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Dementia (J Pillai, Section Editor)

Diagnosis and Management of Seizures in Neurodegenerative Diseases

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Abstract

Purpose of Review This review presents a critical appraisal of epileptic seizures in common neurodegenerative diseases related to proteinopathy, including Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal dementias, and prion diseases. Studies on prevalence, seizure type, and treatment are reviewed, and tentative management recommendations made. Gaps in the evidence base are indicated.
Recent Findings Epidemiological studies show that patients with AD are at increased risk of epileptic seizures. Cumulative seizure frequency of > 10% is reported and may be higher if subtle seizure features are sought by means of a proforma. Seizures may be associated with more rapid cognitive decline. The evidence base for treatment with anti-epileptic drugs in AD is weak, and potential benefits must be weighed against the risk of adverse events. Animal studies indicate that the abnormal protein species, amyloid peptides and tau, accumulating in AD brain may be implicated in epileptogenesis. Fewer data are available for the other neurodegenerative diseases, meaning that seizure treatment is largely empirical.
Summary Epileptic seizures may be an integral part of many proteinopathies of the brain, rather than epiphenomena. Symptomatic treatment of seizures is currently largely empirical. The hope for the future is that seizures, like cognitive impairment, may be susceptible to disease-modifying treatments targeting aberrant protein species.

Introduction

Epileptic seizures may be a feature of many of the neurodegenerative dementia syndromes [1]. A meta-analysis of studies ($n = 19$) reporting on the incidence and/or prevalence of dementia and epilepsy found a pooled period prevalence of epilepsy in people with dementia of 5 per 100 (95% CI = 1–9) in population-based settings and 4 per 100 (95% CI = 1–6) in clinic settings [2]. Late-onset of unprovoked seizures is recognised to be associated with an increased risk of developing dementia [3].

For the purposes of this brief review, neurodegenerative diseases are taken to encompass proteinopathies in which the primary symptoms are cognitive impairment. Neurological disorders which are primarily inflammatory or vascular in origin are excluded, even if neurodegeneration is a recognised component (e.g. multiple sclerosis). For each disorder, consideration is given to recent publications concerning the prevalence and/or incidence of seizures, and where available the evidence base for symptomatic anti-epileptic drug (AED) treatment, as well as the possibilities for future treatments based on an understanding of disease pathophysiology. The emphasis is necessarily on Alzheimer's disease, since this has a higher prevalence than the other neurodegenerative diseases under consideration and has attracted more research attention than the other disorders.

Alzheimer's Disease

Epileptic seizures have been recognised as a feature of Alzheimer's disease (AD) for more than 100 years, indeed were mentioned in one of Alzheimer's original papers (the case of patient Johann F. published in 1911) [4]. However, systematic study in this area has only been undertaken more recently, sufficient to generate reviews of seizures and their treatment in AD [5–10].

Recent attempts to quantify the problem have included both clinic-based and population-based studies, with retrospective and prospective data collection. Epidemiological studies include a nested case-control follow-up based on the UK General Practice Research Database which examined incident diagnoses of epilepsy or seizures in patients with AD ($n = 7086$) and matched dementia-free patients ($n = 11{,}524$). The incidence rate for epilepsy/seizures in patients with AD was 5.6/1000 person years (95% CI = 4.6–6.9) and in the dementia-free group was 0.8/1000 person years (95% CI = 0.6–1.1). AD conferred increased risk of developing seizures or epilepsy compared to controls (OR = 6.6; 95% CI = 4.1–10.6). Patients with longer standing AD (more than 3 years duration) had a higher risk of developing seizures or epilepsy (OR = 10.7; 95% CI = 5.4–21.4) [11]. In a population-based study from Taiwan, 4.7% of AD patients ($n = 937$) developed seizures over a mean follow-up time of just over 4 years. Their risk of seizures was higher than in age-matched controls (hazard ratio [HR] = 1.85; 95% CI = 1.40–2.90) [12]. A retrospective study of electronic medical records in UK primary care practices participating in The Health Improvement Network (THIN) which matched 22,084 AD patients and controls with no baseline history of seizure found a significantly increased risk of seizures in AD (HR = 5.31; 95% CI = 3.97–7.10) [13]. Most recently, a prospective, longitudinal, community-based cohort study from Korea found a higher risk of epilepsy in those with AD than those without (HR = 2.773; 95% CI = 2.515–3.057) and identified a number of risk factors for the development of epilepsy, including male sex, hypertension, hyperlipidaemia, diabetes, and chronic kidney disease [14].

Two significant clinic-based studies have appeared over the last 3 years. In the first of these, a review of medical records collected over a 7-year period at one dedicated US memory clinic, Beagle et al. [15•] reported a cumulative probability of developing seizures in patients with AD ($n = 1320$) of 13.4%. The incidence rate of seizures was 10 times higher than in age-matched controls. As has been previously observed, seizure rates were markedly increased in younger AD patients (only one patient in this study had an autosomal dominant form of AD, namely a presenilin-1 mutation) [15•].

Recently, the findings of the Presentation of Epileptic Seizures in Dementia (PrESIDe) study have been reported [16, 17•]. In this prospective study of 144 patients recruited from a UK memory clinic, a structured proforma was used to identify symptoms suggestive of epilepsy, including subtle features such as altered responsiveness, arrest of speech or behaviour, oral or pharyngeal automatisms, olfactory or gustatory auras, focal motor seizures, other sensory phenomena (including hallucinations), and amnesia on waking. On the basis of the information gathered, a diagnosis of either no, possible, or probable epilepsy was made. Of the 102 patients in the study diagnosed with AD, 13 (= 12.8%) were judged to be "epilepsy probable" and 16 (= 15.7%) were "epilepsy possible" [16]. Of note, at the 12-month follow-up of this patient cohort, those with a suspicion of epilepsy had declined to a greater extent on cognitive testing than patients with no epilepsy, suggesting that epilepsy may be a marker of more rapid decline and worse prognosis [17•]. The small number of patients taking AEDs showed a lesser mean decline in cognitive scores than those not so treated but this difference did not reach statistical significance [17•]. If corroborated, these data indicating greater decline in AD patients with comorbid seizures may enhance the case for early intervention to control seizures in the hope of also mitigating cognitive decline. This might include addressing potentially modifiable risk factors for seizures [14], as well as the initiation of AED treatment.

In this context, the evidence base of clinical trials of AED treatment in AD may perhaps most aptly be described as regrettably thin. A Cochrane systematic review published in 2018 identified only one relevant randomised trial [18], the details of which were deemed inadequate (e.g. of blinding) and which was underpowered to detect any difference in efficacy between the drugs examined [19•]. A number of studies are listed on ClinicalTrials.gov but many are small, open-label trials and unlikely to inform clinical decision-making. This necessarily remains empirical, perhaps informed by accounts of clinical practice in AD and inferences from AED trials in non-demented subjects.

Patient age and comorbidities will clearly influence any prescription of AEDs in AD patients, as will potential drug adverse effects on cognition and mood, and drug interactions. Such considerations have prompted recommendations to avoid many AEDs, including topiramate, zonisamide, phenobarbitone, benzodiazepines, vigabatrin, tiagabine, carbamazepine, oxcarbazepine, eslicarbazepine, gabapentin, pregabalin, sodium valproate, and phenytoin [7]. A large population-based study from Finland found an increased relative risk of death in AD patients using AEDs compared to non-users (HR = 1.23; 95% CI = 1.12–1.36), mainly due to deaths from dementia and with the highest risk in the first 90 days of AED use, suggesting that these patients were more severely affected or had more advanced disease. No increased risk of death from cardiovascular or cerebrovascular causes was observed in those receiving AEDs

[20]. This study suggested the need for careful consideration when initiating AEDs in AD and the need for monitoring of adverse events.

Based on the clinical semiology, seizures in AD are most likely to be localisation-related (focal aware, focal with impaired awareness, or focal to bilateral tonic-clonic). Hence, evidence from pragmatic studies of AEDs in the treatment of focal seizures might inform appropriate treatment of seizures in AD [21]. The Standard and New Antiepileptic Drugs (SANAD) trial of treatment of partial epilepsy reported lamotrigine to be significantly better than carbamazepine, gabapentin, and topiramate in terms of the time to treatment failure, and showed non-inferiority of lamotrigine to carbamazepine in the proportion of patients achieving a 12-month seizure remission [22]. Hence, on the basis of these data, there may be a case for using lamotrigine in AD patients with seizures. However, it should be noted the mean age of patients in the SANAD trial was around 40 years.

Published experience using lamotrigine for seizures in AD is limited. For example, the one randomised trial [18] included in the aforementioned Cochrane systematic review [19•] included only 29 patients receiving lamotrigine. Smaller numbers have been reported in other accounts of clinical experience [23–25]. Nevertheless, lamotrigine may be judged an acceptable AED option for seizures in AD based on good seizure control and tolerability [7, 10]. Theoretically, lamotrigine might exacerbate the myoclonus that is seen in some AD patients (cumulative probability of myoclonus approximately 45%, based on Figure 1C of Beagle et al.), as seizures and myoclonus are significantly associated [15•].

Scarcely, more clinical experience has been reported with levetiracetam in AD patients (as for lamotrigine, we suspect that many more patients have been treated empirically than are reported in the literature). For example, the one randomised trial [18] included in the Cochrane systematic review [19•] included only 38 AD patients receiving levetiracetam, and similar or smaller numbers have been presented in other reports of clinical experience [23, 25, 26]. From this limited evidence base, levetiracetam may be judged an acceptable AED option for seizures in AD based on good seizure control and tolerability [7, 10], although the potential adverse effects on mood may need to be considered in this context. The findings of the SANADII trial may give additional information pertinent to this recommendation. Further information is also required regarding the possible utility of lacosamide, perampanel, and brivaracetam.

If seizures are an integral part of the AD phenotype, rather than epiphenomena of disease progression, then targeting pathophysiological pathways might offer a viable alternative to traditional symptomatic AED therapy. Both network hyperexcitability and cognitive decline may be consequences of common disease mechanisms [8, 10]. In AD, treatment based on this approach might involve addressing the pathways of the two characteristic protein species accumulating in the signature pathological changes, namely amyloid peptides (plaques) and hyperphosphorylated tau (neurofibrillary tangles and neurites), as well as inflammatory and vascular changes [27, 28].

A number of factors point to the possible involvement of amyloid peptides in epileptogenesis. Generally, a high frequency of seizures has been reported in autosomal dominant forms of familial AD due to deterministic mutations in the presenilin 1 gene which increase the synthesis of amyloid peptides [29–32], although in symptomatic participants in the Dominantly Inherited Alzheimer

Network observational study (DIAN-OBS) cohort, the prevalence of seizures (2.8%; 95% CI = 0.5–5.9) was lower than in a published data cohort of autosomal dominant AD cases (20.3%; 95% CI = 17.4–23.2) [33]. These clinical studies were prompted in part by the observation of seizures in transgenic mice harbouring AD mutations which lead to overexpression of amyloid peptides [34–36]. A high prevalence of abnormal cerebrospinal fluid (CSF) $A\beta_{1-42}$ and progression to AD has been reported in patients with late-onset epilepsy of unknown origin [37]. Additional, anecdotal, evidence of the relevance of amyloid peptides in epileptogenesis comes from the examination of archive tissue from Alzheimer's patient with epilepsy, Johann F [4], .which showed exclusively amyloid pathology [38]. In Down syndrome, which shows the same evolution of biomarkers as AD and which may therefore be regarded as a form of genetically determined AD [39], development of seizures and dementia were found to be associated in both retrospective [40] and prospective [41] studies. The possibility therefore arises of a self-perpetuating vicious cycle (or bidirectional relationship) based on amyloid peptides: seizure-related increases in synaptic activity lead to increased amyloid peptide production, and hence to further seizures [42]. However, the failure to date of anti-amyloid therapies, the holy grail of AD treatment over the past 20 years, to transfer to clinical practice means there is no prospect, let alone any evidence, to address this possibility.

Of possible relevance in this context are observations of the effects of levetiracetam in transgenic mice carrying AD mutations. It has been reported to have beneficial effects, reducing abnormal EEG spikes and reversing hippocampal remodelling, behavioural abnormalities, synaptic dysfunction, and deficits in learning and memory [43], as well as decreasing neuropathological burden and reversing spatial memory deficits [44]. Such observations have prompted ongoing studies of the role of levetiracetam in the treatment of AD without seizures (e.g. ILiAD and LEV-AD studies).

Whatever the role of amyloid peptides, evidence also points to possible involvement of tau peptides in epileptogenesis, including the observation that seizure-related increases in synaptic activity may lead to increased tau production [45], and that CSF tau may be a risk factor for the development of seizures in AD [46]. Seizures have been reported on occasion in patients with inherited tauopathy (specifically the tau gene point mutation P301S) [47] and in transgenic animal models harbouring tau gene mutations [48]. Treatments targeting tau are still very much at the experimental stage but a report of reductions of tau, using antisense oligonucleotides that selectively decrease endogenous tau expression, protecting against seizures in a non-transgenic mouse model has appeared [49].

Epilepsy and dementia may share common vascular risk factors [8]. It is well-recognised that patients diagnosed clinically with AD may in fact have mixed pathology with concurrent cerebrovascular changes [50]. Patients with vascular dementia are more likely to develop epilepsy and AD patients are at increased risk of stroke. For example, in the UK General Practice Research Database study [11], in patients with vascular dementia ($n = 4438$), the incidence rate for epilepsy/seizures was 7.5/1000 person years (95% CI = 5.7–9.7) and the relative risk of developing seizures or epilepsy was OR = 5.7 (95% CI = 3.2–10.1). The THIN study [13] matched 19,902 AD patients and controls with no baseline history of stroke and found an increased risk of stroke in AD (HR = 1.29; 95% CI = 1.11–1.50). Whether modification of vascular risk factors such

as hypertension, hypercholesterolaemia, and smoking might impact on seizures and/or cognition in AD remains to be determined, but pending definitive evidence, it would seem a good practice point to address these factors.

Dementia with Lewy Bodies

Contrary to a previous review which erroneously stated that "dementia with Lewy bodies (DLB) is not reported to be associated with epileptic seizures" [1], epilepsy may be common in DLB. In a review of medical records collected over a 7-year period at one dedicated memory clinic, a cumulative probability of developing seizures in DLB patients (n = 178; this included patients with mixed pathology of both probable DLB and probable AD) of 14.7% was reported, higher than that observed in AD [15•]. The highest seizure prevalence was in the mixed pathology DLB-AD group (20.7%). Because DLB is characterised by fluctuations, seizures of non-motor type may be difficult to detect, and even if suspected may be unconfirmed.

Understandably in light of high seizure frequency, this has prompted questions on how seizures impact on DLB treatment [51•]. No clinical trial data are available, to our knowledge, to inform judgements on seizure treatment in DLB. As for AD, patient age and comorbidities will influence decisions on AED treatment, as may AD co-pathology. Pragmatism dictates that any AED chosen should be suitable for localisation-related seizures, with avoidance of AEDs that might aggravate other symptoms of DLB (e.g. cognitive impairment) or interact with other medications being prescribed for other symptoms of DLB. Based on such considerations, Cretin and Blanc concluded that theoretically the most suitable first-line drugs for seizures in DLB were lamotrigine, levetiracetam, lacosamide, or brivaracetam, with second line gabapentin or pregabalin [51•]. Theoretically, lamotrigine might exacerbate the myoclonus that is seen in some DLB patients (cumulative probability of developing myoclonus in DLB patients was 58.1% in the Beagle et al. study [15•]).

The Lewy bodies which characterize the pathology of DLB are composed of the protein alpha-synuclein. Network hyperexcitability related to increased alpha-synuclein production has been described in transgenic animals [52], raising the possibility that alpha-synuclein might be a plausible treatment target.

The high frequency of seizures in mixed DLB-AD cases has suggested the possibility of epileptogenic synergy between alpha-synuclein and tau or amyloid-peptides [15•]. Treatments targeted at the latter might thus also have application in DLB patients. Likewise, concurrent vascular pathology in DLB patients [50] suggests that vascular risk factors might also be addressed, as for AD patients with mixed pathology.

Frontotemporal Dementias

The frontotemporal dementias (FTD) are heterogeneous at the clinical, neuroimaging, neuropathological, and genetic levels. Some schemata of classification encompass not only the primarily cognitive presentations, with either predominantly behavioural or linguistic deficits, but also motor disorders with concurrent cognitive deficits such as progressive

supranuclear palsy (PSP) and corticobasal degeneration (CBD). The pathology of these disorders may involve predominantly tau or TDP-43 inclusions [53].

In a review of medical records collected over a 7-year period at one dedicated memory clinic, Beagle et al. reported a cumulative probability of developing seizures in patients with FTD ($n = 348$; this included patients with PSP and corticobasal syndrome due to CBD as well as behavioural and linguistic variants of FTD) of 3.0%. This was significantly lower than that observed in AD and DLB [15•], but nonetheless higher than anticipated in disease-free individuals, suggesting that the paucity of prior publications on epilepsy/seizures in FTD indicates underascertainment and/or under reporting.

As previously mentioned, tau peptides may be implicated in epileptogenesis [45–49] and hence may be relevant to seizure pathophysiology and treatment in FTD. Of note in this context, no seizures were recorded in patients with the semantic variant of primary progressive aphasia (svPPA, also known as semantic dementia) which has exclusively TDP-43 pathology of a particular type (type C) [54]. That svPPA is not associated with seizures may also point to the culpability of tau in other forms of FTD.

Prion Diseases

Prion diseases constitute a group of rare neurodegenerative diseases which are heterogeneous in their symptom presentation, including cognitive, cerebellar, visual, psychiatric, extrapyramidal, and pyramidal features, and in their pathogenesis, occurring in sporadic, inherited, and iatrogenic forms. Of these, sporadic Creutzfeldt-Jakob disease (CJD) is the most common.

Epileptic seizures are listed amongst the unusual clinical presentations of CJD, being confined to case descriptions or small case series [55]. Certainly, there are a number of reports of CJD presenting as non-convulsive status epilepticus or as focal impaired awareness seizures, although these epileptic phenomena have also been reported as mimics of CJD (EEG interpretation in the early stages of CJD may be difficult) [56].

The exact frequency of seizures in prion disease does not appear to be clearly defined. One report cited epileptic seizures as the initial presenting feature of sporadic CJD in 3% of cases and occurring in less than 15% of cases in total [57]. Appel et al. found a significant difference in frequency of epilepsy when comparing sporadic CJD (3/7 patients = 43%) with familial prion disease due to the E200K point mutation in the prion protein gene (5/57 patients = 9%) [58], but obviously the number of sporadic cases included in this report was very small. Moreover, previous studies had reported a higher frequency of seizures (ca. 27–40%) in E200K familial CJD [59] and a lower frequency in sporadic CJD (8%) [60].

No effective treatment currently exists for prion disease, in part related to the difficulty of conducting clinical trials, the performance of which may necessitate novel approaches, for example in those harbouring disease-causing prion gene mutations [61]. It has long been known that the cellular prion protein may have a role in epileptogenesis [62], so seizure activity (both clinical and subclinical [63]) might be a reasonable outcome measure in such trials. In the meantime,

empirical treatment of seizures as and when they emerge in the course of CJD will guide best practice.

Discussion and Conclusion

Although the occurrence of epileptic seizures in neurodegenerative diseases has long been recognised (for over 100 years in Alzheimer's disease!), progress in defining treatment has been slow, and this currently remains symptomatic rather than disease-modifying. We suggest a number of possible reasons which may have contributed to retarding the pace of progress (this listing does not claim to be exhaustive).

Firstly, seizures are either not recognised or marginalised in consensus diagnostic criteria for neurodegenerative disorders. For example, the AD criteria of 1984 (NINCDS-ADRDA) stated that epileptic seizures in advanced disease were consistent with a diagnosis of probable AD, whereas epileptic seizures at onset or early in the course of the illness made the diagnosis of probable AD uncertain or unlikely [64]. The early occurrence of seizures remained an exclusion criterion for typical AD in the IWG-2 criteria of 2014 [65]. This contrasts with the empirical findings of seizures in the early stages of AD which have been increasingly reported in recent years [23, 24, 66]. In the latest iteration of the diagnostic criteria for DLB, transient episodes of unresponsiveness, which "may represent an extreme form of cognitive fluctuation", are mentioned amongst the supportive criteria, but neither seizures nor epilepsy is alluded to [67]. This contrasts with the empirical findings of seizures occurring in the early stages of DLB in some patients [15•]. Seizures are not mentioned in widely accepted and commonly used diagnostic criteria for FTD [68] or sporadic CJD [69]. Clinicians required to operationalize these criteria in clinical practice may therefore not be primed to the possibility of seizures occurring in these conditions, and may not consider them to be a priority in patient management in comparison to the cognitive or motor features of disease. This may determine a reactive rather than proactive approach to seizures in neurodegenerative diseases, and so contribute to the lack of definition of the extent of the problem of seizures in these disorders. Many of the available data emanate from retrospective studies [15•], although prospective studies are beginning to emerge [16, 17•].

Secondly, there are difficulties in the diagnosis of seizures in neurodegenerative disorders at both the clinical and investigational levels. For the most part, seizures are of non-motor type, and may be subtle. As such, they may elude the observation of carers, upon whose account clinicians may be entirely dependent. Even if described, seizures may be misdiagnosed, perhaps as syncope (not infrequent in DLB, perhaps related to autonomic involvement), delirium (not infrequent in AD or DLB), or as "transient episodes of unresponsiveness" in DLB [67]. Non-convulsive seizures in particular may be difficult to diagnose in the context of neurodegenerative disease [63, 70, 71]. Accordingly, use of a proforma, perhaps of the type used in the PrESIDe study [16], may be required to ensure that subtle seizure phenomena are not inadvertently overlooked. In the context of diagnosis, the possibility that de novo late-onset seizures may be a reflection of an underlying neurodegenerative disease also needs to be emphasized [3, 72]. As yet, no consensus guidelines for appropriate follow-up evaluations for use in these circumstances (e.g. monitoring of CSF $A\beta_{1-42}$ levels

[37], or search for evidence of early parietal lobe, especially precuneus, involvement of AD [73]) have been developed.

Recourse to investigational techniques is also problematic. Standard EEG recordings not only lack sensitivity but it may also be difficult for cognitively impaired patients to cooperate with the testing. In addition to clinical seizures, subclinical EEG abnormality may also be present in these conditions [63], which may require prolonged (ambulatory) and/or invasive EEG recording to detect [74, 75], facilities for which may not be widely available.

Thirdly, even if seizures are suspected and diagnosed, there is a conspicuous lack of high-quality evidence (randomised controlled treatment trials) to inform clinical decision-making on the prescription of AEDs in neurodegenerative diseases [19•]. A previous call advocating for pragmatic studies of AEDs in AD [21] appears to have fallen on deaf ears, perhaps because such trials would be difficult to conduct and would not be likely to attract commercial backing. Accordingly, empirical approaches to treatment may currently constitute best practice.

Fourthly, there remains a lack of understanding of seizures in neurodegenerative diseases at the pathophysiological level. The idea that seizures are simply an epiphenomenon of degenerating brain is now giving way to evidence of the possible role of accumulating protein species, such as amyloid peptides, tau, alpha-synuclein, and misfolded prion protein, in epileptogenesis. These studies, principally conducted in transgenic animal models of disease, may give insights which feed in to the development of novel seizure treatments, possibly related to disease modification strategies. The role of vascular, and possibly also inflammatory, pathological change also remains to be fully defined.

Addressing each of these issues represents a significant challenge. However, if it proves to be the case, as has been suggested by some studies, that seizures exacerbate cognitive decline in neurodegenerative diseases and represent a more aggressive form of disease, then the incentive to identify and treat seizures early in these conditions will be increased. To do so effectively may require significant expansion of the evidence base.

In the meantime, pending more definitive guidance from research, how should clinicians manage patients with neurodegenerative disorders who develop epilepsy? Some general principles are evident from the management of patients with epilepsy in other clinical contexts. A risk:benefit assessment for or against commencing AED therapy should be made, accepting that for AD this is a challenging decision based on currently available evidence: the possible impact on disease progression might argue for early treatment [16, 17•], but the possible increased relative risk of death might urge caution when considering initiation of treatment [20]. Discussion of these uncertainties with patients and their relatives will be necessary for individualised decisions. If treatment is deemed to be indicated, selection of an AED appropriate to seizure type and with an acceptable adverse effect profile (low risk of cognitive and mood adverse effects, minimal drug interactions) should be made. Low starting dose and slow titration is appropriate. Monitoring of efficacy and, particularly, unwanted effects should be undertaken. Because of the potential overlap of vascular risk factors for epilepsy and some neurodegenerative disorders, particularly AD, it would seem good practice to address these, although definite evidence of benefit is currently lacking.

Note Added in Proof

Further data on epilepsy risk in dementia and AD have been published since acceptance of this article by Mahamud et al. (Seizure. 2020;82:118-24) and Vöglein et al. (J Neurol. 2020;267:2941-8).

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Larner AJ. Epileptic seizures in neurodegenerative dementia syndromes. J Neurol Neurosci. 2010;1(1):3.
2. Subota A, Pham T, Jetté N, Sauro K, Lorenzetti D, Holroyd-Leduc J. The association between dementia and epilepsy: a systematic review and meta-analysis. Epilepsia. 2017;58:962–72.
3. Keret O, Hoang TD, Xia F, Rosen HJ, Yaffe K. Association of late-onset unprovoked seizures of unknown etiology with the risk of developing dementia in older veterans. JAMA Neurol. 2020;77:710–5.
4. Alzheimer A. Über eigenartige Krankheitsfalle des sapteren Alters. Z Gesamte Neurol Psychiatr. 1911;4:356–85.
5. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol. 2017;16:311–22.
6. Giorgi FS, Guida M, Vergallo A, Bonuccelli U, Zaccara G. Treatment of epilepsy in patients with Alzheimer's disease. Expert Rev Neurother. 2017;17:309–18.
7. Cretin B. Pharmacotherapeutic strategies for treating epilepsy in patients with Alzheimer's disease. Expert Opin Pharmacother. 2018;19:1201–9.
8. Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain. 2018;141:1592–608.
9. Asadollahi M, Atazadeh M, Noroozian M. Seizure in Alzheimer's disease: an underestimated phenomenon. Am J Alzheimers Dis Other Dement. 2019;34:81–8.
10. Powell G, Ziso B, Larner AJ. The overlap between epilepsy and Alzheimer's disease and the consequences for treatment. Expert Rev Neurother. 2019;19:653–61.
11. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. Epilepsia. 2013;54:700–7.
12. Cheng CH, Liu CJ, Ou SM, Yeh CM, Chen TJ, Lin YY, et al. Incidence and risk of seizures in Alzheimer's disease: a nationwide population-based cohort study. Epilepsy Res. 2015;115:63–6.
13. Cook M, Baker N, Lanes S, Bullock R, Wentworth C, Arrighi HM. Incidence of stroke and seizure in Alzheimer's disease dementia. Age Ageing. 2015;44:695–9.
14. Lyou HJ, Seo KD, Lee JE, Pak HY, Lee JH. Association of Alzheimer's disease with risk of developing epilepsy: a 10-year nationwide cohort study. Dement Neurocogn Disord. 2018;17:156–62.
15.• Beagle AJ, Darwish SM, Ranasinghe KG, La AL, Karageorgiou E, Vossel KA. Relative incidence of seizures and myoclonus in Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia. J Alzheimers Dis. 2017;60:211–23.

Although a retrospective study, this is currently the best available evidence on the frequency of seizures in DLB and FTD.

16. Baker J, Libretto T, Henley W, Zeman A. The prevalence and clinical features of epileptic seizures in a memory clinic population. Seizure. 2019;71:83–92.
17.• Baker J, Libretto T, Henley W, Zeman A. A longitudinal study of epileptic seizures in Alzheimer's disease. Front Neurol. 2019;10:1266.

Two reports from the prospective Presentation of Epileptic Seizures in Dementia (PrESIDe) study found evidence of seizures in up to 25% of AD patients and more rapid cognitive decline over 12 months in this group.

18. Cumbo E, Ligori LD. Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. Epilepsy Behav. 2010;17:461–6.
19.• Liu J, Wang LN, Wu LY, Wang YP. Treatment of epilepsy for people with Alzheimer's disease. Cochrane Database Syst Rev. 2018;12:CD011922.

The most recent iteration of the Cochrane review of the treatment of epilepsy in AD, highlighting the significant shortcomings of the available evidence base: no randomized double-blind placebo-controlled study has been reported.

20. Sarycheva T, Lavikainen P, Taipale H, Tiihonen J, Tanskanen A, Hartikainen S, et al. Antiepileptic drug use and mortality among community-dwelling persons with Alzheimer disease. Neurology. 2020;94:e2099–108.
21. Larner AJ, Marson AG. Epileptic seizures in Alzheimer's disease: another fine MESS? J Alzheimers Dis. 2011;25:417–9.
22. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblended randomised controlled trial. Lancet. 2007;369:1000–15.
23. Vossel KA, Beagle AJ, Rabinovici GD, Shu H, Lee SE, Naasan G, et al. Seizures and epileptiform activity in

the early stages of Alzheimer disease. JAMA Neurol. 2013;70:1158–66.
24. Cretin B, Sellal F, Philippi N, Bousiges O, di Bitonto L, Martin-Hunyadi C, et al. Epileptic prodromal Alzheimer's disease, a retrospective study of 13 new cases: expanding the spectrum of Alzheimer's disease to an epileptic variant? J Alzheimers Dis. 2016;52:1125–33.
25. Sarkis RA, Dickerson BC, Cole AJ, Chemali ZN. Clinical and neurophysiologic characteristics of unprovoked seizures in patients diagnosed with dementia. J Neuropsychiatr Clin Neurosci. 2016;28:56–61.
26. Belcastro V, Costa C, Galletti F, Pisani F, Calabresi P, Parnetti L. Levetiracetam monotherapy in Alzheimer patients with late-onset seizures: a prospective observational study. Eur J Neurol. 2007;14:1176–8.
27. Sanchez MP, Garcia-Cabrero AM, Sanchez-Elexpuru G, Burgos DF, Serratosa JM. Tau-induced pathology in epilepsy and dementia: notions from patients and animal models. Int J Mol Sci. 2018;19(4):E1092.
28. Giorgi FS, Saccaro LF, Busceti CL, Biagioni F, Fornai F. Epilepsy and Alzheimer's disease: potential mechanisms for an association. Brain Res Bull. 2020;160:107–20.
29. Larner AJ. Presenilin-1 mutation Alzheimer's disease: a genetic epilepsy syndrome? Epilepsy Behav. 2011;21:20–2.
30. Zarea A, Charbonnier C, Rovelet-Lecrux A, Nicolas G, Rousseau S, Borden A, et al. Seizures in dominantly inherited Alzheimer disease. Neurology. 2016;87:912–9.
31. Ryan NS, Nicholas JM, Weston PS, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. Lancet Neurol. 2016;15:1326–35.
32. Vöglein J, Noachtar S, McDade E, Quaid KA, Salloway S, Ghetti B, et al. Seizures as an early symptom of autosomal dominant Alzheimer's disease. Neurobiol Aging. 2019;76:18–23.
33. Tang M, Ryman DC, McDade E, Jasielec MS, Buckles VD, Cairns NJ, et al. Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network Observational Study (DIAN-OBS). Lancet Neurol. 2016;15:1317–25.
34. Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, et al. Aberrant excitatory neuronal activity and compensatory remodelling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. Neuron. 2007;55:697–711.
35. Palop JJ, Mucke L. Amyloid beta induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. Nat Neurosci. 2010;13:812–8.
36. Gschwind T, Lafourcade C, Gfeller T, Zaichuk M, Rambousek L, Knuesel I, et al. Contribution of early Alzheimer's disease-related pathophysiology to the development of acquired epilepsy. Eur J Neurosci. 2018;47:1534–62.
37. Costa C, Romoli M, Liguori C, Farotti L, Eusebi P, Bedetti C, et al. Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology. Neurobiol Aging. 2019;73:61–7.
38. Möller HJ, Graeber MB. The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. Eur Arch Psychiatry Clin Neurosci. 1998;248:111–22.
39. Fortea J, Vilaplana E, Carmona-Iragui M, Benejam B, Videla L, Barroeta I, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet. 2020;395:1988–97.
40. Lott IT, Doran E, Nguyen VQ, Tournay A, Movsesyan N, Gillen DL. Down syndrome and dementia: seizures and cognitive decline. J Alzheimers Dis. 2012;29:177–85.
41. McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. J Intellect Disabil Res. 2017;61:843–52.
42. Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, et al. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. Neuron. 2005;48:913–22.
43. Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. Proc Natl Acad Sci U S A. 2012;109:E2895–903.
44. Shi JQ, Wang BR, Tian YY, Xu J, Gao L, Zhao SL, et al. Antiepileptics topiramate and levetiracetam alleviate behavioral deficits and reduce neuropathology in APPswe/PS1dE9 transgenic mice. CNS Neurosci Ther. 2013;19:871–81.
45. Wu JW, Hussaini SA, Bastille IM, Rodriguez GA, Mrejeru A, Rilett K, et al. Neuronal activity enhances tau propagation and tau pathology in vivo. Nat Neurosci. 2016;19:1085–92.
46. Tábuas-Pereira M, Durães J, Lopes J, Sales F, Bento C, Duro D, et al. Increased CSF tau is associated with a higher risk of seizures in patients with Alzheimer's disease. Epilepsy Behav. 2019;98:207–9.
47. Sperfeld AD, Collatz MB, Baier H, Palmbach M, Storch A, Schwarz J, et al. FTDP-17: an early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. Ann Neurol. 1999;46:708–15.
48. Garcia-Cabrero AM, Guerrero-Lopez R, Giraldez BG, et al. Hyperexcitability and epileptic seizures in a model of frontotemporal dementia. Neurobiol Dis. 2013;58:200–8.
49. DeVos SL, Goncharoff DK, Chen G, et al. Antisense reduction of tau in adult mice protects against seizures. J Neurosci. 2013;33:12887–97.
50. Rahimi J, Kovacs GG. Prevalence of mixed pathologies in the aging brain. Alzheimers Res Ther. 2014;6:82.
51.• Cretin B, Blanc F. How does epilepsy impact the pharmacotherapeutic management of patients with

dementia with Lewy bodies? Expert Opin Pharmacother. 2020;21:377–9.
A careful consideration of the treatment options for seizures in DLB.
52. Morris M, Sanchez PE, Verret L, Beagle AJ, Guo W, Dubal D, et al. Network dysfunction in alpha-synuclein transgenic mice and human Lewy body dementia. Ann Clin Transl Neurol. 2015;2:1012–28.
53. Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol. 2010;119:1–4.
54. Mackenzie IRA, Neumann M, Baborie A, Sampathu DM, du Plessis D, Jaros E, et al. A harmonized classification system for FTLD-TDP pathology. Acta Neuropathol. 2011;122:111–3.
55. Baiardi S, Capellari S, Bartoletti Stella A, Parchi P. Unusual clinical presentations challenging the early clinical diagnosis of Creutzfeldt-Jakob disease. J Alzheimers Dis. 2018;64:1051–65.
56. Mead S, Rudge P. CJD mimics and chameleons. Pract Neurol. 2017;17:113–21.
57. Wieser HG, Schindler K, Zumsteg D. EEG in Creutzfeldt-Jakob disease. Clin Neurophysiol. 2006;117:935–51.
58. Appel S, Chapman J, Cohen OS, Rosenmann H, Nitsan Z, Blatt I. Seizures in E200K familial and sporadic Creutzfeldt-Jakob disease. Acta Neurol Scand. 2015;131:152–7.
59. Meiner Z, Gabizon R, Prusiner SB. Familial Creutzfeldt-Jakob disease. Codon 200 prion disease in Libyan Jews. Medicine. 1997;76:227–37.
60. Brown P, Goldfarb LG, Gibbs CJ Jr, Gajdusek DC. The phenotypic expression of different mutations in transmissible familial Creutzfeldt-Jakob disease. Eur J Epidemiol. 1991;7:469–76.
61. Vallabh SM, Vallabh Minikel E, Schreiber SL, Lander ES. Towards a treatment for genetic prion disease: trials and biomarkers. Lancet Neurol. 2020;18:361–8.
62. Walz R, Castro RM, Velasco TR, et al. Cellular prion protein: implications in seizures and epilepsy. Cell Mol Neurobiol. 2002;22:249–57.
63. Ng MC, Westover MB, Cole AJ. Treating seizures in Creutzfeldt-Jakob disease. Epilepsy Behav Case Rep. 2014;2:75–9.
64. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Service Task forces on Alzheimer's disease. Neurology. 1984;34:939–44.
65. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13:614–29 [Erratum Lancet Neurol. 2014;13:757].
66. Lozsadi DA, Larner AJ. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;22:121–4.
67. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017;89:88–100.
68. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–77.
69. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain. 2009;132:2659–68 [Erratum Brain. 2012;135:1335].
70. Mutoh T, Eguchi K, Yamamoto S, Yasui N, Taki Y. Arterial spin labeling magnetic resonance imaging in the assessment of non-convulsive status epilepticus in Alzheimer's disease: a report of two cases. Am J Case Rep. 2019;20:1883–7.
71. Valls-Carbó A, Gajate V, Romeral M, Gutiérrez-Viedma Á, Parejo-Carbonell B, Cabrera-Martín MN, et al. Non-convulsive status epilepticus in behavioral variant frontotemporal dementia. J Alzheimers Dis. 2020;77:in press:985–91.
72. Ford E, Greenslade N, Paudyal P, Bremner S, Smith HE, Banerjee S, et al. Predicting dementia from primary care records: a systematic review and meta-analysis. PLoS One. 2018;13(3):e0194735.
73. Horvath A, Kiss M, Szucs A, Kamondi A. Precuneus-dominant degeneration of parietal lobe is at risk of epilepsy in mild Alzheimer's disease. Front Neurol. 2019;10:878.
74. Vossel KA, Ranasinghe KG, Beagle AJ, Mizuiri D, Honma SM, Dowling AF, et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. Ann Neurol. 2016;80:858–70.
75. Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. Nat Med. 2017;23:678–80.

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