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Electroencephalography in the diagnosis and management of treatment-resistant depression with comorbid epilepsy: a novel strategy

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INTRODUCTION

Depression, a common mental disorder, is a leading cause of disability worldwide, with a global prevalence ranging from 20% to 25% in women and 7% to 12% in men,[1] and it has exhibited an increasing trend in recent decades.

Despite being known for decades, a consensus on the definition and diagnosis of treatment-resistant depression (TRD) is still lacking. A commonly accepted criterion requires a failure of at least two trials of antidepressant medications of adequate dosage and duration, given sequentially or in combination, to achieve a satisfactory response. The optimal duration of treatment for each trial is typically 4–6 weeks when the targeted dose is achieved. Non-response is defined as <25% improvement on a standardised rating scale, and partial response is defined as >25% but <50% improvement.[2] Treatment-resistant depression is a major contributor to premature mortality due to suicide and associated medical conditions.[3] By standardising diagnostic criteria, researchers and clinicians will better understand the prevalence and characteristics of TRD, which can pave the way for developing effective treatment strategies.

Based on analysis of evidence from several studies that exhibit an existence of inherent and intrinsic reciprocal comorbidity between depression and epilepsy, the author believes that the categorisation of TRD based on the mere failure of two antidepressants could appear premature and erroneous. Therefore, in view of this analysis, this brief paper proposes a justified deliberation for revising the diagnostic criteria for TRD.

CLINICAL IMPORTANCE OF ELECTROENCEPHALOGRAPHY IN PSYCHIATRY AND NEUROLOGY

Electroencephalography (EEG) measures the electrical activity of the brain and is a primary diagnostic tool that aids in diagnosing epilepsy and differentiating it from other neurological disorders. Interictal epileptiform discharges (IEDs) are considered hallmarks of epilepsy and influence cerebral blood flow and metabolism; they can also affect cognition.[4] These properties of IEDs signify their non-benign nature and warrant due consideration, study and clinical correlation when detected in a neuropsychiatric illness. Indeed, some researchers have raised the possibility of IEDs functioning as a biomarker for mood disorders in temporal lobe epilepsy (TLE).[5]

Several other researchers have highlighted the utility of an EEG in treatment selection,[6 7] and classification of mood disorders[8 9]; an EEG can even aid in the identification of subgroups within a psychiatric population.[10] One study suggests that EEG can also assist in differentiating patients with depression from other clinical disorders and from normal individuals.[11]

The application of EEG in clinical settings is constantly evolving with emerging developments. Advances in machine learning and artificial intelligence have the potential to automatically analyse EEG data and identify patterns that are associated with specific disorders. The importance of quantitative EEG (QEEG) is increasingly recognised and is expected to be used for diagnosing and managing psychiatric illnesses such as depression and schizophrenia. Therefore, QEEG offers an economical alternative to other functional brain imaging modalities in psychiatric disorders.[6] QEEG analysis has

revealed several consistent abnormalities in patients with depression. Decreased delta power, increased high-frequency power, reduced interhemispheric coherence and altered frontal EEG alpha asymmetry scores have been shown in patients with depression.[11 12] For example, abnormal EEG with epileptiform activities has been proposed as a possible predictor of lithium resistance in bipolar disorder.[7]

EEG has not been given the significance it deserves in diagnosing and managing patients with TRD for several reasons, despite that the inventor of the EEG, Hans Berger, was a psychiatrist. First, there has been a lack of consensus among mental health professionals about the potential role of EEG in the diagnostic process. Second, EEG has been viewed as an infrastructure-intensive, manpower-intensive and time-consuming procedure and, thus, not feasible for widespread use in routine clinical practice. Third, large-scale clinical studies that could demonstrate the potential value of EEG in diagnosing and managing TRD have been lacking. An EEG should be considered an important tool in managing TRD because it can aid in identifying underlying and concomitant TLE and assist in strategizing a more effective treatment modality for TRD.

The importance of EEG in psychiatric diseases is increasingly being recognised as it has the potential for diagnosis and to guide treatment. The Psychiatric EEG Evaluation Registry (PEER) is a clinical phenotypic database comprising data correlating EEGs and medication treatment outcomes for various mental health diagnoses.[13] The purpose of PEER is to collect and analyse data to better understand the relationship between EEG findings and medication treatment outcomes and to improve diagnosis and treatment in psychiatry and neurology. An EEG can help identify specific brain patterns or biomarkers associated with depression. The further availability of a publicly accessible database for EEG recordings annotated with clinical features and clinical outcomes in psychiatric diseases will enhance research in this direction.

RECIPROCAL COMORBIDITY BETWEEN DEPRESSION AND EPILEPSY

The comorbidity and reciprocal relationship between depression and epilepsy, especially TLE, appears inherent and intrinsic. This relationship has been known since ancient times as it was mentioned in Hippocrates' writing around 400 BC: 'melancholics ordinarily become epileptics, and epileptics, melancholics'. The comorbidity of epilepsy and depression has been increasingly recognised in recent times.

In one study, the prevalence of depression in patients with epilepsy was 27% (95% CI: 23% to 31%) in the general population and nearly 34% (95% CI: 30% to 39%) in clinical settings.[14] The exact reason for this high prevalence of depression in those with epilepsy is not apparent, but it may be due to a combination of factors such as the stress of living with a chronic illness, side effects of antiepileptic medications and changes in brain function and neurotransmitter levels. Depression can negatively impact the management of epilepsy, leading to reduced adherence to treatment, increased stress levels and increased seizure frequency. The prevalence of depression is even higher in patients with refractory epilepsy and can reach as high as 54%.[15]

The relationship between depression and epilepsy has intrigued neurologists and psychiatrists for many years. TLE is considered a suitable biological model for understanding the common structural link between depression and epilepsy. The temporal lobe is the most epileptogenic region of the human brain, and TLE is the most frequent form of partial epilepsy in adults. Furthermore, TLE is frequently drug-resistant, necessitating non-pharmacological adjunctive therapies, and is often associated with mental disorders, especially depression and anxiety.[16–18]

The longitudinal studies evaluating the prevalence of epilepsy in patients with depression are lacking. One population-based study of 83 cases with incident unprovoked seizures and 130 control subjects found that a history of depression increased the risk for the development of unprovoked seizures by sevenfold.[19] In a controlled study, the incidence of major depression in patients having unprovoked seizures was 6%, which was six times higher than in controls.[20] Another recent population-based cross-sectional study from Iran reported a prevalence of 4.8% (95% CI: 2.9% to 7.4%) of epilepsy in children and adolescents with depression.[21] Cohort studies evaluating the causal effect of depression on epilepsy are lacking; however, evidence suggests that the relationship is bidirectional, and depression has been reported to predate the onset of epilepsy in some studies.[22–24]

In patients with TLE caused by mesial temporal sclerosis, the frequency of depression reported is as high as 50%–60%.[25 26] Comorbidity of epilepsy with depression has been reported in other studies also[16 18 27–29]; as mentioned earlier, patients with TLE are more likely to exhibit this comorbidity in comparison with other epilepsy forms. In addition, several other studies have demonstrated an association between hippocampal volume loss and mood disorders,[30–33] indicating a possible involvement of the limbic system in depression, a finding also observed in patients with TLE.

Epilepsy and depression also share a similar neurocircuitry involving temporal lobes and neocortex, the frontal lobes with cingulate gyrus, subcortical structures (such as basal ganglia and thalamus) and their connecting pathways.[34] Thus, both clinical and structural evidence indicates that depression and epilepsy probably represent an epiphenomenon, and therefore not surprisingly, neural networks are also shared commonly. Voxel-based morphometry studies have also provided strong evidence in favour of the notion that depression and mesial TLE represent an epiphenomenon sharing similar neural networks that involve several brain regions.[34] Neuroimaging studies have revealed a common neuroanatomic

localisation in TLE and depression, with hippocampal volume loss in both disorders.[35]

Patients with depression have shown that reduction in hippocampal volume and grey matter[30] resembles hippocampal atrophy found in patients with TLE.[35] In view of this, the author opines that neuroimaging and EEG cannot be overlooked in depression, even if frank epileptic episodes are absent or unreported.

Some findings suggest that frontal lobe dysfunction is involved in the development of depression in patients with TLE. Functional brain imaging in patients with depression has shown a reduction of regional cerebral blood flow and glucose and oxygen consumption in the left frontal regions,[36] reflecting a hypometabolic state with a concomitant hypermetabolic state in the right prefrontal regions. Electroencephalographic studies also reveal interhemispheric asymmetry of frontal activation in favour of the left hemisphere, the rate of asymmetry correlating with depression clinical scores.[12 37]

There are several treatment challenges in patients with comorbid depression and epilepsy. Although some patients with depression and epilepsy may respond well to standard treatments with antidepressants and antiepileptic drugs, there is an increased risk of TRD in the presence of comorbid epilepsy.[15] When depression and epilepsy co-occur, treatment resistance can develop in either or both conditions. In these cases, the comorbidity of TRD and epilepsy can be complex and challenging to manage as it can increase the risk of adverse effects and drug interactions and impair adherence to a management strategy.

AUTHOR'S POSTULATION

A lack or absence of an objective marker could contribute to compromised efficacy in the drug management of mental illnesses. In depression, generally, after the failure of two antidepressants of adequate dosage and optimum duration, a diagnosis of TRD is framed. Management is then initiated along the lines of TRD that involve non-pharmacological interventions, such as cognitive behavioural psychotherapy and non-invasive brain stimulation (NIBS) techniques like electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation.[38] ECT is commonly viewed as a preferable therapy for TRD, especially when associated with suicidal tendencies. It is effective and successful in such patients, except for potential post-ECT relapse, which poses a significant challenge.[39] Vagus nerve stimulation and deep brain stimulation are two other neurostimulation techniques that have been explored as treatment modalities for TRD.

In the author's opinion, and given their intrinsic comorbidity, depression and epilepsy appear inseparable disease entities. Therefore, diagnosing TRD without an EEG and the oversight of highly probable comorbid epilepsy could sound premature and erroneous. Along similar lines, managing TRD without considering the probability of concomitant epilepsy could also be incomprehensive and compromised, leading to apparently premature and possibly unjustified referral for aggressive NIBS techniques like ECT that retain an association with a social stigma.

Anecdotal experiences (including the author's personal experience) also report that patients with TRD, even those with suicidal tendencies, have exhibited temporal lobe IEDs (unilateral or bilateral, but predominantly left-sided). Successful treatment of IEDs has resulted in a marked decline in the severity of depression and even total elimination of suicidal tendencies and ideation. The author thus proposes that the possibility of the role of IEDs in aggravating the severity of depression and suicidal ideation cannot be ruled out totally and warrants an in-depth exploration.

From the above-cited studies, it is evident that concomitant EEG changes are common in depression. Therefore, diagnosing TRD may be premature in the absence of an EEG, which is an invaluable, simple, non-invasive and cost-effective investigation, especially for the detection of IEDs required for the clinical diagnosis of epilepsy. Therefore, an EEG of all patients with TRD before being referred for NIBS techniques appears justified and is strongly recommended.

Furthermore, the concomitant presence of subtle or microseizures that escape notice by patients and their caretakers and thus remain unreported and untreated cannot be ruled out completely. Several medications commonly prescribed for depression are known to lower the seizure threshold. If administered oblivious to the possibility of concomitant subtle seizures, these medications may precipitate a frank epileptic attack (for which neither the patients nor the clinicians may be prepared) and cause worsening of the depressive state. In managing patients with attention deficit hyperactivity disorder (ADHD), several researchers have observed that the removal of medication that lowers seizure threshold coupled with the addition of an anticonvulsant has resulted in outcomes based on which they have recommended stabilisation of IEDs to ensure effective therapy,[40 41] thus underscoring the utility of an EEG. In accordance with evidence from the same studies on ADHD,[40 41] the author opines that the failure of antidepressants in a significant number of patients with depression could be due to a possibility of concomitant undetected epilepsy or IEDs that can also contribute to the symptomatology of depression, in which case the utility of an EEG cannot be overemphasised. Thus, in patients with depression with IEDs, stabilisation of IEDs by an antiepileptic can function as a priming effect for antidepressants.

In line with several other researchers who have advocated augmentation and adjunctive strategies,[42] the author strongly recommends EEG as a novel adjunctive strategy and its inclusion as a guideline/criterion in the diagnosis of TRD in an attempt to favourably impact the management and quality of life of patients with TRD. In most cases of TRD, the possibility of comorbid epilepsy is generally ignored, potentially leading to an

inadvertent significant treatment gap; treatment of TLE might actually make the management of depression more effective and successful. Therefore, there is a need to reframe guidelines and include EEG as an adjunctive strategic tool in the diagnosis of TRD. This would involve updating clinical practice guidelines, promoting research and providing training and resources to mental health professionals to help them use EEG in the diagnosis and management of TRD.

CONCLUSION

The current diagnostic criterion (ie, failure of two antidepressants) therefore, can lead to the erroneous inclusion of a larger-than-justified number of patients in the category of TRD as a significant number of patients could actually be treatable by drugs alone upon considering the possibility of concomitant epilepsy and its treatment if found to co-occur. The inclusion of EEG in clinical practice can thus aid in diagnosing concomitant TLE in patients with TRD, potentially leading to better therapeutic outcomes.

Therefore, serious deliberation on revising the current diagnostic criteria that could aid in improved treatment of TRD and possibly spare many patients from being subjected to unwarranted NIBS techniques, like ECT, appears justified and is strongly recommended. However, despite significant evidence in favour of the utility of EEG in TRD, well-designed retrospective and prospective studies are recommended to validate the author's postulation on including an EEG as a guideline/criterion in TRD.

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