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Get Out the Door: Ambulatory EEG Trumps Routine EEG in the Detection of Interictal Epileptiform Abnormalities After a First Unprovoked Seizure

Diagnostic Accuracy of Ambulatory EEG vs Routine EEG in Patients With First Single Unprovoked Seizure

Hernandez-Ronquillo L, Thorpe L, Feng C, Hunter G, Dash D, Hussein T, Dolinsky C, Waterhouse K, Roy P, Jette N. *Neurol Clin Pract.* 2023;13(3). doi:10.1212/CPJ.0000000000200160

Background and Objective: To evaluate the diagnostic accuracy of the ambulatory EEG (aEEG) at detecting interictal epileptiform discharges (IEDs)/seizures compared with routine EEG (rEEG) and repetitive/second rEEG in patients with a first single unprovoked seizure (FSUS). We also evaluated the association between IED/seizures on aEEG and seizure recurrence within 1 year of follow-up. Methods: We prospectively evaluated 100 consecutive patients with FSUS at the provincial Single Seizure Clinic. They underwent 3 sequential EEG modalities: first rEEG, second rEEG, and aEEG. Clinical epilepsy diagnosis was ascertained based on the 2014 International League Against Epilepsy definition by a neurologist/epileptologist at the clinic. An EEG-certified epileptologist/neurologist interpreted all 3 EEGs. All patients were followed up for 52 weeks until they had either second unprovoked seizure or maintained single seizure status. Accuracy measures (sensitivity, specificity, negative and positive predictive values, and likelihood ratios), receiver operating characteristic (ROC) analysis, and area under the curve (AUC) were used to evaluate the diagnostic accuracy of each EEG modality. Life tables and the Cox proportional hazard model were used to estimate the probability and association of seizure recurrence. Results: Ambulatory EEG captured IED/seizures with a sensitivity of 72%, compared with 11% for the first rEEG and 22% for the second rEEG. The diagnostic performance of the aEEG was statistically better (AUC: 0.85) compared with the first rEEG (AUC: 0.56) and second rEEG (AUC: 0.60). There were no statistically significant differences between the 3 EEG modalities regarding specificity and positive predictive value. Finally, IED/seizure on the aEEG was associated with more than 3 times the hazard of seizure recurrence. Discussion: The overall diagnostic accuracy of aEEG at capturing IED/seizures in people presenting with FSUS was higher than the first and second rEEGs. We also found that IED/seizures on the aEEG were associated with an increased risk of seizure recurrence. Classification of Evidence: This study provides Class I evidence supporting that, in adults with First Single Unprovoked Seizure (FSUS), 24-h ambulatory EEG has increased sensitivity when compared with routine and repeated EEG.

Commentary

> "An adult person presents to a clinic with a recent first unprovoked seizure."

This clinical scenario is a frequent everyday occurrence globally. However, high-quality evidence has been surprisingly lacking in this commonly observed scenario. Which EEG test do we order? What are the likely results of this test? How do we interpret the abnormal test? What is the likelihood of a second unprovoked seizure and, thereby, the establishment of epilepsy with or without an abnormal test?[1] It is logical to assume that increasing the EEG sample size will increase sensitivity. An analogy is the well-established increased yield of prolonged cardiac monitoring for detecting arrhythmia.[2] However, based on anecdotal experiences and published research,[3] a similarly increased yield of detection of interictal epileptiform discharges (IEDs) on EEG has not followed this trend.

From the patient's perspective, the first seizure can be life-changing. Providing a concrete management plan and outcomes-based results can calm fears linked to the unpredictable nature of seizures.[1]

Typically, after a first single unprovoked seizure (FSUS), the clinician orders an MRI brain and a short-duration EEG—either routine (rEEG) or sleep-deprived. Without high-quality evidence, a short-duration EEG was deemed reasonable due to its accessibility, cost-effectiveness, and minimal patient inconvenience. Alternatives such as ambulatory EEG (aEEG) exist

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but are less prevalent, more resource-intensive in the form of technician and EEG reviewer time, more expensive, and more burdensome for the patient.

In this vacuum, the study by Hernandez-Ronquillo et al lands with a thunderous bang in favor of ambulatory EEG.[4] This elegant study performed prospectively over 4 years aimed to evaluate the yield of aEEG compared to a first and a repeat rEEG for detecting IEDs/seizures after FSUS. The study cohort had ages between 17 and 82 years, but racial distribution was not disclosed. The authors recruited 100 consecutive patients from a First Seizure Clinic at a university hospital in Saskatoon, Canada. Board-certified electroencephalographers reviewed all EEGs. The first rEEG was performed during the first outpatient consultation. The second rEEG preceded the aEEG as part of the same study and was performed a few weeks after the first rEEG. The patients were tracked for up to a year for the occurrence of subsequent seizures.

This study demonstrated high-quality evidence that aEEG has outstanding specificity (>95%) and good sensitivity (81%-85%) for the identification of IEDs/seizures compared to first and second rEEGs. The positive predictive value and specificity for predicting a second seizure were consistent across all 3 studies, but aEEG had a higher negative predictive value (75%) than rEEGs (around 50%). aEEG identified IEDs/seizures with 72% sensitivity, compared to 11% and 22% for the first and second rEEGs, respectively. Those diagnosed with epilepsy were 39 times more likely to show IEDs/seizures on aEEG than on an initial rEEG and 12 times more likely than those undergoing a second rEEG. aEEG significantly outperformed rEEG, as evidenced by the area under the curve values: 0.85 for aEEG versus 0.56 and 0.60 for the first and second rEEGs, respectively. Based on life tables, the projected recurrence of seizures after FSUS was 36% at 52 months, which aligns with the commonly cited "one-third of people will have a second seizure" and with the 21% to 45% at 48 months found in evidence-based guidelines.[1]

Several factors can increase EEG sensitivity, such as the close proximity of performing EEG to index seizure, repeating rEEGs, sleep deprivation, sleep capture during EEG, use of video and induction procedures such as hyperventilation and photic stimulation.[5-9] In this study, first rEEG was performed on average 8.5 weeks after FSUS. An EEG within 24 to 48 hours after index seizure is known to increase its sensitivity. This delay could be one of the reasons for the low sensitivity of the first rEEG in this study, but the latency to the first rEEG likely mimics real-world experience. Comparing a rEEG performed closer to the FSUS with an ambulatory EEG could be tackled in future studies. The presence of sleep captured during EEG increased progressively from the first rEEG (28%) to the second rEEG (45%) to aEEG (100%) and likely led to increasing sensitivity.

Despite being conducted at a tertiary care center, the ability of any physician to refer the patients to the first seizure clinic means that the study cohort more closely resembles a community practice. One of the study's limitations is the performance of the second rEEG in all patients, irrespective of whether they had an abnormal first rEEG. However, the second rEEG will only be performed in clinical practice if the first rEEG is normal. The lack of inconclusive results due to artifacts with aEEG was an interesting finding but possibly challenging to replicate in the real world.

What are the real-world clinical implications of this study? Should aEEG be the primary EEG after FSUS, where available? This practice change will no doubt increase the burden on EEG reviewers that, to some extent, could be alleviated by spike/seizure detection software, which are still a work in progress.[10,11] Or should an aEEG closely follow rEEG if it is normal? Emergency room presentation of FSUS provides a unique opportunity to perform rEEG in-house and, if normal, discharge the patient with aEEG—presumably, many patients present to emergency department with FSUS rather than directly to a clinic.[12]

If aEEG is more sensitive at detecting IEDs, does this mean more patients will be treated with anti-seizure medications (ASM) as the risk of a second unprovoked seizure has "increased"? Or, more importantly, have we previously underestimated this risk due to reliance on rEEGs? What is the true risk of a second unprovoked seizure and hence epilepsy?[1] The true risk is what happens in actuality, and the aEEG seems more accurate in predicting the true risk.[4] It is important to note that ASM treatment does not change the long-term risk of second unprovoked seizure and epilepsy.[1]

An interesting finding in the study cohort was that older adults (>60 years) were more likely to have recurrent seizures. However, the risk was decreased in those with IEDs on aEEG, suggesting that IEDs are not predictive of recurrent seizures in older adults. Clinicians should estimate risk of second seizures and consider ASM initiation based on other clinical and social factors in older adults.

The optimal use of EEG in predicting seizure recurrence leaves room for exploration in low-resource communities, minimum duration requirements to capture an IED/seizure,[13] and consistency across different epilepsy types.[14] In conclusion, the authors have provided high-quality evidence that clinicians should consider aEEG as the initial EEG after FSUS in practices with the resources to conduct them.

Rohit Marawar, MD
Department of Neurology,
Wayne State University

ORCID iD

Rohit Marawar https://orcid.org/0000-0003-0215-4057

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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