The Prevalence and Clinical Features of Epileptic Seizures in a Memory Clinic Population

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Abstract:

Purpose: To determine the prevalence and clinical features of epileptic seizures occurring in a memory clinic population

Method: We recruited patients receiving a diagnosis of dementia or mild cognitive impairment (MCI) at a regional memory clinic. We interviewed patients and informants using a proforma designed to elicit symptoms suggestive of epilepsy. Informants also completed the Clinical Dementia Rating Scale (CDR) and the Cambridge Behavioural Inventory- Revised (CBI-R). Patients underwent cognitive testing using the Addenbrooke's Cognitive Examination – III (ACE-III). We also recruited an age- and gender- matched control group with no history of cognitive impairment. Diagnoses of dementia/MCI were checked against current diagnostic criteria.

Results: We recruited 144 patients (mean age 77.98, mean ACE-III 74.16, 124 with dementia, 20 with MCI). We diagnosed epilepsy in 25.7%: probable in 12.5% (17 with dementia, 1 with MCI), possible 13.2% (18 with dementia, 1 with MCI). Seizure features included altered responsiveness, speech/behavioural arrest, oral/pharyngeal automatism, olfactory/gustatory aura, focal motor seizure, other sensory phenomena (including hallucination), and amnesia on waking. Epilepsy prevalence was significantly increased in the dementia and MCI group vs controls (p=0.004). Cognitive performance in the patient groups did not distinguish those in whom epilepsy was suspected from those in whom it was not. Patients in whom epilepsy was suspected were more impaired on informant completed measures of daily function.

Conclusions: The prevalence of epilepsy is increased in dementia. The seizures are often subtle and easily missed. The presence of epilepsy predicts more severe impairment in the activities of daily living.

Key Words: Epilepsy, Dementia, seizure prevalence

Introduction

Patients with dementia are at risk of developing epileptic seizures (1-5). This was reported by Alzheimer himself in his description of Johann F in 1911 (6). However, the extent to which this risk is increased has been disputed and remains unclear (7). Estimates of the prevalence of epilepsy in patients with Alzheimer's disease range from 0.5% (8) to 64% (9). Moreover, whilst conventional wisdom has considered epilepsy to be a feature of advanced disease in these patients (10), more recent evidence has reported patients developing epilepsy early in the course of clinical disease (11) and in some cases even before a diagnosis is made (12). In addition, studies have suggested that epileptic seizures may contribute to and even accelerate the cognitive decline seen in these patients (13). Finally, whilst several studies have looked at the prevalence of epileptic seizures in Alzheimer's disease, these studies have typically focussed on tertiary specialist centres, with a higher proportion of patients with early onset Alzheimer's disease, in which the increased prevalence of epileptic seizures is well-described (14, 15), and complex cases, in which features such as seizures, are again likely to be more common (16). We aimed to use the memory clinic, the most common setting for dementia diagnosis in the UK, as the pool for our participants, in order to provide a real-world and clinically relevant estimate for the prevalence of epilepsy in this population.

In the UK, the diagnosis of dementia, or of mild cognitive impairment (MCI) is usually made at a memory clinic in secondary care. These clinics have been established throughout the UK following a governmental initiative, and provide a rapid, 'one-stop', method of assessment for patients with memory disorders (17, 18) . Patients, typically referred by their general practitioner (GP), attend alongside a reliable informant (most commonly their spouse) and

undergo assessment by several members of the mental health team, yielding a cognitive profile and diagnostic formulation.

In the Presentation of Epileptic Seizures in Dementia (PrESIDe) study we investigate the prevalence and characteristics of epilepsy in a cohort of memory clinic patients. While this does not strictly provide a community-based sample, the National Institute for Health and Care Excellence (NICE) recommends referral to the memory clinic for all patients in whom dementia is suspected (19). As the memory clinic is the first contact patients will have with a specialist clinician in this field, determining the prevalence of epilepsy in this population is of great clinical value.

Given that seizures occurring in the context of dementia can be subtle, and are probably underreported (12, 20), we designed a proforma to elicit symptoms suggestive of seizures for use in interviews with patients and informants (appendix 1). We used accepted current diagnostic criteria to confirm dementia diagnoses. The main aims of our study were therefore to establish the prevalence of epilepsy in a relatively unselected group of patients with MCI/early dementia and to determine their clinical features. We compared the prevalence of epilepsy in the patient group with the prevalence assessed using the same approach in a group of healthy participants matched for age, sex and years of education. Our findings underline current uncertainties regarding the appropriate management of epilepsy occurring in early dementia.

Materials and Methods

Participants

144 patients and 80 age- and gender-matched control participants were recruited to the study. Patients were identified through their attendance at the memory clinic in Exeter, Devon, UK, and were considered eligible for inclusion if a diagnosis of MCI or dementia (of any kind) was made at their memory clinic assessment. All eligible patients who had attended the memory clinic over an 18 month period (January 2016 - June 2017) and who had consented to take part in research were approached. The control group was identified with the help of the Exeter 10,000 study. The Exeter 10,000 (EXTEND)/Peninsula Research Bank (PRB) was set up to collect and store genetic, biological, clinical and lifestyle information on 10,000 adults individuals living in Exeter. This has established a sampling framework from which individuals can be selected, on the basis of (genetic/non) genetic predisposition/protection factors, to be invited for further research into the mechanisms of health and common disease. It is managed through the NIJR Exeter Clinical Research Facility (Exeter CRF) https://crf.exeter.ac.uk/web/content/exeter-10000-peninsula-research-bank. In the control group there was no reported history of cognitive impairment, and these patients had not previously been seen by the memory clinic. A preceding history of epilepsy was not an exclusion criterion. We used regional postcodes as a surrogate marker of socioeconomic status between the control and study populations.

Interview

Patients with a diagnosis of MCI or dementia were interviewed at their own home, in the company of a reliable informant, who was subsequently seen independently. The interview was guided by a standardised proforma designed for this purpose. Validated diagnostic criteria (21-24) were used to specify the clinical dementia diagnosis.

Background demographic data were gathered. Subsequent questioning focussed on three main areas 1) past medical and family history 2) history of dementia / MCI symptoms and 3) presence of clinical features suggestive of epilepsy.

Cognitive testing using the Addenbrooke's cognitive examination – version III (ACE-III) (25) was performed. This examination had been performed on all participants at the time of their memory clinic appointment. It was repeated at the time of initial study assessment after a mean delay of 235.5 days (SD 106.5 days). Diagnostic criteria state that individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers, although these ranges are for guidance rather than cut-off scores (21). For this study we chose to use the memory component of the ACE-III for this purpose. In keeping with diagnostic criteria MCI was defined as a score >1 standard deviation below the mean in this test, but with preservation of independence in functional abilities. Informants were asked to complete two further questionnaires: the Cambridge Behavioural Inventory - Revised (CBI-R) and the Clinical Dementia Rating (CDR). These validated questionnaires were chosen to provide an additional insight into the impact of the cognitive impairments experienced by our study participants, as witnessed by those closest to them (26, 27). The CBI-R has been shown to effectively discriminate between different dementia subtypes (28). The CDR- sum of boxes (CDR-SOB) is a summated score which incorporates the different domains examined in this questionnaire.

Expected seizure phenotypes in this population were identified from reviewing previous literature comprising generalised tonic-clonic seizures, behavioural arrest, amnesia on waking, olfactory hallucinations, abnormal movements including myoclonus, and the presence of a clear aura preceding the abnormal episode (11, 29). Patients were categorised

in to one of three groups: epilepsy probable, epilepsy possible, no clinical evidence of epilepsy (NCEE). The criteria for this categorisation are outlined in table 1.

Cognitive performance of the control group was assessed using the ACE-III, and the same seizure identification questions were asked to each control participant and a reliable informant to determine the prevalence of epilepsy.

Statistical analysis

Between-group analysis of demographic features, cognitive test performance and informant completed questionnaire scores was performed using independent sample t-tests. Chi-square testing was performed to compare proportions between participants and controls. Multiple linear regression analysis was performed to assess the relationship between dependent and independent variables. A Bonferroni correction was made to adjust for multiple comparisons. Statistical significance was judged as any p-value <0.05. IBM SPSS statistics 22.0 and STATA were used to perform data analysis.

Ethical approval for this project was awarded through the Integrated Research Application System (IRAS) and provided by the London – Bromley Research Ethics Committee.

Results

<u>Demographic characteristics</u>:

144 patients were recruited to the study: 53% male, 47% female. The age at onset of memory symptoms varied from 51yrs to 91yrs (mean 75.10, SD 7.07). The age at memory clinic assessment ranged from 57yrs to 94yrs (mean 77.98, SD 6.75).The demographic features of the memory clinic sample are similar to the memory clinic population (n=300) from which

they were recruited: age - mean 76.82 (SD 9.94), 52% male, 48% female. The standard deviation for the memory clinic population is greater than the study population. This is a result of younger patients being more likely to be excluded (no diagnosis of dementia or MCI made) and older patients less likely to consent to study participation when contacted. Of the 156 patients who were initially contacted but did not take part in the study, 102 (65.38%) declined involvement. 43 (27.56%) patients did not respond to follow-up telephone calls to discuss their potential involvement. 11 (7.05%) patients were not appropriate for inclusion.

The control group (n= 80) was well-matched for gender (55% male, 45% female) and age (mean= 77.39, SD = 4.31) with the patient group. The size of the control group was determined through a calculation in order to detect a statistically significant difference (α level P=0.05, power 80%). There was no significant difference between the control group and the study group in terms of total years of education. The only significant difference between the study group and the control population was, as expected, cognitive function as measured by the ACE-III examination (table2).

The memory clinic cohort and the control group were also compared in terms of medical comorbidities. No significant differences between these groups were identified (table 3).

Diagnosis:

102 participants were diagnosed with Alzheimer's disease. Of the remainder, 20 received a diagnosis of MCI, 16 a diagnosis of vascular dementia, 4 dementia with Lewy bodies, 1 FTD and 1 posterior cortical atrophy (PCA) variant of AD. At the time of memory clinic assessment the duration of memory symptoms reported by the patients ranged from 6 months to 120 months (mean 31.9, SD 15.4).

Cognitive testing:

A decline in ACE-III scores was seen in all three seizure categories between their initial memory clinic assessment and study interview. The difference between these two time points was significant only in the no clinical evidence of epilepsy group. The difference in the size of decline between the different groups was not significant. One participant (EX035) had a mini-mental state examination (MMSE) performed at the time of their memory clinic appointment, instead of an ACE-III. This participant has therefore been excluded from comparisons of cognitive test scores.

Seizure Prevalence:

We reached a diagnosis of epilepsy in 37 (25.69%, 95% CI 19%-33%) patients (table 4) using the diagnostic criteria described above. 18 patients (12.50%) were categorised as 'Seizure Probable', 19 (13.19%) as 'Seizure Possible' and 107 (74.31%) as 'No Clinical Evidence of Epilepsy' (NCEE). The rate of 'Seizure Probable' participants is significantly higher than in the control population, in whom only one patient was found to have a remote history of epilepsy while none of the remaining 79 control patients were found to have any of the seizure features investigated in this study ($\chi^2(1, N=224)=8.347$ ($p=0.004$) .

This suspicion of epilepsy had been documented in 10 patients prior to their assessment as part of the study. In the remaining 27 there w no previous evidence that epilepsy had been suspected.

This statistically significant difference in prevalence between groups was also seen upon restricting the group only to patients who received a diagnosis of Alzheimer's disease

(102/144). Of these patients, 29/102 (28%) reported features suggestive of epilepsy, (χ^2(1, N=182)=23.45 (p<0.001)).

There was a significantly higher rate of epilepsy in the MCI group than in the control group when combining probable and possible cases (χ^2(1, N=100)=4.17 (p=0.041).

In patients with a primary diagnosis of vascular dementia 3/16 patients (18.75%) were included in the epilepsy probable group and 1/16 (6.25%) were included in the epilepsy possible group. This represented a significant increase compared to controls for the combined probable and possible patients (χ^2(1, N=96)=15.08 (p<0.001).

Seizure features:

The most common seizure type was impaired awareness / behavioural arrest seizures. This was seen in 15 of the Probable Epilepsy group (83%). 4 patients in this group (22%) experienced generalised tonic-clonic seizures. A range of further seizure features were also seen (table 4). These included motor automatisms, sensory abnormalities (including olfactory hallucinations), amnesia on waking, and focal onset motor seizures.

Combining the epilepsy possible and epilepsy probable groups, the mean reported duration from the onset of memory symptoms until the first seizure, based on informant accounts was 12.2 months (median 18 months, range -96 to 60, excluding two patients with onset of epilepsy in childhood) (Figure 1).

The results of the informant completed questionnaires (CBI-R and CDR questionnaires) are shown in table 5, revealing a significant difference in both measures when the epilepsy

probable group (and the combined probable and possible group) is compared with the NCEE group.

Medication:

Of the 144 patients in our study 40 were taking a medication (Donepezil (29), Rivastigmine (7) or Memantine (4)) specifically licenced for the treatment of dementia in the UK. There was no significant difference in the prevalence of the use of these medications between the combined epilepsy group (11/37, 29.7%) and the NCEE group (29/107, 27.1%). Six patients in the epilepsy probable group were prescribed an anti-epileptic medication at the time of assessment (Lamotrigine (2), Levetiracetam (2), and Sodium Valproate (1), Phenobarbitone (1)). This group included the two patients with seizures since childhood, and one patient who had experienced seizure onset 8 years prior to the onset of memory symptoms. Of the remaining patients, 2 had experienced generalised tonic-clonic seizures and one had experienced focal onset seizures following a stroke. In addition, one patient in the NCEE group was currently prescribed Carbamazepine for the treatment of neuropathic pain. No other participants were on anti-epileptic medication for any other indication. Therefore 66.67% patients in the probable group and 100% in the possible epilepsy group were not on anti-epileptic treatment at the time of the study.

Discussion

The prevalence of epilepsy is increased among patients with dementia but the extent of this increase remains controversial. We have identified a prevalence of clinically diagnosed epilepsy of between 12.5 and 25.7% in a memory clinic population with MCI and early dementia, using a standardised proforma to elicit symptoms suggestive of epilepsy in

interviews with patients and their carers. To our knowledge, this is the first UK based study that has recruited a population of participants from the memory clinic, with all dementia diagnoses, and aimed to investigate the prevalence of epilepsy in this group.

The seizures were predominantly subtle and non-convulsive, and started on average less than two years after memory symptom onset. While cognitive performance did not differ between patients with or without epilepsy, patients with epilepsy were more impaired on standard measures of behavioural performance assessed by informant interview. Given suggestive evidence (11, 13, 30) from other work that epilepsy can accelerate cognitive decline in patients with dementia, these results may challenge current practice which tends to overlook subtle seizures in patients with dementia and to be reluctant to treat epilepsy given the potential side-effects of anti-epileptic medication (31-33). We consider each of these main findings in turn before considering limitations of our study.

Prevalence:

The prevalence of epilepsy in our memory clinic sample was significantly increased when compared to a population without cognitive impairment matched for age, gender and education. This increase was seen for the memory clinic population as a whole, but also for patients with Alzheimer's disease, vascular dementia and MCI when these conditions were considered separately. Patients with seizures did not differ from those without epilepsy in age at dementia symptom onset, duration of symptoms or cognitive test score. Epileptic seizures were not a feature of advanced disease in these patients.

Clinical Features:

The seizures in our patients were often subtle and easily missed. Brief periods of unresponsiveness, behavioural arrest and staring were common. In many cases, these features had been noted previously, but had been considered a feature of the underlying dementia, rather than as evidence of epilepsy. The features described in our participants are in keeping with previous research in this area which has shown that only a minority of patients experience generalised tonic-clonic seizures (13, 20, 30). Moreover, it is in keeping with the reported semiology of temporal lobe epilepsy, where more subtle features such as staring, blinking and behavioural arrest are frequently described, particularly in more elderly populations (34-36). The spectrum of mesial temporal lobe epilepsy also includes transient epileptic amnesia (TEA), in which seizures are characterised by brief periods of amnesia during which other cognitive functions remain intact (37, 38). It is possible that seizures of this nature also occur in patients with dementia, but would be particularly difficult to identify given the baseline cognitive deficits in these patients. However, the presence of olfactory hallucinations, and episodes of amnesia on waking in our group, which have frequently been described in patients with TEA (39, 40), suggests that seizures similar to those described in TEA can occur in patients with dementia, as previously reported (41, 42).

Cognitive Decline:

The ACE-III examination scores for the group as a whole were significantly lower at the time of study assessment than at memory clinic baseline. In all three seizure sub-groups there was a drop in the ACE-III score between baseline memory clinic assessment and study assessment. This drop was largest in the epilepsy possible group, but only reached statistical significance in the large NCEE group, probably as a result of its size and the resulting statistical power to detect such a change. The differences between groups was not significant at either time point.

However, the CDR-SOB was significantly higher in the epilepsy group than in the NCEE group. This difference suggests that seizures in these patients are associated with accelerated impairment in terms of activities of daily living and an increased disease burden as identified by the people spending the most time with these patients – typically their spouse. This score, which reflects observations by carers over a number of weeks or months is likely to be more sensitive to global impairment than a single cognitive test result (27, 43, 44).

It is unclear from our data whether the seizures in our patients are a cause of more severe impairment – i.e. lead to accelerated decline – or reflect a more severe form of disease which independently causes accelerated functional impairment with epileptic seizures as an incidental feature, However, numerous studies, looking at mouse models of dementia have investigated this question (45-47). These studies report that the pathological changes seen in Alzheimer's disease are associated with neuronal hyperexcitability which increases the potential for epileptic seizures to occur (45, 48-50). In addition further studies have shown that the epileptic seizures seen in these models facilitate the more rapid and anatomically diffuse spread of Alzheimer's pathology which has been associated with an accelerated cognitive decline in these animals (51, 52). Current randomised controlled trials investigating the effects of anti-epileptic medication in patients with dementia and epileptic seizures, will shed further light on this issue (53, 54).

Implications

It is clear that patients and their carers are rarely aware themselves of the risk of epileptic seizures in dementia and have not been prepared to recognise them if they occur. Providing education about the risk of epilepsy for those caring for people with dementia would help to

identify patients with seizures earlier in the clinical phase of their illness and therefore increase the window of opportunity to provide anti-epileptic treatment.

Limitations:

We diagnosed probable and possible epilepsy in this study based on clinical grounds. Whilst the clinical history obtained in these patients is suggestive of epileptic seizures and in keeping with the seizure phenotypes described elsewhere (11, 13) it would be beneficial to have confirmatory evidence, provided by EEG recordings, of the presence of abnormal epileptiform activity to support this diagnosis. However, as has been shown in previous work (7, 55), standard clinical EEG is not a sensitive means of identifying abnormalities in these patients. Research has shown that more prolonged EEG recordings, especially those that involve overnight recordings and sample sleep, are particularly valuable in these patients (56). In our study, participants were routinely asked if they had had an EEG performed, only two patients recalled this. In both cases the reports of these recordings were reviewed. In one case clear epileptiform abnormalities were identified (Left fronto-temporal (EX138)). In the other case no clear abnormalities were reported (EX149).

We diagnosed and subtyped dementia in this study on clinical grounds, supporting the diagnosis of MCI using standard neuropsychological testing. Whilst recent developments in the use of biomarkers have shown these to be useful in confirming diagnoses, clinical decision making based on the history provided and the findings on examination remains a sensitive means of reaching a diagnosis in these patients. This is the approach advocated by the diagnostic criteria for AD which emphasise that the core clinical criteria provide very good diagnostic accuracy and that whilst biomarker evidence 'may increase the certainty' that the diagnosis is due to AD pathology they are often uninformative when a diagnosis of probable

AD is made (23). The utility of these biomarkers increases when the diagnosis is less certain, in atypical cases of dementia, in the earlier stages of disease, or in predicting the likelihood of progression from MCI to dementia (57-59).

We report the prevalence of epileptic seizures in patients recruited from a regional memory clinic. Given that all patients in whom there is a suspicion of dementia should be referred to this service, our results should also reflect prevalence rates for patients with MCI or dementia in the community more widely. However, as this is not a true community-based study our findings should be extrapolated with caution. Likewise, whilst the memory clinic could be considered to represent patients who are early in the course of clinical disease, we have shown a wide variation in both the duration of memory symptoms prior to assessment in the memory clinic and the cognitive performance as measured by ACE-III testing at this time and therefore our group does not definitively represent the prevalence of epilepsy in patients with MCI or early dementia. We can, however, be confident that the patients recruited to this study are representative of the memory clinic population more broadly, in terms of age, gender and cognitive function.

As indicated above, our data cannot answer the question of whether dementia-related seizures accelerate cognitive or behavioural decline. There is suggestive evidence that this may be so (13) and current trials will help to answer the question of whether anti-epileptic medication is beneficial (53, 60). At present many clinicians are reluctant to prescribe anti-epileptic medications in these patients due to concerns with their cognitive side effects, compliance, interaction with other medications and potential for commonly used medications to lead to problems with sleep. In our study the only patients currently prescribed anti-epileptic medication were those with seizure onset during

childhood/adolescence, with a long interval (8 years) from the onset of seizures to the onset of memory symptoms, or who had had witnessed generalised tonic-clonic seizures, or focal onset seizures following a stroke.

Conclusion

The prevalence of epileptic seizures is increased in patients diagnosed with MCI or dementia. The onset of seizures in our patient group occurred within two years of the reported onset of memory symptoms. At the time of seizure onset, patients with seizures were not different to those without seizures in terms of age or cognitive test score, but were significantly more impaired on measures of the global impact of dementia.

Highlights:

- The Prevalence of epileptic seizures in dementia is between 12.5 and 25.7%
- At initial assessment cognitive scores did not differ in patients with epilepsy from those without
- Patients with epilepsy were more disabled as measured by informant completed questionnaires (CDR, CBI-R)

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