

This was an observational study conducted at a tertiary care hospital in New Delhi between 2015–2016. Fifty patients aged more than 12 years and those with a minimum of four years of formal education fulfilling the diagnostic criteria for JME were included in the study. Subjects were explained advantages and risks for participation and

* Corresponding author.
E-mail address: kamakshidhamija@gmail.com (K. Dhamija).

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Table 1
Video-EEG protocol.

- Recording of background activity, awake, for 50 min
- Eyes opened/closed (5 min)
- Conventional provocative methods (5 min each;2 min interval between them)
  1. Intermittent photic stimulation
  2. Hyperventilation
- Cognitive tasks (in random order; 2 min interval between them)
  1. Reading a difficult text in patient's first language (a medical text describing seizures)
  10 min silently
  10 min aloud
  2. Speaking aloud for 5 min (patients were asked to describe their seizures, their lives, and the impact of epilepsy)
  3. Writing for 5 min (patients were asked to write about their seizures)
  4. Mental calculation: subjects were asked to respond aloud with answers to arithmetic problems(e.g 18 −7,35−17,15 + 7,23 + 46, 11 * 11,43*4,125 /5,369/3); when calculation was difficult, an easier problem was presented
  5. Written calculation: patients were asked to respond in writing to increasingly difficult arithmetic problems (15 *67, 23 * 48)
  6. Drawing: patients were instructed to draw a fish, an apple, a house, and a clock showing quarter to four
  7. Spatial construction: Patients were asked to perform a sequence of tasks i.e organising a Rubik's cube for 5 min

written informed consent was obtained from them or from their guardians in case of minor patients. Pregnant women and patients having clinical signs of antiepileptic drug intoxication were excluded. A standardised self-perception questionnaire was administered during a personal interview. The objective was to investigate whether patients were aware of certain situations that could potentially trigger their seizures. If identified, these factors were compared with the results of activations that occurred during video-EEG. Medications were maintained in all treated patients. As appropriate treatment we included sodium valproate, levetiractem, phenobarbital, benzodiazepines, lamotrigine, and topiramate, in monotherapy or in different combinations. Treatment with carbamazepine, oxcarbazepine, or phenytoin was considered inappropriate. Each patient was then subjected to video-EEG on a 26-channel recording (Nicolet software) using the 10–20 International Electrode System. To increase the probability of recording epileptiform discharges in the baseline period (for assessing inhibition) the patients were sleep deprived, and all recordings were performed in the morning. After having slept for not more than 6 h, all patients were subjected to the video-EEG protocol as described in Table 1.

3. Analysis of electroencephalographic recordings

If a task induced epileptiform discharges or seizures, reproducibility was confirmed by retrial of the same task. The effect of both conventional procedures as well as cognitive tasks on the occurrence of IEDs was assessed by two methods – arbitrary and statistical methods. By arbitrary method, provocation was considered when the number of IEDs per unit time during a test condition was greater than twice that of during the baseline, and inhibition when the number of IEDs/time during a test condition, was less than half that of the baseline period. To account for the spontaneous fluctuations of IEDs, 95% confidence interval (CI) was determined from the IEDs counted per 5 min epoch in the baseline period of each patient. This was in accordance with the method used earlier by Beniczky et al. [6]. A test condition was considered as having a provocative effect when the number of IEDs during that test exceeded the upper limit of the 95% CI and inhibition when it was below this interval. The procedures were thereby classified into (1) **provocative effect**, when there was induction of discharges; (2) **inhibitory effect**, when there was reduction of discharges; (3) **no effect**. Thereafter different modalities of tasks were categorized into **action-programming** (reading aloud, speaking, writing, written calculation, drawing, and spatial construction) and **thinking** (reading silently and mental calculation) categories [7]. All recordings were video documented to allow identification of any seizures or myoclonic jerks occurring during the investigation. Statistical analysis was done with SPSS software. All categorical data was analysed using Chi square test or Fischer exact test. Continuous variables were analysed using student-t test. The level of significance was set at p value < 0.05.

Table 2
Clinical profile of our patients.

Total number of patients	50
Age in years (mean ± SD)	23.06 ± 5.55
Age range (years)	12-33
Age of onset of GTCS in years (mean ± SD)	14.61 ± 4.79
Age of onset of myoclonus in years (mean ± SD)	15.09 ± 4.67
History of absence seizures n(%)	10(20%)
Family history of seizures n(%)	13(26%)
Drug naive patients n(%)	12(24%)
Patients on monotherapy n(%)	30(78.9%)
Patients on combination therapy n(%)	8(21.1%)

4. Results

4.1. Demographic and clinical profile

The mean age of the study group was 23.06 ± 5.5 years with majority of the participants (60%) between 21–30 years. The female to male ratio in our study was 1.1:1. 24% (n = 12/50) of our patients were drug naive at the time of recruitment. The clinical profile of our patients is summarised in Table 2 and the drug status in Table 3.

The patients in our study group had disease onset ranging from 5 to 26 years with mean age of onset of GTCS being 14.61 ± 4.79 years and that of myoclonic jerks being 15.09 ± 4.67 years (range 6–30 years). A history of absence seizures was present in 20% (n = 10) and family history in 26% (n = 13) patients. All of the participants were able to identify one or more triggers that were usual precipitants for their seizures. Most common identified triggers were sleep deprivation (76%) followed by stress (48%) and mental concentration (30%). Table 4 depicts the various trigger factors identified by patients in our study.

4.2. EEG characteristics

4.2.1. Baseline record

Routine 26 channel EEG recording revealed an abnormal baseline record in 44% (22 out of 50 participants). 36.3% (8 out of 22 patients) of these patients with abnormal record, were drug naive at the time of recruitment.

4.2.2. Sleep EEG

Sleep was found to provocative in 8 out of 50 participants i.e. (16%) by both arbitrary and statistical methods (p value = 0.5). By arbitrary method, sleep was found to inhibit the IEDs in 14 out of 22 participants

Table 3
Antiepileptic drugs used by our patients.

Drugs	n	%
Sodium Valproate	19	50
Levetiracetam	5	13.3
Carbamazepine	2	5.3
Phenytoin sodium	4	10.5
Sodium Valproate plus Levetiracetam	2	5.3
Levetiracetam plus Lamotrigine	1	2.6
Carbamazepine plus Levetiracetam	1	2.6
Carbamazepine plus Sodium Valproate	1	2.6
Phenytoin sodium plus Sodium Valproate	1	2.6
Levetiractem plus Clobazam	1	2.6
Sodium Valproate plus Levetiracetam plus Clobazam	1	2.6
Total	**38**	**100**

Table 4
Self identified triggers reported by our patients.

Self identified triggers	n	%
Sleep Deprivation	38	76
Stress	24	48
Mental Concentration	15	30
Fatigue	9	18
Menstruation	8	16
Reading	5	10
Flashing Lights	4	8
Writing	3	6
Alcohol	2	4
Computer	2	4
Fever	1	2
Smoking	1	2
Written Calculations	1	2

who showed IEDs during the baseline EEG i.e (63.64%). This meant that in sleep 63.64% of the patients displayed interictal epileptiform discharges that were half less frequent than in an awake record. When compared to baseline by statistical method, only 2 patients (9.09%) displayed inhibition of discharges during sleep. Thus, the difference between two methods was statistically significant as far as inhibition during sleep was concerned (p value = < 0.001). Either sleep was not attained or there was no precipitation of discharges in 38 (i.e. 76%) of the patients.

4.2.3. Eye closure sensitivity

By arbitrary method, none of the patients exhibited eye closure sensitivity while by statistical method 2 patients (n = 4%) showed provocation of discharges.

4.2.4. Photic stimulation

Both by arbitrary method as well as statistical method, 4 patients (8%) showed provocation of discharges by photic stimulation. We observed that of the 18 out of 22 patients who showed IEDs in baseline EEG, (81.82%) showed inhibition of IEDs during photic test by arbitrary method. However while testing for spontaneous fluctuations by statistical method, only 1 patient (n = 4.55%) showed inhibition of IEDs (p value < 0.001).

4.2.5. Hyperventilation

By arbitrary method, 10 patients (n = 20%) showed provocation of discharges during the task of hyperventilation while by statistical method, 14 patients (n = 28%) showed provocation during the task (p value = 0.174). Out of 10 patients who reported a positive history of absences, 8 exhibited an abnormal record on hyperventilation while only 2 had normal record on this task. Forty patients did not report a history of absences and majority of them (n = 32; 80%) had a normal record during hyperventilation. The correlation between hyperventilation and history of absences was statistically significant (p value < 0.001). We observed inhibition of IEDs by hyperventilation in 63.64% (n = 14) by arbitrary method while in only one patient (4.55%) by statistical method (p value < 0.001).

4.2.6. Cognitive tasks

We observed a robust inhibitory effect of cognitive tasks on interictal discharge frequency. The mean discharge frequency at baseline was 0.4 ± 1.16 per min and during the cognitive procedures decreased to 0.1 ± 0.38 per min (p value = 0.029). We did not observe any task specific inhibition as all the cognitive tasks employed inhibited the IEDs in an almost equal proportion of subjects (each task inhibited IEDs in > 90% of subjects having IEDs at baseline). There was no statistically significant difference in the rates of inhibition by action programming and thinking tasks. Action programming tasks were found to inhibit the discharges in 18 out of 22 participants (81.82%) and thinking tasks seemed to inhibit the discharges in 20 patients (90.91%) [p value −0.190]. When arbitrary and statistical methods were compared, it was further observed that cognitive tasks had inhibitory effect in 20 out of 22 patients who had IEDs at baseline (90.91%) by arbitrary method and in only 5 patients (22.73%) according to the statistical method (p < 0.0001).

Tables 5 and 6 illustrate the comparative analysis of arbitrary and statistical methods for conventional procedures and cognitive tasks respectively.

4.2.7. Added benefit of cognitive tasks

We observed that although there was no significant difference between conventional and cognitive tasks with regards to provocation of discharges (conventional procedures −24%; cognitive tasks −12%; p value −0.059) but there were 4 patients in whom there was an exclusive provocation of discharges on cognitive testing. One of these patients was drug naive at the time of recruitment in our study, and all the conventional tasks had been non contributory in him. Rest of the three patients were already on sodium valproate.

4.2.8. Antiepileptic drugs and modulation by conventional and cognitive tasks

We found that although conventional procedures were provocative for IEDs in a higher number of drug naive patients as compared to cognitive tasks (25% vs 8%), this did not reach statistical significance (p value −0.137). Among the patients who were already on AEDs, majority of them were either on monotherapy of appropriate AEDs i.e. sodium valproate, levetiracetam, lamotrigine or a combination of these (71%). In patients who were on 'inappropriate' AEDs, both cognitive tasks as well as conventional procedures were provocative in an equal number of patients (17% each).

4.2.9. Association between self reported and actual observed trigger factors

We did not observe any positive correlation between the self reported trigger factors by the patients and actual provocation of IEDs during the EEG recordings. In our study, out of 38 patients who reported precipitation of their seizures in a sleep deprived state, only 8 patients (21%) had an abnormal EEG record in a sleep deprived state, while majority of them (n = 30.79%) had a normal EEG record. Similarly, out of 15 patients who reported triggering of their seizures with mental concentration, none of them had an abnormal EEG record during the task of mental calculation. Furthermore, only 2 of them had an abnormal EEG during written calculations (13.3%) while none of them had any abnormality on EEG during the task of spatial

Table 5
Modulation of IEDs by various conventional procedures using arbitrary and statistical methods.

	Provocation			Inhibition		
Task	Arbitrary method	Statistical method	p-value	Arbitrary method	Statistical method	p-value
Sleep	8(16%)	8(16%)	0.5	14(63.64%)	2(9.09%)	< 0.001
Eyes open/close	0(0%)	2(4%)	0.077	16(72.73%)	3(13.64%)	< 0.001
Photic stimulation	4(8%)	4(8%)	0.5	18(81.82%)	1(4.55%)	< 0.001
Hyperventilation	10(20%)	14(28%)	0.174	14(63.64%)	1(4.55%)	< 0.001

Table 6
Modulation of IEDs by various cognitive tasks using arbitrary and statistical methods.

	Provocation			Inhibition		
Task	Arbitrary method	Statistical method	p-value	Arbitrary method	Statistical method	p-value
Reading silently	5(10%)	5(10%)	0.5	20(90.91%)	3(13.64%)	< 0.001
Reading aloud	2(4%)	2(4%)	0.5	21(95.45%)	4(18.18%)	< 0.001
Writing	2(4%)	2(4%)	0.5	20(90.91%)	3(13.64%)	< 0.001
Mental calculation	0(0%)	0(0%)	–	20(90.91%)	3(13.64%)	< 0.001
Written calculation	4(8%)	4(8%)	0.5	20(90.91%)	5(22.73%)	< 0.001
Drawing	0(0%)	0(0%)	–	22(100%)	5(22.73%)	< 0.001
Spatial construction	0(0%)	0(0%)	–	20(90.91%)	3(13.64%)	< 0.001
Speaking aloud	1(2%)	1(2%)	0.5	21(95.45%)	4(18.18%)	< 0.001

construction. The same finding was observed in the case of writing. None of the three patients who reported exacerbation of their symptoms while writing actually displayed any abnormality during writing on EEG. Five patients in our study reported reading as a trigger, but only 1 of them had an abnormal EEG record during the task of silent reading. We did not observe any myoclonus during EEG recordings with any of the reported trigger task. As majority of our patients were already on drugs, this could have been a major suppressing factor for occurrence of IEDs.

5. Discusson

EEG is a valuable aid in the diagnosis of JME. However the interictal EEG in JME is abnormal in 50%–85% of untreated patients and in only 5%–10% of patients treated with AEDs. We too found that only 67% of our drug naive patients had an abnormal baseline record. Earlier workers had similar experiences. Thus routine awake EEGs were only able to correctly diagnose JME in two-thirds of the cases [2,8,9]. This calls for the need of further provocative testing in order to diagnose this condition. Conventional provocative methods are routinely employed to assist in the diagnosis. However equally well known is the fact that photosensitivity in JME is found in 30% of the cases [10] and eye closure sensitivity is seen in one-fourth of the cases only [11]. Thus given the sensitivity of the seizures reported by the patients to certain mental activities and praxis, researchers evaluated the role of higher cognitive functions in modulation of epileptiform EEG discharges in patients with JME [3]. The rates of provocation of IEDs by cognitive tasks reported by earlier studies range from 8 to 76% [4,12,13]. We found in our study that cognitive testing was provocative in 12% of our patients. The task of 'silent reading' was the most provocative task (10%) followed by written calculations (8%), loud reading and writing (4%). There was a higher (albeit non-significant) provocative effect of conventional procedures over cognitive testing in our study group. The results are in agreement with previous studies done by Guaranha et al. and Beniczky et al. [3,6], though a few groups have also witnessed the contrary [14,15]. Matsuoka et al. in their study found that the neuropsychological activation was more efficient than drowsiness, hyperventilation, and intermittent photic stimulation in provocation of epileptiform EEG discharges [14]. Mayer et al. similarly found that cognitive tests were provocative in 40% versus hyperventilation in 28% and intermittent photic stimulation in 20% [15]. These diverging results could possibly be explained by the effect of antiepileptic drugs, as majority of our patients were already on drugs that seemingly affected the provocation rate of conventional as well as cognitive procedures.

In our study, there were 4 patients who exhibited IEDs exclusively on cognitive testing, three of whom were already on appropriate AEDs. Taking into account the drug status of the patient, we also observed that among drug naive patients, conventional procedures were provocative in 25% of the patients while cognitive tasks in 8%, however this difference was not statistically significant (p-value −0.137). The yield of cognitive tasks increased from 8% to 13% in the patients who were already on drugs at the time of study. Moreover in the group of patients who were on inappropriate AEDs, the yield of cognitive tasks approached that of conventional provocative procedures (17% each). This additional yield of cognitive tasks over and above that offered by conventional provocative procedures has not been considered in previous studies.

Surprisingly, the groups studying 'provocative' effect of cognitive tasks have witnessed a marked 'inhibitory' influence of these procedures too. Some studies have impressively reported this occurrence to be around 90%. Guaranha et al. found that twenty-nine of their 76 patients (38.2%) presented provocative effect, while inhibition was seen in 28 of 31 (90.3%) with neuropsychological testing [3]. Matsouka et al. also found that neuropsychological protocol had an inhibitory effect on EEG discharges in 133 (63.9%) of 208 patients with discharges in the awake EEG [4]. Beniczky et al. also reported a similarly high (94%) occurrence of inhibition with mental tasks in patients with JME [6]. We too found that 20 out of our 22 patients with an abnormal EEG at baseline displayed inhibition of IEDs on these tasks (i.e. 90.91%). None of the mental tasks studied was superior over another in causing inhibition and all of them caused inhibition to a similar extent. Given the non specificity of various tasks in causing this inhibition, we support the earlier proposed hypothesis by Benizcky et al. that inhibitory effect of cognitive tasks seems to be a result of non specific 'cognitive activation' in general [6].

Previous studies have not taken into account the spontaneous fluctuation of IEDs while assessing the effect of various tasks. As far as best of our knowledge, this fluctuation has been considered only in a single study conducted by Beniczky et al. in 2012 [6]. This group highlighted the fact that the robust amount of inhibition seen during cognitive testing in patients with JME is largely accounted by the spontaneous fluctuation of IEDs as assessed by the statistical method. We in our study had a similar observation. What seemed to be a more than 90% inhibition on arbitrary method, was found to be only around 23% by the statistical method. We did observe inhibition of IEDs with conventional procedures too, but the extent of inhibition observed by statistical method was negligible as compared to that seen with the arbitrary methodology (4.54% vs 45.45% respectively). Since the provocation of discharges by cognitive tasks was observed in fewer number of patients, the provocative effect of cognitive tasks was not found to differ if spontaneous fluctuation of IEDs was taken into account. Cognitive tasks had a provocative effect in 6 patients (12%) according to the arbitrary method, and in 8 patients (16%) using the statistical method ($p = 0.5644$).

We did not get any positive correlation between self reported trigger factors and observed provocation of IEDs on the respective tasks during the EEG recording. However previous studies have observed a positive correlation between the two. In a study done by Rego CCS et al. they found that self-perception of stress (81.82%), flashing lights (22.73%) and reading (13.64%) as triggering factors was significantly associated with triggering myoclonic seizures during the video-EEG recording [16]. We understand that the sample size of our study was small and majority of patients in our study were already on drugs at the time of recruitment into the study. These facts may have confounded the above results.

6. Conclusion

As observed, cognitive tasks may assist in the diagnosis of JME by provocation of typical discharges over and above the yield offered by conventional provocative procedures, especially in patients who are already on 'appropriate' drugs. The increased yield of an EEG carries an important therapeutic connotation for the patient, as this is a condition which requires life long treatment. On the other hand the observed inhibition with the cognitive tasks may provide a therapeutic opportunity in designing patient specific treatment approaches in form of different behavioural modifications that can be inculcated in the lifestyle to minimise the risk of seizure recurrence. Future studies recruiting more number of patients may provide better insight into the role of higher cognitive activation in patients with JME.

Conflict of interest

No competing interests to declare.

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