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Transcranial magnetic stimulation/electromyography biomarker for differential diagnosis of adult patients with psychogenic nonepileptic seizure from patients with epileptic seizure and healthy subjects: An experimental study

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Psychogenic Nonepileptic Seizures; Epileptic Seizure; TMS/EMG; Biomarkers

Abstract

Background: Epilepsy is a prevalent disease worldwide which affects 1% of the global population, making it the fourth most common disease. The primary category of epilepsy, psychogenic nonepileptic seizures (PNES), can lead to significant time and financial burdens if not promptly diagnosed. Diagnosing epileptic seizures (ES) can be complex, with video electroencephalography (VEEG) monitoring, history taking, and interviews being the most effective methods. However, VEEG is costly and not always accessible.

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This study aimed to develop a cost-effective diagnostic approach using transcranial magnetic stimulation (TMS)-derived indicators. The motor threshold (MT), a key brain and spinal cord excitability indicator, differentiated ES from PNES.

Methods: The study compared 24 patients with ES, 24 patients with PNES, and 24 healthy individuals in the control group, all aged between 31-57 years.

Results: The mean MT for individuals with ES and those with PNES was the same (73.5%), and there was no significant difference in the mean MT between the two groups of patients and individuals without any medical conditions ($P > 0.05$). The findings indicated that VEEG remained the preferred method for diagnosing various forms of epilepsy, particularly PNES.

Conclusion: The MT derived from TMS and the general assessment of motor cortex excitability may not be a suitable diagnostic criterion for distinguishing ES from PNES.

Introduction

Epilepsy, a significant issue in public health acknowledged by the World Health Organization (WHO) and collaborating organizations, is a neurological condition distinguished by repetitive seizures. These seizures stem from irregular neuronal discharges or heightened excitability of neurons, causing a rapid increase in electrical activity in the brain. The disruption in the balance between excitation and inhibition ultimately culminates in the occurrence of seizures.[1] Epilepsy, a prevalent neurological disorder on a global scale, impacts an estimated fifty million individuals across the world. Although the frequency of seizures may differ among individuals, the root cause remains consistent: an irregularity in the brain's electrical functioning. The traditional interpretation of seizures as a result of synchronized, overactive neuronal firing has prompted the creation of antiepileptic drugs (AEDs). These medications work by either inhibiting excitatory neuronal pathways or enhancing inhibitory mechanisms, thus managing seizures.[2] Seizure types range from epileptic seizures (ES) to psychogenic nonepileptic seizures (PNES) and physiological nonepileptic events, which may include syncope, transient ischemic attacks (TIAs), parasomnias, migraines with aura, and paroxysmal extrapyramidal disorders.[3] PNES with syncope is frequently misdiagnosed as epilepsy, being the second most common misdiagnosis. PNES presents with sudden and temporary signs and symptoms that resemble ES, posing a challenge in distinguishing between the two conditions.[4]

Despite the frequent misdiagnosis of PNES as epilepsy, it is essential to emphasize that a significant portion, ranging from 10% to 15%, of individuals with persistent PNES also concurrently experience epilepsy. This co-occurrence of the two conditions underscores the complexity and challenges in accurately diagnosing and treating patients presenting with seizure-like episodes.[3] Understanding the unique features of ES and nonepileptic events is crucial to providing patients with the most effective care and management strategies tailored to their specific condition.[5] When clinical data and patient history do not yield a conclusive diagnosis, electroencephalography (EEG) and video EEG (VEEG) monitoring emerge as essential instruments for differentiating seizure types.

An ordinary EEG recording may not conclusively rule out the presence of epilepsy, as specific types of ES, such as simple partial seizures and frontal lobe epilepsy (FLE) seizures, may not be detectable on scalp EEG. The preferred method for distinguishing ES involves a combination of video recording, EEG, and electrocardiography (ECG). VEEG recordings are considered a dependable approach for differentiating between ES, PNES, and nonepileptic seizures of physiological origin. If the EEG appears normal before, during, and after an epileptic episode, and VEEG recordings correspond with clinical characteristics associated with PNES, a diagnosis of PNES can be established.[6]

The presence of reduced amplitude and decreased brain wave activity observed on an EEG may indicate a nonepileptic seizure stemming from physiological factors, potentially of cardiac origin. In contrast, the occurrence of positive EEG findings, when corroborated by a relevant clinical history, points towards an ES. While VEEG monitoring is a valuable tool in this context, it is not infallible and may sometimes fail to capture critical events required for a precise differential diagnosis. This limitation can hinder its ability to distinguish between PNES and ES. Nevertheless, integrating VEEG with a thorough analysis of seizure semiology can markedly improve diagnostic accuracy.[7]

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation method that has gained significant traction in clinical and experimental neuroscience. This innovative

technology is increasingly recognized as a valuable therapeutic and diagnostic resource in neurology and psychiatry.[8,9] At present, the stimulation level is established based on a metric of cortical excitability known as motor threshold (MT). MT refers to the lowest intensity of stimulation administered to the primary motor cortex (M1) required to evoke a motor response consistently. This response can be quantified as an electromyographic (EMG) signal surpassing 50 μV or as a noticeable twitch in a particular muscle on the contralateral side of the body.[9,10] TMS provides the means to evaluate the excitability and functionality of corticospinal pathways that extend to nearly all muscles in the human body, encompassing even the sphincters. This makes TMS an invaluable instrument for conducting unbiased assessments of the motor system.[10,11] TMS is commonly utilized in assessments; however, there is a lack of a thorough and up-to-date prioritized list for the diagnostic application of motor-evoked potentials (MEPs) based on recent literature. This gap exists despite the guidance the International Federation of Clinical Neurophysiology (IFCN) provides.

However, TMS studies offer the opportunity to improve the diagnostic evaluation and classification of a range of neurological disorders, such as multiple sclerosis (MS), post-traumatic, neoplastic, and compressive myelopathies, amyotrophic lateral sclerosis (ALS), stroke, epilepsy, and dystonia.[11-13] Furthermore, MTs determined through visual estimation of twitches typically tend to be around 10% higher, ranging from 0% to 30%, compared to those calculated using EMG recordings. This discrepancy highlights the importance of utilizing more objective measures, such as EMG, to accurately determine the MT during TMS procedures.[14] Across various studies in healthy individuals, the mean MT of abductor pollicis brevis (ABP) muscle was approximately 39%-61%.[15,16] Like other neurological disorders, epilepsy can change the MT by increasing brain excitability.[17]

A research investigation revealed notable differences in MTs among individuals with moderately controlled epilepsy, those experiencing poorly controlled epilepsy, and healthy participants.[18] Normal subjects exhibited substantially lower MTs than both patient groups.[18] Research conducted on individuals with epilepsy indicated markedly increased MTs in both the left and right hemispheres when contrasted with healthy individuals. Nonetheless, no significant asymmetry was detected in MT of the healthy control group or patients with epilepsy group. Furthermore, there was no discrepancy in MT between patients prescribed a pure channel-blocker AED and those prescribed a mixed AED. The statistical power of the analysis was constrained by the small sample sizes in these subgroups.[19] In a subsequent investigation, it was found that the mean MT intensities were significantly elevated in individuals with epilepsy compared to those without the condition.

Although there was no notable distinction in MT intensities between individuals with primary generalized epilepsy (characterized by generalized tonic-colonic seizures) and healthy controls, the MT intensity was higher in patients with partial epilepsy. Conversely, individuals with primary myoclonic epilepsy displayed markedly lower MT intensities than healthy controls and patients with partial epilepsy. Moreover, among individuals with epilepsy, those who were prescribed phenytoin (PHT) exhibited higher MT intensities than those who were receiving carbamazepine (CBZ) or valproate (VLP). Additionally, MT intensities were higher in patients on polytherapy (combining three or more anticonvulsants) than in patients on monotherapy.[20]

The financial burden associated with the VEEG program poses significant challenges for numerous patients, compounded by the restricted access to these facilities, which leads to extended waiting periods. Our study sought to enhance the differential diagnosis process by utilizing biomarkers derived from TMS. We examined the feasibility of using MT measurements obtained from TMS as a diagnostic instrument. In particular, we assessed whether these measurements exhibited variations among healthy subjects, individuals diagnosed with epilepsy, and those suffering from PNES.

Materials and Methods

Subjects: In this diagnostic project, subjects were recruited nonrandomly from the psychiatry and neurology clinics of Imam Hossein Hospital, Tehran City, Iran. They were classified in terms of PNES and ES diseases by physicians with experience in diagnosing epilepsy and an experienced neurologist based on the subject's history and routine EEG recordings. Subjects were assigned to three groups, each consisting of 24 individuals (24 PNES subjects, 24 ES subjects, and 24 healthy controls, all right-handed). The PNES group included 16 women and

8 men, the ES group included 15 women and 9 men, and the control group included 16 women and 8 men. Participants in the sample were 17 or older, with a mean age of 31.37 years for the PNES group, 32 years for the ES group, and 37.7 years for the control group. Exclusion criteria were set to ensure the safety and tolerability of a single TMS session. Individuals with implanted devices or metallic objects in their bodies were excluded. Individuals with neurological pathologies, ongoing neurological illnesses, severe bodily or mental illnesses, cardiac or vagal stimulators, or pregnancy were excluded from participation.

Additionally, healthy subjects of the control group with a history or family history of epilepsy were ineligible for participation. All subjects, consisting of patients in both groups and healthy ones (control group), were instructed to abstain from alcohol, coffee, and strong tea for 24 hours before the investigation. Patients had at least one seizure one month ago. None of the subjects experienced ES during TMS or the following days. This study recruited adult subjects between the ages of 17 and 57 who have had at least one seizure in the past month. For eligibility, subjects should also have at least one hour of free time available and be willing to commit to the study's duration.

Procedure: TMS was applied to the left M1 (APB area of hand motor control) using a figure-of-eight coil (70 mm internal diameter) that was linked to two Magstim-200 HP magnetic stimulators (Magstim Company, Dyfed, Wales, UK). A snug-fitting Lycra swimming cap was donned to demarcate the stimulation site, corresponding to the scalp region where TMS elicited maximal peak-to-peak MEP amplitude in the targeted muscle. The landmark for stimulation was C3, which corresponds to the left M1. To locate C3, we first divided the distance between nasion (Ns) and inion (In) in half. Then, we split the distance between the two tragi (points on the ear) in half to find the vertex. The C3 hand motor area was located 5 centimeters to the left of the vertex. The coil handle was held roughly perpendicular to the skull, oriented at a 45° angle in the mid-sagittal plane, to induce an electrical current flowing from posterior to anterior in the cortex.

The resting MT (RMT) was determined by finding the lowest stimulus intensity that could reliably produce an MEP exceeding 50 mV in amplitude (peak-to-peak), achieved by delivering ten consecutive stimuli and requiring at least five to elicit a response meeting the amplitude criterion. Complete split muscle relaxation was carefully monitored throughout the procedure using audio and visual feedback. This study primarily employed MT, replacing RMT. The results were presented as a percentage. After identifying the hotspot, we subtracted five from the number of hotspots. If no stimulation occurred, we would add two units and continue this process until APB muscular torsion was observed.

This research project, approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, under reference number of 1403.098, was conducted with informed verbal consent obtained from the participants.

Using GraphPad Prism 8.4.3 for data analysis, we encountered non-normal distributions in our samples as determined by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Kruskal-Wallis test investigated potential differences in mean MT values among three groups. The significance level was 0.05 for all exploratory comparisons.

Results

A total of 72 adult subjects, ranging in age from 17 to 57 years, were recruited in this research and assigned to three groups: 24 with PNES, 24 with ES, and 24 with healthy controls. The male-to-female ratio was approximately 1:2, with 8 men in both the PNES and control groups and 9 men in the ES group. The MT, an indicator of brain excitability, was measured and recorded for each subject, and it varied between 62% and 90% across the study population (Table 1).

The findings from the Shapiro-Wilk and Kolmogorov-Smirnov tests demonstrated that the data did not conform to a normal distribution (Table 2). The mean MT of APB was 73.5% in both the PNES and ES groups, while the mean MT of APB in the control group was 68.4%. There was no significant difference in MT between the ES and the PNES groups in the study ($P > 0.99$).

Statistical analysis revealed no significant differences in MT between the control group and the ES group or between the control group and the PNES group ($P = 0.18$, $P = 0.37$, respectively) (Table 3). Figure 1 presents a schematic illustration of the mean MT comparison between the three groups.

Discussion

The study findings suggested no significant difference in the mean MT between epilepsy and the group with PNES.

Table 1. Demographics of all subjects in three groups of study

Subjects	PNES group			ES group			Healthy control		
	Gender	Age (year)	MT (%)	Gender	Age (year)	MT (%)	Gender	Age (year)	MT (%)
1	Woman	19	85	Man	24	74	Woman	37	73
2	Woman	26	60	Man	18	75	Woman	17	70
3	Woman	55	65	Woman	54	68	Woman	27	95
4	Woman	25	65	Woman	54	70	Woman	35	67
5	Woman	39	56	Woman	37	66	Woman	57	60
6	Man	55	67	Woman	48	63	Man	40	90
7	Woman	25	69	Woman	44	75	Woman	45	75
8	Man	31	78	Woman	40	66	Woman	25	70
9	Man	35	80	Woman	18	80	Woman	54	73
10	Woman	29	63	Woman	33	80	Woman	39	52
11	Man	22	64	Man	17	90	Man	31	85
12	Man	25	70	Man	18	80	Woman	52	66
13	Woman	30	87	Man	32	80	Woman	50	75
14	Woman	39	70	Man	41	70	Man	28	62
15	Woman	18	80	Man	17	85	Man	19	56
16	Woman	28	90	Woman	22	76	Woman	23	48
17	Woman	48	65	Woman	28	70	Man	32	55
18	Woman	42	75	Woman	34	72	Man	44	56
19	Man	29	80	Man	22	74	Woman	26	57
20	Woman	27	65	Man	40	78	Woman	50	68
21	Man	18	70	Woman	23	65	Woman	55	73
22	Woman	42	90	Woman	40	56	Woman	42	74
23	Man	25	80	Woman	36	77	Man	37	62
24	Woman	21	90	Woman	28	74	Man	27	80
Mean		31	73		37	73		31	68

PNES: Psychogenic nonepileptic seizure; ES: Epileptic seizure; MT: Motor threshold

Table 2. Normality test

Test for normal distribution			
Shapiro-Wilk test			
W	0.90	0.95	0.93
P	0.02	0.43	0.11
Passed normality test (alpha = 0.05)	No	Yes	Yes
P value summary	*	NS	ns
K-S test			
K-S distance	0.18	0.11	0.12
P	0.04	> 0.99	> 0.99
Passed normality test (alpha = 0.05)	No	Yes	Yes
P value summary	*	ns	ns
Number of values	24	24	24

KS: Kolmogorov Smirnov; NS: Not statistically significant
*Did not pass the normality test

Even though the mean MT of both patient groups differed from that of the control group, this variance did not reach statistical significance. It was initially hypothesized that any form of epilepsy would heighten brain excitability and consequently reduce the MT.[17] However, the findings, consistent with the research conducted by Pawley et al.,[18] revealed that the mean MT in the epilepsy group was higher than that of healthy individuals, likely attributed to the use of antiepileptic medications. The results of the present study are inconsistent with those of Tataroglu et al.[20] investigation due to the decreased mean MT in the healthy group in contrast to the primary myoclonic epilepsy patient group. Nonetheless, the outcomes in various epilepsy categories closely match our study findings.

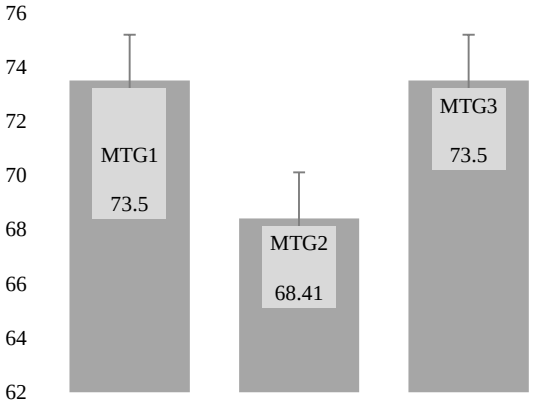

Figure 1. Motor threshold of psychogenic nonepileptic seizures (PNES) group (MTG1), motor threshold of normal group (MTG2), motor threshold of epileptic seizures (ES) group (MTG3)

Table 3. Kruskal-Wallis test result

Kruskal-Wallis test result						
Number of families	1					
Number of comparisons per family	3					
Alpha	0.05					
Dunn's multiple comparisons test	Mean rank diff.	P	Summary	Adjusted P		
MT PNES vs. MT normal	9.25	No	NS	0.37	A-B	
MT PNES vs. MT ES	-2.00	No	ns	> 0.99	A-C	
MT normal vs. MT ES	-11.25	No	ns	0.18	B-C	
Test details	Mean rank 1	Mean rank 2	Mean rank diff.	n1	n2	Z
MT PNES vs. MT normal	38.92	29.67	9.25	24	24	1.53
MT PNES vs. MT ES	38.92	40.92	-2.00	24	24	0.33
MT normal vs. MT ES	29.67	40.92	-11.25	24	24	1.86

MT: Motor threshold; PNES: Psychogenic nonepileptic seizure; ES: Epileptic seizure; NS: Not statistically significant

TMS has discovered variations in cortical excitability among patients with epilepsy who are on AEDs and healthy controls in both generalized and focal epilepsy. However, the outcomes have been inconclusive. The disparities in findings across studies are possibly due to differences in AED treatment and variations in seizure frequency.[20-26] Several factors can cause variations in MT among individuals, including biological variances and the use of sodium channel-blocking medications that elevate RMT levels.[27] The responsiveness of excitatory glutamatergic synapses, which establish connections between the cortico-cortical fibers and the corticospinal neurons, also affects MT.[28] Another minor factor involves the differences in the thickness of the convexity of the skull bones across individuals, impacting the distance between the stimulating coil and the excitable elements. Moreover, the number and density of cortico-cortical axons and corticospinal neurons, particularly target muscles, are also influential.[29,30]

Variations among individuals, whether at a microscopic level like ion channels, macroscopic level such as skull thickness, or even in terms of behavior like sleep patterns, can impact the brain's excitability. Complete control over confounding variables is not always feasible. Assessing patients based on these factors before the initial study and managing behavioral issues can enhance the reliability of subsequent analyses.

Regarding the study's limitations, it was conducted in a hospital with a referral status, where patients are referred after unsuccessful treatment in other cities. These patients were already in the midst of treatment and taking medication, making it ethically impossible to discontinue their medications. Consequently, the use of anticonvulsants will certainly affect their irritability. It is recommended that diagnostic studies be conducted in the early stages of the disease, before medication intake, to prevent the impact of confounding variables.

Conclusion

The MT derived from TMS and the general assessment of motor cortex excitability may not be a suitable diagnostic criterion for distinguishing ES from PNES. Factors such as the use of AEDs, which can interfere with and be challenging to regulate, might influence this process. If all these variables can be managed proactively, VEEG results, the patient's history, and input from their family members will serve as the most reliable diagnostic indicators.

Conflict of Interests

The authors declare no conflict of interest in this study.

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