Identifying patterns in signs and symptoms preceding the clinical diagnosis of Alzheimer's disease: Retrospective medical record review study and a nested case -control design

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Abstract

Objective

Evidence suggests that individuals with Alzheimer's disease (AD) are often diagnosed in the later stages of their disease with a poor prognosis. This study aimed to identify patterns in signs and symptoms preceding the clinical diagnosis of AD to suggest a predictive model for earlier diagnosis of the disease in the primary care.

Design

A retrospective medical record review; nested case control design.

Participants

Participants included one hundred and nine patients from three general practice (GP) surgeries in Milton Keynes and Luton Clinical Commissioning groups (CCG) (37 cases with AD and 72 controls without AD).

Main outcome measure

A retrospective analysis using the logistic regression of the presence of signs and symptoms before the diagnosis of AD was attained. Identification of the timing and sequence of appearance of these presentations as first reported before the clinical diagnosis was measured.

Result

Episodic memory with an odds ratio of 1.85 was the most frequent presentation, documented in 1.38% of the controls and 75.6% in cases. Auditory disturbance with an odds ratio of 3.03, which has

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not previously been noted except in the form of auditory hallucination, could have a diagnostic value.

Conclusion

Auditory disturbance, which occurred mostly in the Caucasian females, could discriminate individuals with AD from those without. The symptom, which presented up to 14.5 (mean time) years prior to clinical diagnosis, was identified in Caucasians and mixed race individuals only.

Strengths

- The study demonstrates that auditory disturbance could allow an earlier diagnosis of AD in Caucasian females.

- Episodic memory was confirmed as being frequently noted in AD patients prior to a clinical diagnosis as per previous publications.

- This study supports the development of a scoring system for the earlier diagnosis of AD.

- The data used was free from the confounding effects of misinformation, as this was written at the point of collection, thereby benefitting from the use of GP data that is diversified, reliable and valid.

Limitations

- Limited sample size that will not allow for generalisation of less frequent observations due to their low prevalence in case notes.

- Randomisation was not achieved; however, the best available non-randomisation which is consecutive sampling was used.

- Patterns identified were in LOAD, the baseline could vary with other geographical areas.

Introduction

AD remains the highest cause of mortality in individuals 65 years and above, displacing ischaemic heart diseases and accounting for 12 % of registered deaths in 2016 (1). Part of its high associated morbidity can be accounted for because the disease is diagnosed late. The lack of a distinct and AD specific pattern of signs and symptoms has contributed to the late diagnosis and misdiagnosis of the disease leading to its' confusion with other conditions. The current diagnostic criteria (2) is based on biomarkers and situated in the tertiary institutions. Results of several studies (3; 4; 5) have shown how important the pattern of signs and symptoms are in aiding the diagnosis of the disease. Patterns in signs and symptoms have been used to develop predictive models in other diseases, enabling earlier detection and the diagnosis of diseases (6; 7; 8). Yet studies on the early signs and symptoms of AD are limited in content that will help to identify AD in the early stages, the stage at which clinical intervention would work best (9; 10; 11). The manifestation of AD includes a wide range of neuropsychiatric symptoms (NPS); the association between these symptoms and AD have widely been reported elsewhere (12; 13; 14; 15). The type and severity of these presentations have also been described (16; 17), indicating their importance in discriminating AD from other diseases (18). However, there is no clear pattern in the timing and sequence of these signs and symptoms in the earliest stages of AD (19) that could support an earlier diagnosis of AD in the primary care setting. Given the rise in morbidity and mortality of AD and the devastating effect of worsening cognitive impairment, providing GPs with a predictive model for earlier detection and timely intervention is essential. This would minimise the occurrence of misdiagnosis, which is often emphasised by the critics of early diagnosis (20), who call for "research principle of caution" that supports a restrictive disclosure, as the benefit of early assessment outweighs the potential adverse effect. The model will also support the current diagnostic criteria. Even though, the clinical value for therapeutic options for dementia remains questionable and

hinder the adoption the early diagnosis in PC (21), early diagnosis of AD would enable deliverable timely interventions including lifestyle changes such as physical exercise, healthy diet, cognitive stimulation and disease-modifying therapy, which have been shown to have significant impact on patients with 11% fewer cases of AD and reduce institutionalisation costs by 33% (22; 23).

Methods

Study participants, recruitment and logistics.

This study is a retrospective pooled analysis of signs and symptoms that appeared on average 27 years preceding the clinical diagnosis of AD in notes of 109 adults patients (cases n=37 and control n=72). Patients diagnosed between the year 2006-2016 with LOAD (FOO.1*) and controls in three general practice (GP) surgeries in Milton Keynes and Luton. These surgeries are integrated primary health care that served about 7,000- 30,000 patients. From these clinics, consecutive sample of cases were selected (all the prevalence in these surgeries), who had been evaluated by the GPs with mini-mental state examination (MMSE) (a score of 4-29 was recorded) and the neuropsychiatric inventory (NPI). These individuals were subsequently diagnosed with AD in the memory clinics, using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA), diagnostic criteria for "probable" AD dementia. They all had the same amount of follow-up. Those without the evaluation and diagnosis of AD were excluded. Controls were selected based on gender, age and location.

Ethical consideration

Ethics protocol was observed following the approval from National Health Service Research Ethics Committee (NHS-REC), London, Health Research Authority (HRA), GP surgeries included and the University (UREC) of Bedfordshire Research Ethics Committee, which stressed and ensured that non-identifiable data was collected and processed.

Data management

The task of managing the data was undertaken by extracting the data from the medical record into a case report form, which was then transferred to the spreadsheet for analysis. The patients' consultation and diagnosis; signs and symptoms; memory test results and confounding factors as well as covariates such as age, gender, ethnicity and comorbidities were profiled. Comorbidities were diagnosed separately from AD and met the standard measurement of index of coexistent disease (ICED), while making sure that the timing and sequence of the presentation of the signs and symptoms were collected.

Signs and symptoms

This study sets out to identify patterns in fourteen signs and symptoms (apathy, agitation, anxiety, anosognosia, aberrant motor behaviour or the inability to sit still (irregular movement behaviour), acalculia, alexia, anomia, disinhibition, dysphoria, irritability, hallucination, olfactory disturbances and weight loss) previously identified as early presentations of the disease (24; 13). We also wanted to identify novel signs and symptoms not yet identified in the literature. These signs and symptoms were presented by the patients and confirmed by the GP during their consultations. A computation was made on the timing and sequence of the presentations, i.e from the time of reporting to the official diagnosis of the disease. The analysis was undertaken on the frequency of four or more individual signs and symptoms for the cases.

Data analysis

The main outcome measure was the patterns regarding the sequence and timing of signs and symptoms associated with AD, measured with the OR and associated 95 % confidence intervals (CI). The researcher initially estimated the prevalence and distribution of these signs and symptoms in both groups (cases: patients with AD and controls: age and gender-matched individuals without AD) after the data was cleaned and variables checked for accuracy. The timing and sequence of signs and symptoms before the diagnosis was established as reported by the patients. The data analysis was undertaken with SPSS and MedCalc software. The binary logistic regression was the standard of measurement. The OR and 95 % CI determined the association of the signs and symptoms to AD. The analysis was undertaken for gender, ethnicity and locality for all the samples while reporting the OR and p values.

Results

Descriptive analysis

The ethnicity of participants (**Table 1)** indicated that majority of individuals were whites (63.3 %), closely followed by mixed race with 22.9%. However, the ethnic minority including Asians, Africans, Caribbean and Middle Eastern ethnic groups constituted 13.8%. The demographic result could be due to the fact that these towns are mainly Caucasian with a diverse ethnic minority. The socioeconomic characteristics of the patients could not be established, as this information was not completely collected at baseline; 70.6 % of the sample educational status was not declared, 8.3 % were retirees and 21.1 were a mixture of professionals including consultant, pharmacist, engineers, nurses, carers and a dentist. The missing data were missing completely at random and was ignored.

Table 1 Characteristics of the sample including cases and controls.

Variable	Cases N (%)	Controls N (%)
Males	12(32.4)	32(44.4)
Female	25(67.6)	40(55.6)
Whites	25(67.6)	53(73.6)
Non-Whites	12(32.4)	19(26.4)
AAD(age at diagnosis)		
60-65	0(0.0)	1(1.39)
65-70	4(10.8)	27(37.5)
71-80	17(45.9)	26(36.7)
81-90	12(32.4)	14(19.4)
91-100	4(10.8)	4(5.5)

The majority (65) of the samples were females representing 59.6 % of the total sample, with 39.4% within 71-80years old.

The overall prevalence of these symptoms and signs were higher in cases than controls (**Table 2**), however, individually, there was heterogeneity in their prevalence. There was a higher prevalence of these symptoms among white women especially those between the ages of 70-55 and 80-85 years (16.21 % respectively). Episodic memory was the symptom with the highest prevalence and more frequent in the cases (75.6 %) than controls (1.38 %). This was followed by depression with 13.76 % in the entire sample.   Symptoms that were identified in cases only included abdominal pain (8.1 %), agoraphobia (2.7 %), dehydration (2.7 %), excessive sweating (2.7 %), hallucinations (8.1 %), poor appetite (2.7 %) and tiredness (5.4 %). Among the previously identified signs and symptoms of AD, only anxiety, depression, episodic memory loss, hallucinations, irritability and weight loss were identified in the study, out of which irritability was only identified in one sample of the control group (**Table 2**).

Table 2 Prevalence (%) of the signs and symptoms in cases and controls.

Signs and symptoms	Cases		Controls	
	N	%	N	%
Episodic memory loss	28	75.6	1	1.38
Depressed mood	7	18.9	8	11.1
Auditory disturbances	8	21.6	6	8.33
Anxiety	2	5.40	3	4.16
Irritability	1	2.70	1	1.38
Hallucinations	3	8.10	0	0
Olfactory disturbances	0	0	1	1.38
Other symptoms previously not associated with AD				
Constipation	2	5.40	2	2.77
Headache	3	8.10	2	2.77
Indigestion	2	5.40	2	2.77

| Weight loss | 2 | 5.40 | 2 | 2.77 |

Among the previously identified signs and symptoms of AD, only anxiety, depression, episodic memory loss, hallucinations, irritability and weight loss were identified in the study, out of which irritability was only identified in one sample of the control group.

Others signs and symptoms identified with considerable frequency included backache, headache, constipation and indigestion. However, agoraphobia, dehydration, dizziness, drowsiness, excessive sweating, flatulence, poor appetite and leg cramp, previously not identified with AD, were identified in single measures in the cases respectively; their frequency was not sufficient to be included in the statistical analysis. Out of the symptoms identified in the cases, episodic memory was presented as the first symptom in 16 (43.2 %) of the 37 cases, auditory disturbances in eight (21.6 %), depression in five (13.5 %) and headache in one (2.7 %).

Individual symptoms and signs in cases

The mean in the timing of the signs and symptoms reporting to diagnosis in cases (**Table 3) showed that** depression had the highest mean in cases (mean=16.4 %) and was not associated with medication or comorbidity. However, the symptom was presented in the control group with a mean time of 12.5 years before the pseudo-diagnosis (non-AD conditions) with a higher prevalence (53.3 %) in this group than the cases (46.3 %).

Table 3 Years before the diagnosis of signs and symptoms in cases and controls

Symptom	Mean in years (SD) cases	Mean(SD) in years (SD) controls	T-test	P-Value
Anxiety	1 (0)	17.3 (15.5)		0.7
Auditory disturbance	14.5 (8.94)	4.8 (3.1)	0.029	0.05
Backache	9.25 (10.7)	6 (2.6)		0.19
Depression	16.4 (21.1)	12.5 (17.8)		0.2

Episodic memory	3.48 (3.42)	11 (4.3)	0.040	0.0001
Headache	26.8 (36.1)	5.5 (4.9)		0.2
Weight loss	0.5 (0.14)	3 (2.82)		0.0001

The table shows the means in years of the symptoms, with depression, having the highest mean in years of 16.4 (SD=21.1) in cases and anxiety with 17.3 (SD=15.5) in the control group. The p-value for episodic memory loss was 0.0001 and auditory disturbance p=≤0.050.The p-value for weight loss was significant, however, the sign was observed less than a year before diagnosis.

Auditory disturbance which has not been fully identified with AD was the third symptom sequentially, presented with a mean time of 14.5 years before the diagnosis of AD with a prevalence of 21.6 % in this group. The symptom was, however, presented 8years before diagnosis in the control group with a prevalence of 16.2 %. Backache followed with a mean of 9.2 % and a prevalence of 10.5 %.

Episodic memory, which is the most common symptom linked with AD especially LOAD, was presented six years before diagnosis with a mean of 3.4 % and had the highest prevalence in this group. Hallucination was next and presented three years (mean=1.8 %) before the diagnosis of AD.

Constipation and tiredness were presented five years respectively before diagnosis; however, tiredness was not associated with the control group.

The adjusted analysis further indicates a significant association between episodic memory and AD (OR 2.57 95%CI 1.44-4.60), with 46.4 % of the prevalence among the white females and 17.8 % for white males (**Table 4)**. The table also indicates that individuals with auditory disturbances are 79 % at increased odds for associating with AD, with a p-value of ≤ 0.050.

Other signs and symptoms with increased odds but not very significant were abdominal pain and hallucination, with p values of ≤ 0.07 respectively. The table also shows that individuals with depression had 54 % increased odds of association with AD, however, with p values > than 0.1.

Table 4 Signs and symptoms reported in relation to AD.

Variable	**Model 1**	**Model 2**	**Model 3**
	OR (95% CI)	OR (95%CI)	OR (95%CI)
Auditory disturbance	3.03*** (0.96-9.53)	2.12*** (0.90-5.03)	1.79*** (0.84-3.82)
Depression	1.89*** (0.61-5.62)	2.71*** (1.48-4.96)	2.54*** (1.41-4.56)

Episodic memory   22.0*** (26.7-182.)   2.71 ***(1.48-4.97)   2.57*** (1.44-4.60)

Model 1: crude: model 2 adjusted for gender; and model 3 adjusted for gender and ethnicity*.
The crude model considers how individual symptom/sign is associated with AD while ignoring other variables; model 2 adjusts to incorporate gender, while model 3 incorporates ethnicity as a covariate. ***: p<0.001

Ethnicity, gender and geographical location have an influence on the outcome of cases (**Table 4**). The Wald statistics and the all-important OR Exp (B), shows that the variables were not very significant or positive in the overall effect. However, when controlling for gender and auditory disturbance, the OR indicates that the female gender has a twofold (2.12) increased odd more likely to be associated with AD compared with men. Even though the Wald statistic was significant for Luton locality, the OR was not significant and could be accounted for due to the limited sample size. However, for the other ethnic groups, the result was insignificant.

The majority of these signs and symptoms were diagnosed at age 70-80 in both the cases and controls, followed by those within 80-90-year-old age group**.** When considering the sequence of the appearance of the signs and symptoms in years prior to a diagnosis of AD, it was found that headache was the first symptom to be reported averagely 26.8 years prior to diagnosis. This was reported as early as 14 years into the life of the patient. In comparison to the control group, however, the symptom was presented 11 years before the pseudo (non-AD conditions) diagnosis. The symptom was followed by depression in 16.4 years, auditory disturbance 14.5 years, backache 9.25, hallucination 5 years and episodic memory 3.48 years before diagnosis averagely (**Table 3)**.

When considering episodic memory and gender, the result indicates that 62 % of those cases in which episodic memory loss was recorded, were females**.** Only 3.4 % of the prevalence of the symptom was recorded in the control group. The distribution of auditory disturbances in the sample was found to be 85.7 % in females, with 75 % in the cases, indicating a female predilection for developing the disease following auditory disturbances or with the pre-clinical occurrence.

 Of the 29 samples with the symptom of episodic memory loss, 75.8 % were Caucasians and 75 % in cases. However, this symptom was not recorded in the Asians or the Caribbean, with only 3.4 % being noted in the African community. This indicates that individuals in the

Caucasian ethnic group with this symptom were three times more likely to be diagnosed with AD than any other ethnic groups.

Out of the 14 samples with auditory disturbances, 57.1 % were Caucasians, followed by a 35.7 % of mixed race individuals. However, the symptom was not recorded in the African, Asian or the Caribbean ethnic groups. This shows that the white female ethnic group with auditory disturbance were twice likely to be diagnosed with AD than any other ethnic group. While the Africans, Asians and Caribbean were less likely to be diagnosed with AD despite having the symptom.

Comorbidities

Concomitant health conditions have been associated with AD, which can act as confounders or effect modifiers. In this study, multiple comorbid conditions were isolated with AD including hypertension with the highest prevalence and tremor with the least. The number of comorbidities per individual was between zero and nine in cases. Of the 37 cases, fourteen cases had one comorbid condition each, while the controls had 0-4, with seven controls having one each. The most frequently reported comorbid condition was hypertension, reported by 20 cases (40.5 %), chronic kidney disease followed with 10.8 %, high cholesterolemia and ischaemic heart attack with 8.1 % respectively. Asthma, depression, biventricular heart disease and sciatica were reported by 5.4 % of cases respectively, while others including osteoarthritis, gastritis, adnexia, tinnitus, paresthesia, gallstones, hyperthermia, ocular hypertension cataract, cardiovascular accident, asthma, bilateral fine drusen, cerebral atrophy, diverticular disease and hypothyroidism were reported in one individual respectively. The frequently reported comorbidities had a mean of 3.8 (3.1 SD).

Discussion

In this study, we explored the possibility of identifying patterns in the signs and symptoms preceding the clinical diagnosis of AD. The researcher discovered that individuals with AD have higher odds of auditory disturbances. This finding, to my knowledge, is novel and this is the first study that has reported auditory disturbances as being predictive of AD, excluding auditory hallucinations, which are considered to be frequent psychotic symptoms of AD

(25). There could be biological plausibility that could be investigated with a larger sample, as the result is of borderline significance due to small sample size.

The three most distant presentations included headache, which was presented more than two decades before diagnosis, followed by depression and auditory disturbances before episodic memory loss. Weight loss, however, presented less than a year before diagnosis, closely tailed by anxiety and hallucinations, opining and supporting literature stating that these presentations are late mechanisms and indicate the progression of the disease (26; 27; 28). The result is contrary to the current literature stating that anxiety is an early presentation (29; 30). In our study, the contrasting result could be due to the small sample size and the restriction of the study to a geographical area in England of Luton and Milton Keynes. Analyses of a bigger AD patient cohort for both anxiety and auditory disturbances could help accurately predict the signs and symptoms preceding a clinical diagnosis of AD.

The symptoms and signs associated with AD were more striking in the white population than any other ethnic group, supporting findings from previous study that AD is more highly prevalent in Caucasians than any other ethnic groups (31) and contrary to more recent research indicating a higher prevalence in African Americans and Asians (32). However, the prevalence found in this research could be due to the high population of whites in the areas, geographical location and chance, as it might be difficult for an ethnic minority individual to go for a check-up for memory issues than their white counterparts, especially as, the interviews indicate issues of language barriers and translation issues, which could confound the diagnosis.

Additionally, the study indicates that female gender had a higher prevalence of the signs and symptoms of AD than their male counterparts with increased odds of having episodic memory and auditory disturbance respectively. The female gender has been associated with the risk factor gene for AD A POE-E4 allele (33) with two of the most prominent non-modifiable risk factors for AD identified as the female gender. However, episodic memory has only been associated with the female gender in measures and type, not the prevalence, even though the symptom correlates with high levels of amyloid deposition (34).

Excessive sweating, dehydration, poor appetite, abdominal pains, weight loss and constipation were all identified with AD. However, even though weight loss has been identified as an early sign and significant in this research (p-value <0.0001), the gastrointestinal symptoms have been associated with adverse effects of AD medications (35; 36; 37), especially the clinical effects of memantine monotherapy. Dehydration and excessive sweating could be risk factors rather than signs; this is because AD is associated with dietary deficiency including water even at the mild to moderate stage of the disease (38).

Depression was also associated with AD, which is consistent with the Rosenberg (39) study, indicating the symptom as an AD mechanism. However, depression could be a reverse causality, as individuals reported the symptom as early as 60 years before diagnosis in this study, which could indicate the presence of depression with AD as a resulting factor.

Irritability was not identified with the cases in this study, which also supports existing literature (40) indicating that it is a less prevalence sign in AD. This is because the sign is related to functional connectivity alterations in the salience network (41); without the connectivity alterations, the sign could be a rare mechanism in AD.

Among the comorbidities associated with AD in this study, hypertension had the highest prevalence and supports other studies indicating that the symptom is one of the predominant comorbid conditions associated with AD. In a Spanish study of 72,815 patients over 64, hypertension had the highest prevalence as a comorbid condition with 38.6% for men and 44.9% for women (42). However, literature (43) suggests that hypertension could be a modifiable risk factor rather than a symptom, as hypertension accelerated cognitive deficits, microvascular deposits of β amyloid and vascular inflammation (44).

High cholesterolemia was also identified as comorbidity for AD. Even though the Framingham study (45) showed that the condition is not a risk factor for developing AD, others have identified it as a causative factor (46). However, this is still debatable (47) due to the blood-brain barrier mechanism that restricts the entry of blood-derived products into the brain including cholesterol.

Conclusion

The research demonstrates that auditory disturbance, which was more striking in the Caucasian female gender, could predict a diagnosis of AD. While further research is advocated on a larger scale, the results support future plans for a predictive model to enable an earlier diagnosis of AD. A study in Japan (48) distinguished between cognitive normal individuals and elderly people with cognitive impairment using prosodic signals extracted from speech; even though the study was applicable to older adults in Japan, a similar study is advocated in the UK, which incorporates all signs and symptoms in both the early and late onset AD, for the development of the predictive model for early detection of the disease. Another systematic review (49) that identified the functional alterations in the retina as an early biomarker for late-stage AD could to support the predictive model and could discriminate individuals at different stages of the disease.

While the hearing loss may suggest an early warning sign for cognitive impairment and could be a biomarker for the disease, as individuals with hearing loss are associated with higher incidence of dementia (50), hearing impairment might be related to future cognitive decline due to behavioural mechanisms such as social isolation and the relationship between the auditory pathways and the cognitive control network (51). Auditory disturbance identified in our study could support the specific prediction of AD in the early stage. Our study had no recall bias and the data collected was written at the point of collection.

The limitation of this study includes a sample size that will not allow the generalisation of the signs and symptoms preceding a clinical diagnosis of AD, even though sufficient data was acquired for a statistical analysis. The small sample size is not sufficiently representative of adults followed-up in primary care nor the overall adult population in the Luton and Milton Keynes areas. However, the controls were specifically selected and comorbidities and symptoms presented are similar to what is known of this population. Other cases of AD presented with headache and backache; a baseline that may vary with comorbidities and geographical location.

Abbreviations

AD: Alzheimer's disease; CCG: Clinical Commissioning Group; CI: Confidence Interval; Early Onset Alzheimer's disease; GP: General Practitioner; HRA: Health Research Authority; ICED: Index of Coexistent Disease; LOAD: Late Onset Alzheimer's disease; MMSE: Mini-Mental State Examination; NHS: National Health Service; NINCDS-ADRDA: National Institute of Neurological and Communication Disorders and Stroke- Alzheimer's Disease and Related Disorders Association; NPS: Neuropsychiatric Symptoms; OR: Odds Ratio; UREC: University Research Ethics Committee.

Declarations:

Authors' contributions

FB, BG and YP conceived the study and participated in the design and drafting of the manuscript. DP suggested the design, participated in the analysis and helped to draft the manuscript. FB developed the protocol for the study, collected analysed and drafted the manuscript. FB, DP, BG and YP read and approved the final manuscript for this publication.

AR and NP helped with the data collection process.

Ethics opinion:

The study sought and acquired a favourable ethics opinion from the Office of the Research Ethics Committee, London (16/LO/1521), the University of Bedfordshire Ethics Committee and the Health Research Authority.

Consent for publication: Not applicable as data is anonymised.

Availability of data: The data that support the finding of this study is available from the corresponding author but restrictions apply to the availability of these data, which were generated and used under license for the current study and so, not publicly available. With permission and reasonable request, data is available from the authors.

Competing interest: "We have read and understood the policy on the declaration of interests and declare that we have no competing interests".

Author's information: Not applicable.

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