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Restoring EEG to its Rightful Place in Alzheimer Disease Care

Association of Epileptiform Abnormalities and Seizures in Alzheimer Disease

Lam AD, Sarkis RA, Pellerin KR, et al. *Neurology*. 2020;95(16):e2259-e2270. doi:10.1212/WNL.0000000000010612

Objective: To examine the relationship between scalp electroencephalography (EEG) biomarkers of hyperexcitability in Alzheimer disease (AD) and to determine how these electric biomarkers relate to the clinical expression of seizures in AD. Methods: In this cross-sectional study, we performed 24-hour ambulatory scalp EEGs on 43 cognitively normal elderly healthy controls (HC), 41 participants with early-stage AD with no history or risk factors for epilepsy (AD-NoEp), and 15 participants with early-stage AD with late-onset epilepsy related to AD (AD-Ep). Two epileptologists blinded to diagnosis visually reviewed all EEGs and annotated all potential epileptiform abnormalities. A panel of 9 epileptologists blinded to diagnosis was then surveyed to generate a consensus interpretation of epileptiform abnormalities in each EEG. Results: Epileptiform abnormalities were seen in 53% of AD-Ep, 22% of AD-NoEp, and 4.7% of HC. Specific features of epileptiform discharges, including high frequency, robust morphology, right temporal location, and occurrence during wakefulness and rapid eye movement (REM), were associated with clinical seizures in AD. Multiple EEG biomarkers concordantly demonstrated a pattern of left temporal lobe hyperexcitability in early stages of AD, whereas clinical seizures in AD were often associated with bitemporal hyperexcitability. Frequent small sharp spikes were specifically associated with epileptiform EEGs and thus identified as a potential biomarker of hyperexcitability in AD. Conclusion: Epileptiform abnormalities are common in AD but not all equivalent. Specific features of epileptiform discharges are associated with clinical seizures in AD. Given the difficulty recognizing clinical seizures in AD, these EEG features could provide guidance on which patients with AD are at high risk of clinical seizures.

Commentary

Sometimes a scientific study uses a method so common that it is hard to believe that it has not been applied to a common clinical problem before. That is the case with the report by Lam et al.[1] The authors used the results of 24-hour ambulatory EEGs to compare the rate of interictal epileptiform features among 3 sets of patients: those with a diagnosis of Alzheimer disease (AD) plus a history of seizures, those with a diagnosis of AD but no history of seizures, and a set of age-matched healthy controls. Patients had been well-characterized in specialized AD clinics. The group of AD patients with a history of seizures had the highest rate of interictal epileptiform features on EEG (53%), the healthy controls the lowest rate (4.7%). Of most interest was the AD group with no history of seizures: fully 22% had epileptiform features on their EEGs. Most of these abnormalities were localized to the temporal regions, which makes sense. It is well known that both AD and epilepsy target the hippocampus.[2] Pathological associations between AD changes and neuronal hyperexcitability exist. For example, beta-amyloid increases neuronal hyperexcitability.[2]

This finding is not surprising. The strength of the association between epilepsy and AD has become more and more obvious. The wonder is that it has taken so long to recognize. A PubMed search on "Seizures and Alzheimer's disease" turns up nothing before 1986,[3] though the association of aging with epilepsy has been known for 50 years. It is likely that a segment of persons with late-life onset epilepsy heretofore considered to have an unknown etiology includes many persons with frank or incipient Alzheimer pathological changes.

Electroencephalographs are not considered to be sensitive in the diagnosis of early AD or mild cognitive impairment (MCI). In the 1980s, I was told by a grant reviewer that "EEG has no place in the diagnosis of Alzheimer's disease." Perhaps so in the narrow sense of diagnostic specificity, but we should want to know if AD or MCI suspects have seizures for three good reasons: seizures in AD tend to recur (70%), they are associated with a worse cognitive prognosis, and we can treat them.[4] It is uncertain whether the seizures are the cause or just a marker of a worse variant of the AD, but this is one of the few things about AD that we can treat effectively.

Electroencephalographs can be criticized because of the subjectivity of interpretation. Lam et al[1] have addressed this problem by a meticulous process of verification of EEG features. Readers blinded to the diagnosis were employed, followed by the unusual step of validation by an outside expert panel. Furthermore, they classified the interictal features very precisely. They concluded that all spikes are not the same: Features associated with a history of seizures were "robust" spike morphology, right temporal location, and spikes during wakefulness and REM sleep, as well as temporal intermittent rhythmic delta activity. Unexpectedly, they also found that "small sharp spikes" (SSS) correlated with a history of epilepsy and with more classical epileptiform features. One electroencephalographer's small sharp spike may be another's *form fruste* of a seizure focus, but the example included in the paper certainly looks like a "benign" SSS.

What shall we make of the findings of this study? One conclusion is that some persons with a diagnosis of AD or MCI have unrecognized seizures. That is certainly true. A more disturbing possibility for an individual patient would be that the diagnosis of AD was wrong, with the abnormal cognition entirely caused by seizures. We do not want to miss that. These scenarios should be suspected in persons with episodic or fluctuating mental functioning or behavior, but it is often hard to be sure of that: People with AD often have "good days" or "bad days." That is disconcerting and suggests that we should make more vigorous efforts to rule out epilepsy.

Should all persons with suspected MCI or AD have an EEG? My opinion is yes. It is reported that 5% of persons with AD have epilepsy,[5] but this study[1] makes a provocative case that 1 in 20 is only the tip of the iceberg. Electroencephalographs in this group should include sleep.[1] Should all persons with AD or suspected AD have a 24-hour ambulatory EEG recording? Probably not, but a case can be made for that in anyone with a hint of a fluctuating course of cognition over a time frame of hours or days. Semi-invasive electrode recording, such as with foramen ovale electrodes, may be useful in an occasional case.[6] Subspecialties of neurology sometimes operate in silos. Epileptologists and cognitive disorders neurologists need to talk more, as Lam et al[1] have clearly demonstrated.

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