Epileptic Seizures in Alzheimer’s Disease: Another Fine MESS?

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Abstract. Much remains uncertain about epileptic seizures in the context of Alzheimer’s disease: pathogenesis, frequency, semiology, natural history, treatment. The authors suggest a pragmatic approach to developing the evidence base in order to inform decisions on seizure treatment, based on prior pragmatic studies in epilepsy.

Epilepsy in Alzheimer’s disease (AD) is a topical issue [1, 2]. This has been prompted, at least in part, by the laboratory findings of seizure activity in transgenic animals harboring genetic mutations deterministic for AD [3, 4]. These findings have suggested that seizure activity may be a consequence of the disrupted neuronal networks in AD brain and may contribute to cognitive decline rather than being simply epiphenomena. A reappraisal of clinical observations of epileptic seizures in AD in light of these findings suggests that they may be regarded as an integral part of the AD phenotype, becoming more prevalent with disease duration [2]. If seizures do reflect dysfunction in the same pathogenic pathways that cause dementia, then they may likewise be preventable with disease-modifying therapy when this becomes available.

As with most human epilepsy, the basic mechanisms of epileptogenesis in AD brain remain to be fully defined, although a number of possibilities have been considered. Accumulation of amyloid-β peptides in transgenic animals has been associated with neuronal hyperexcitability and spontaneous non-convulsive seizure activity [3, 4], although the extent to which such laboratory models reliably mimic human adult-onset AD may be questioned. Concurrent cerebrovascular pathology is very common in the clinical population and, since this is a recognized risk factor for the development of epilepsy with increasing age [5], may also contribute to epileptogenesis. Neurofibrillary pathology in AD brain reflecting disorder of the neuronal cytoskeleton tau protein may lead to structural morphological changes including neuronal sprouting and aberrant neuritic connections which may sustain hypersynchronous electrical discharges. GABAergic sprouting, with enhanced synaptic inhibition and deficits in synaptic plasticity, was observed in the dentate gyrus in transgenic mouse models with spontaneous non-convulsive seizure activity [3].

Whilst research to elucidate these basic mechanisms continues, how should clinicians address epileptic seizures in the AD patient? Assuming no differential diagnostic concerns (e.g., syncope, delirium), the issue is not simple for at least two reasons: first, uncertainty about the natural history of seizures in AD; and second, uncertainty about the efficacy of anti-epileptic drugs in AD.

It is said that between 10% and 22% of AD patients have at least one unprovoked seizure during the course of AD [5]. Hence it might appear that the majority of AD patients do not have seizures. But this statement
masks the absence of robust longitudinal data. Seizures in AD patients may go unobserved, or unrecorded as such, perhaps particularly if they are complex partial seizures, in which case they might be labeled as "confusion" or delirium.

There is essentially no evidence base upon which to formulate judgments about seizure management in AD [2], nor other neurodegenerative dementias [6]. The few observational studies published to date [7–9] suggest little difference in the efficacy of various antiepileptic drugs (AEDs), but differences in side effect profiles and hence suitability for use in this patient population.

How might these uncertainties be addressed? One way might be to consider the findings of the MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) which examined the risk of further seizures in patients with single seizures or early epilepsy for whom the place of treatment with AEDs was uncertain [10–12]. As such, MESS was paradigmatic of studies which address pragmatic clinical questions where, for want of evidence, there is uncertainty. The trial established that immediate treatment with AEDs reduced seizure occurrence in the next 1 to 2 years, but did not affect long term remission [10]. Prognostic modeling showed that significant factors influencing risk of future seizures were the number of seizures at presentation, the presence of a neurological disorder, and an abnormal EEG. These factors permitted definition of low, medium, and high risk groups for future seizures, the latter being those with two of these features or more than three seizures [11].

In the light of MESS, what recommendations might be made regarding treatment of seizures in AD? It might be argued that AD patients with a seizure be treated empirically as "high risk" since they have a neurological disorder (and likely an abnormal EEG as well). However, as the MESS authors point out, the prognostic model "should be used with caution in populations not represented in MESS" [11] which would encompass most AD patients since only a minority of patients in MESS were aged >60 years (142/1843 = 7.7%) [10]. There may possibly be problems in extrapolating data from trials of adult patients to the elderly or those with dementia, but against this patient age did not appear to be a factor contributing to the MESS prognostic model of future seizures [11].

If treatment for seizures is to be embarked upon, which AEDs should be used? The pragmatic Standard and New Antiepileptic Drugs (SANAD) study suggested that lamotrigine may be the most appropriate medication for seizures of partial origin [13], which is likely to be the most common seizure type in AD [5, 8]. Carbamazepine might also justify consideration [13], as well as levetiracetam (not examined in SANAD) given its lack of interactions in a patient population often taking multiple medications [7, 9].

In view of persisting uncertainty, another option would be to undertake a further unmasked pragmatic trial in which AD patients presenting with new seizures were randomized to receive immediate or delayed AED treatment, with similar outcome measures as for MESS, in the hope of gaining more definitive evidence on which to base treatment decisions. Undertaking such a trial would not be without problems, including but not limited to: difficulty in obtaining consent for randomizing into a trial in this group of patients; problems engaging several specialties in trial recruitment (geriatricians, old age psychiatrists, neurologists); and limited survival time of AD patients [14, 15] which might curtail adequate (5 year) follow up. Although no major interactions between current anti-dementia drugs (cholinesterase inhibitors, memantine) and AEDs are reported, there may be interactions between AEDs and medications prescribed for the behavioral and psychiatric symptoms of AD which, like seizures, become more prevalent with disease duration.

In conclusion, epileptic seizures may be integral to AD pathogenesis and more common than has been recognized hitherto, but there is no high quality evidence on which to base decisions about treatment. We advocate a pragmatic clinical trial, based on the principles of the MESS trial, to provide evidence to inform clinical practice.

DISCLOSURE STATEMENT


REFERENCES


