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Epileptic seizures in neurodegenerative dementia syndromes

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Summary
Epileptic seizures may be a feature of some neurodegenerative dementia syndromes. There is an increased incidence of seizures in Alzheimer's disease compared to age-matched controls. Seizures also occur in prion disorders and some frontotemporal lobar degeneration syndromes, whereas parkinsonian dementia disorders seem relatively seizure free. Seizure pathogenesis in these conditions is uncertain, but may relate to neocortical and hippocampal hyperexcitability and synchronised activity, possibly as a consequence of dysfunctional protein metabolism, neuronal structural changes, and concurrent cerebrovascular disease. Alzheimer's disease may be a neuronal network disorder, characterised by both cognitive decline and epileptic activity, in which seizures are an integral part of disease phenotype rather than epiphenomena. Treatment of seizures in dementia syndromes currently remains empirical. Greater understanding of dementia pathogenesis may shed light on mechanisms of epileptogenesis and facilitate more rational approaches to seizure treatment.

Introduction

In its canonical definition, the dementia syndrome is characterised as an acquired impairment of cognitive functions, particularly memory, sufficient to interfere with social and occupational functioning (American Psychiatric Association, 2000). In addition to cognitive and functional decline, dementia syndromes may also feature other clinical phenomena, including behavioural and psychiatric symptoms, sleep-related disorders, and epileptic seizures.

The differential diagnosis of dementia is broad (Mendez & Cummings, 2003; Larner, 2008), although in clinical practice Alzheimer's disease (AD) is the most common identified cause. Likewise, the differential diagnosis of cognitive deficits associated with epileptic seizures encompasses various possibilities. Many patients with epilepsy complain of memory problems, which may be multifactorial in origin (Zeman, 2009). They may relate to the underlying brain pathology which causes seizures, perhaps leading to impaired memory consolidation (Blake et al., 2000); or to seizures per se, since these may sometimes be sufficient to simulate neurodegenerative disorders such as AD (Høgh et al., 2002); or to the adverse effects of anti-epileptic drugs (Loring et al., 2007); or to concurrent affective disorders; or to any combination of these factors. A population-based incidence study of epilepsy in adults found 18% to be demented (Forsgren et al., 1996).

In addition to these situations, neurodegenerative dementia syndromes may be attended by the occurrence of epileptic seizures. However, with the exception of AD (McKhann et al., 1984), widely accepted clinical diagnostic criteria for the common dementia subtypes do not mention epileptic seizures, even as an exclusion criterion (Román et al., 1993; McKeith et al., 1996, 1999; Neary et al., 1998; World Health Organisation, 1998; McKhann et al., 2001; Emre et al., 2007). This article briefly reviews seizure phenomena which have been reported in association with the common neurodegenerative dementia syndromes, specifically AD, frontotemporal lobar degeneration syndromes, Parkinson's disease dementia and dementia with Lewy bodies, prion diseases, and Huntington's disease. Because of the pathological overlap between neurodegenerative disease and cerebrovascular changes, especially in AD, seizures in vascular dementia are also considered. Some brief comments on the management of seizures in neurodegenerative dementias are appended.

Seizures in Alzheimer's disease

Epileptic seizures in AD have recently been extensively reviewed (Palop & Mucke, 2009; Larner, 2010). Epidemiological studies have shown that AD is a risk factor for development of late-onset unprovoked seizures, seizure onset occurring on average more than six years into the course of disease, with 10-22% of patients having at least one unprovoked seizure during the course of their illness (Mendez & Lim, 2003). A prospective cohort study of mild AD patients found the cumulative incidence of unprovoked seizures to be 8% after 7 years of follow up (Amatniek et al., 2006).

Defining seizure type in AD may be difficult. Generalised seizures seem to predominate, presumably secondarily generalised from a partial seizure focus (Mendez & Lim, 2003). Complex partial seizures may also occur, although they may be underrecognised in the context of a progressive dementia (Rao et al., 2009).

2010
Vol.1
No. 1:3
doi: 10:3823/302

The widely-accepted NINCDS-ADRDA clinical diagnostic criteria for AD state that seizures in advanced disease are consistent with a diagnosis of probable AD, but seizures at disease onset or early in the disease course make the diagnosis of AD uncertain or unlikely (McKhann et al., 1984). However, seizure onset may be concurrent with onset of cognitive decline in some AD patients (6%), with no explanation for seizures other than AD identified in about half of these patients (Lozsadi & Larner, 2006). Hence, as a rule of thumb, it is probably advisable to investigate seizures in AD patients in the early stages of cognitive decline to exclude alternative symptomatic causes.

AD may be arbitrarily divided into early- and late-onset disease with a threshold of 65 years of age (McKhann et al., 1984), although there is scant evidence to suggest any biological difference in these entities. The relative risk of seizures is markedly increased in patients with early-onset AD (Mendez et al., 1994; Amatniek et al., 2006). This may be related, at least in part, to the higher prevalence of deterministic genetic mutations in early-onset AD. Seizures have been recorded as part of the phenotype in a number of pedigrees harbouring mutations in the presenilin-1 gene on chromosome 14, the commonest deterministic genetic cause of AD (Larner & Doran, 2009a), and with amyloid precursor protein (APP) gene duplications on chromosome 21 (Cabrejo et al., 2006). Down's syndrome (trisomy 21) patients invariably develop AD-type pathology, and late-onset of seizures may correlate with the clinical onset of cognitive decline (Puri et al., 2001).

A number of factors may contribute to the pathogenesis of seizures in AD (Palop & Mucke, 2009; Larner 2010). The amyloid hypothesis of AD pathogenesis suggests that altered metabolism of APP to produce amyloidogenic amyloid _-peptides (A_) is the ultimate cause of AD. Excessive brain levels of A_ in transgenic mice may result in spontaneous non-convulsive seizure activity in cortical and hippocampal networks, even in the absence of frank neurodegeneration (Palop et al., 2007). Hence it is posited that seizure activity may be an integral component of the disrupted neuronal networks of the AD brain and may contribute to cognitive decline, rather than being simply an epiphenomenon. Structural alterations in neurones related to tau pathology, the other hallmark change observed in AD brain, including loss of synaptic contacts and aberrant neuronal sprouting, may facilitate development of recurrent hypersynchronous discharges underpinning seizure activity. Tau deficient transgenic mice do not develop aberrant network activity despite excessive A_ (Roberson et al., 2007). Changes in neurotransmitter activities and concurrent cerebrovascular disease might also contribute to seizures in AD.

Seizures in frontotemporal lobar degeneration syndromes

The frontotemporal lobar degenerations (FTLDs) encompass a heterogeneous group of disorders with respect to both clinical phenotype and neuropathology (Neary et al., 1998; McKhann et al., 2001; Cairns et al., 2007; Mackenzie et al., 2009). Broadly they may be divided clinically into behavioural (behavioural variant frontotemporal dementia) and linguistic syndromes, the latter characterised by either non-fluent output with relatively preserved comprehension (progressive non-fluent aphasia) or fluent output with impaired comprehension (semantic dementia). Clinical or subclinical evidence of motor neurone disease may be found in some FTLD cases. Movement disorders associated with cognitive impairment such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) may also be included under the FTLD rubric (Kertesz & Munoz, 1998). In terms of neuropathology, FTLDs may be categorized according to the protein abnormality presumed to be pathogenic, such as tau, TDP-43, ubiquitin proteasome system, or intermediate filaments (Mackenzie et al., 2009).

Epileptic seizures do not feature in the diagnostic criteria for FTLDs, either as inclusion or exclusion criteria (Neary et al., 1998). However, a normal conventional EEG despite clinically evident dementia is one of the investigational consensus diagnostic criteria (Neary et al., 1998), in contradistinction to AD in which EEG changes, particularly slowing of background rhythms, are common (Stam, 2006), particularly in the later stages of the disease. Although the view that the EEG is normal in FTLDs has been challenged (Chan et al., 2004), nonetheless it remains the case that epileptic seizures are rarely reported in FTLDs. An exception may be FTLD with concurrent hippocampal sclerosis (HS). Initially defined by neuropathological appearances of neuronal loss in the hippocampal CA1 region in a distribution similar to that seen in seizure-associated mesial temporal sclerosis (Corey-Bloom et al., 1997), "pure" HS was later reclassified as a subtype of FTLD based on the neuropathological finding of tau-negative ubiquitin-positive inclusions (Hatanpaa et al., 2004) and the overlap of clinical and neuropsychological features with FTLD (Blass et al., 2004). These cases are probably TDP-43 proteinopathies (Cairns et al., 2007). They were previously reported to have a similar prevalence of seizures to AD (Leverenz et al., 2002).

Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) may result from mutations in genes encoding either the microtubule associated protein tau (MAPT) or progranulin. FTDP-17 resulting from the P301S MAPT gene mutation has been reported with a phenotype including prominent early seizures (Sperfeld et al., 1999), but this seems to be an exceptional occurrence in FTDP-17 with tau gene mutations (Larner & Doran, 2009b).

Seizures in Dementia with Lewy bodies, Parkinson's disease dementia, and other parkinsonian syndromes

Possibly the second most common form of neurodegenerative dementia, dementia with Lewy bodies (DLB) is not reported to be associated with epileptic seizures, nor is the dementia associated with Parkinson's disease which has similar neuropsychological and neuropathological features, both being classified as synucleinopathies. This is perhaps a little surprising since concurrent tau pathology of Alzheimer type is not infrequent in these cases. Although transient loss of consciousness is one of the supportive features in the diagnostic criteria for DLB (McKeith et al., 1996) these are not epileptic seizures, but are more likely to be related to the autonomic dysfunction which is common in this condition (Horimoto et al., 2003).

2010
Vol.1
No. 1:3
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In other neurodegenerative parkinsonian syndromes, seizures have been reported in PSP (Nygaard et al., 1989) but do not seem to be a common feature. There seems to be no literature on epileptic seizures in CBD or multiple system atrophy. Although there are clearly areas of overlap between the fields of epilepsy and movement disorders (Guerrini et al., 2002), this does not seem to be relevant in these late-onset movement disorders.

Seizures in prion diseases

Prion diseases may be of sporadic, inherited or iatrogenic aetiology. Seizures have been reported in sporadic Creutzfeldt-Jakob disease (Cokgor et al., 1999), sometimes as the presenting feature, with focal motor seizures (Aronyk et al., 1984; Yamanouchi et al., 1986), nonconvulsive status epilepticus (Rees et al., 1999; Cohen et al., 2004; Fernandez-Torre et al., 2004; Vaz et al., 2005), and generalised status epilepticus (Neufeld et al., 2003; Karatas et al., 2007) all reported. Localization-related seizures have been reported as the first presentation of variant CJD (Silverdale et al., 2000) but this would seem to be a rare or even exceptional event (Spencer et al., 2002).

Since loss of the cellular prion protein has been reported to be associated with enhanced sensitivity to seizures, with neocortical and hippocampal hyperexcitability and synchronised activity (Walz et al., 2002), it is possible that prion disorders may resemble AD as neuronal network disorders clinically characterised by both cognitive decline and epileptic activity.

Seizures in Huntington's disease

Chorea and a subcortical dementia are the classic features of Huntington's disease (HD) associated with trinucleotide repeat expansions in the IT15 gene on chromosome 4. Epileptic seizures may be a feature of HD, particularly in early-onset disease which is more often associated with the finding of parkinsonian rigidity. Seizure frequencies of 30-40% are cited for juvenile HD, defined as onset before age 21 years, as compared to 1-2% in adult-onset cases (Barker & Squitieri, 2009).

Prominent seizures in an adult patient with a HD-like phenotype should prompt consideration of the diagnosis of dentatorubral-pallidoluysian atrophy, in which condition seizures are much more common than in HD (Egawa et al., 2008).

Seizures in vascular dementias and vascular cognitive impairment

Although it might be objected that cerebrovascular disease (CVD) is not a cause of neurodegeneration per se, nonetheless CVD is a recognised risk factor for late-onset epileptic seizures, presumably resulting, at least in part, from disruption of neuronal interconnections. Moreover, there is clearly overlap between CVD and other causes of dementia: most elderly patients with dementia submitted to autopsy have a combination of both AD and cerebrovascular pathology (MRC CFAS, 2001). Vascular dementia and vascular cognitive impairment are recognised to be heterogeneous entities with respect to both pathology and pathogenesis (Wahlund et al., 2009), including vasculopathic and thrombotic disorders.

Patients with stroke who have epileptic seizures may be at increased risk of dementia. In a cohort of stroke patients without pre-existing dementia, the occurrence of epileptic seizures was an independent predictor of new-onset dementia within 3 years of stroke (Cordonnier et al., 2007). It is possible that some of these patients harboured AD pathology pre-stroke, with clinical expression emerging after the stroke. Certainly an interaction between AD and CVD to lower clinical threshold for expression of AD pathology is recognised (Snowdon et al., 1997). Pre-existing dementia typical of AD has been reported to increase the risk of late (>7 days) post-stroke seizures (Cordonnier et al., 2005).

Because of the common neuropathological overlap of CVD and AD, it may be difficult to ascertain the specific contribution of CVD to seizure pathogenesis in mixed cases. In order to study the effects of CVD per se, relatively pure vascular dementias should be studied. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) resulting from mutations in the Notch3 gene may be associated with seizures as part of encephalopathic episodes (Schon et al., 2003).

Management of seizures in dementia syndromes

There is essentially no evidence base upon which to formulate judgements about seizure management in neurodegenerative dementias. Hence management remains empirical, based on seizure type and risk:benefit analysis for each individual patient.

In AD, the neurodegenerative dementia most likely to be complicated with epileptic seizures, anti-epileptic drug (AED) therapy may not necessarily be required since isolated seizures are common (Mendez & Lim, 2003). Moroever, other, treatable, symptomatic causes for seizures may be identified (Lozsadi & Larner, 2006). If AED therapy is indicated, because seizures are frequent or risk of seizure recurrence is thought to be high (as in the presence of fixed or post-ictal focal neurological signs, abnormal EEG, or early age of AD onset), drug choice may be influenced by seizure semiology. However, seizure type in demented individuals is often uncertain, although partial onset seizures with or without secondary generalisation are probably the most common (Mendez & Lim, 2003). Since AD prevalence increases with age, factors influencing drug clearance and protein binding such as renal and hepatic function also need to be considered, as does polypharmacy and the risk of drug interactions. Use of AEDs with known cognitive and behavioural adverse effects (e.g. phenobarbitone, primidone, phenytoin, topiramate) may be considered undesirable in dementia syndromes.

2010
Vol.1
No. 1:3
doi: 10:3823/302

The response to AED therapy in dementia is not well known. A 79% response rate was reported in a retrospective study of dementia patients with epilepsy although one third of patients had dose-related side effects (Rao et al., 2009). A prospective observational study of levetiracetam in 25 patients with advanced AD and new onset seizures reported good seizure control, with 72% of patients seizure free for at least one year, but 16% of patients discontinued medication because of poor tolerability (Belcastro et al., 2007).

Discussion

Although the clinical observation of seizures in dementia syndromes, particularly AD, is long established, there have been few systematic studies of seizures in these conditions. Mechanisms underlying seizure pathogenesis are unresolved, but recent studies raise the possibility, particularly in AD and possibly in prion disease, that seizures are related to the same pathogenetic processes responsible for cognitive decline, and hence are an integral part of disease phenotype, rather than being simply epiphenomena consequent upon non-specific neuronal loss. Treatment of seizures in dementia syndromes remains entirely empirical. However, future classification of dementia disorders according to pathogenesis (e.g. amyloidopathy, tauopathy, synucleinopathy, TDP-43 proteinopathy, prionopathy) may facilitate understanding of seizure pathogenesis and ultimately guide treatment decisions. Since epileptic seizures may be regarded as part of the AD phenotype, randomised controlled trials of AEDs which might address both symptomatic seizure control and modify pathogenic pathways, such as sodium valproate (Qing et al., 2008) and lacosamide (Larner, 2009), might be considered.

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2010
Vol.1
No. 1:3
doi: 10:3823/302

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2010
Vol.1
No. 1:3
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