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Research Article

The Diagnostic Utility of the "Attended Alone" Sign for Dementia in Patients Presenting for Neuropsychological Evaluation

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Abstract

The diagnostic utility of the "attended alone" sign, defined here as attending a neuropsychological evaluation unaccompanied, was investigated in a sample of patients presenting for neuropsychological evaluation. Data was gathered through a retrospective review of 275 consecutive patients seen by a neuropsychologist in a general psychology clinic setting over a 4-year period in the Northwest United States (December 2014–July 2018). Participants were said to have "attended alone" if they drove themselves to the appointment, coordinated a bus or taxi ride to the appointment alone, or walked to the appointment alone. Participants were said to have "attended with an informant" if they were accompanied to the clinic by a family, friend, or caretaker. The attended alone sign was considered as a measure of dementia and compared with the final diagnosis. Analysis included calculations of sensitivity, specificity, positive and negative predictive values, diagnostic odds ratio, and positive and negative likelihood ratios with 95% confidence intervals. Of the 275 patients, 119 attended with an informant and 156 attended alone. A total of 47 patients were diagnosed with dementia, while 228 were not. In the dementia group, 44 patients attended with an informant and only 3 attended alone. In the non-dementia group, 153 attended alone and 75 attended with an informant. In this sample, the use of the attended alone sign as a diagnostic tool for dementia had an accuracy of 0.72, sensitivity of 0.94 and specificity of 0.67. The positive predictive value was 0.37, though the negative predictive value was very high at 0.98. Positive and negative likelihood ratios were 2.85 and 0.10, respectively. The attended alone sign demonstrated very high sensitivity, which translated to both a very large negative predictive value and a small negative likelihood ratio, indicating that patient's who attended a neuropsychological evaluation alone were extremely unlikely to have dementia. Therefore, the attended alone sign is an underappreciated, yet very sensitive marker for the absence of dementia with very few false negatives. These findings replicate those of a small number of studies specifically investigating this phenomenon in the United Kingdom.

Keywords: *dementia, neuropsychology, attended alone sign*

Introduction

Dementia is an umbrella term indicating cognitive decline severe enough to significantly disrupt an individual's ability to safely perform complex tasks important for independent living, such as driving or coordinating transportation, taking medications as prescribed, managing finances appropriately, grocery shopping, and completing necessary household tasks. There are many causes of dementia, though Alzheimer's disease (AD) is the most common, with pathology found in 60 to 80% of dementia cases [1]. Vascular dementia is the next most common etiology, accounting for 20% of dementia cases, followed by Lewy body dementia (LBD) and Parkinson's disease dementia (PDD), disorders with similar pathology collectively accounting for 10-15% of dementia cases. The spectrum of frontotemporal lobar degeneration (FTLD) and alcohol-related dementias each account for another 5-10% of dementia cases. Mixed pathologies are very common, particularly in elderly individuals. Even in cases diagnosed as probable AD, most post-mortem pathological analyses reveal vascular pathology as well as LBD and FTLD pathology [1,2]. Our knowledge of dementia pathology continues to evolve. Very recent research reveals that a large proportion of elderly individuals meeting clinical criteria for AD also show pathological evidence of a newly described disease entity known as limbic-predominant age-related TDP-43 encephalopathy (LATE) [3].

An accurate diagnosis of dementia requires that all reversible causes of cognitive difficulties be identified and addressed. Common, treatable causes of cognitive decline in older adults include depression, abnormal thyroid function, sleep apnea, nutritional deficiencies, other unidentified or untreated medical disorders, and medications with cognitive side effects. Approximately 9% of individuals with dementia have potentially reversible conditions [2]. The workup for dementia typically includes a detailed history obtained from the patient and a knowledgeable informant, a neurologic examination, brain imaging, appropriate laboratory studies, and neuropsychological assessment. Different dementias can be associated with relatively distinctive clinical presentations including differential patterns of neurocognitive decline, particularly early in their course, and specific structural and functional brain imaging abnormalities [4].

Sensitive and specific diagnostic tests for the presence or absence of dementia represent the ultimate goal in the clinical neurosciences, such that a worldwide investigation for definitive biomarkers has been underway for decades. Unfortunately, no single marker or set of markers with both high sensitivity and high specificity for AD in living patients has been identified. Short of autopsy or biopsy, AD remains a diagnosis of exclusion, made only after ruling out other possible causes of memory disorder or dementia. In many cases, much of the dementia diagnosis ultimately relies on the qualitative characteristics and quantitative pattern of cognitive functioning elicited by neuropsychological assessment [4]. As important investigations for more definitive dementia biomarkers continue, and the field of neuropsychology trends towards truncated evaluations driven by increasing health care demands and cost utilization, there remains a need for simple clinical measures that are reliable and valid methods of diagnosing dementia.

The "attended alone" sign, defined as failure to attend a memory clinic appointment with an informant despite written instruction to do so, is an underappreciated yet very sensitive marker for the absence of dementia specifically investigated in a small number of studies from the United Kingdom [5-8]. The attended alone sign rules out dementia with a high level of accuracy. In the most recent of these studies, Larner investigated the attended alone sign in a sample of 726 consecutive referrals to a memory clinic [8]. The diagnosis of dementia was established using criteria outlined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and clinical judgment following patient assessment by semistructured clinical interview, use of cognitive screening instruments, and structural neuroimaging, supplemented when possible by additional investigations including formal neuropsychological assessment, EEG, and genetic testing. Of the 726 patients, 480 (66.1%) attended with an informant as requested, and 246 attended alone (33.9%). In the attended with an informant group, 216 (45%) were diagnosed

with either dementia or mild cognitive impairment and 264 (55%) were diagnosed as cognitively healthy. In the attended alone group, not one patient was diagnosed with dementia; however, 16 patients (6.5%) were diagnosed with mild cognitive impairment and at risk of progressing to dementia. This left 230 patients (93.5%) diagnosed as cognitively healthy in the attended alone group. In this sample, the attended alone sign as a diagnostic tool for the absence of dementia had an overall accuracy of 0.64, sensitivity of 1.00 and specificity of 0.45. The positive predictive value was 0.48 and the negative predictive value was 1.00. Positive and negative likelihood ratios were 1.82 and 0, respectively [8]. The current study seeks to replicate these results in a different location and clinical setting by investigating the diagnostic utility of the attended alone sign for dementia in a sample of patients referred to a general psychology clinic for neuropsychological evaluation in the Northwest United States.

Materials and Methods

Participants

Data was gathered through a retrospective review of 275 consecutive patients seen by a neuropsychologist in a general psychology clinic setting over a 4-year period in the Northwest United States (December 2014–July 2018). Participants were said to have "attended alone" if they drove themselves to the appointment, coordinated a bus or taxi ride to the appointment alone, or walked to the appointment alone. Participants were said to have "attended with an informant" if they were accompanied to the clinic by a family, friend, or caretaker. Appointment information was formally arranged with patients by phone and supplemented with instructions by mail. In both instances, the patient was encouraged to bring an informant such as a family member or caregiver if necessary but was not required to do so. This slight departure from previous research was prompted by the diverse range of referrals and different setting in which the data was gathered (general psychology clinic vs. memory disorders clinic). The most common referral question was related to subjective cognitive decline in an older adult, though referrals varied with respect to age and context as the current sample included young adults with concussion, neurologic disorders affecting younger adults such as epilepsy and MS, and cognitive problems associated with a wide range of psychiatric and general medical conditions. The majority of patients were referred by neurologists, with other referrals coming from a variety of backgrounds including primary care physicians, psychiatrists, physiatrists, and other clinical providers. A small number of patients were referred in the context of disability and personal injury claims.

The neuropsychological evaluation

The neuropsychological evaluation included a review of medical records, clinical interview with patient (and informant when dementia suspected whether present or contacted later by phone), and comprehensive neuropsychological testing. A flexible neuropsychological battery was administered depending on the referral question, though all evaluations included standardized assessment of attention, executive functions, learning and memory, language, and visual spatial and construction skills.

Diagnosis of dementia and other diagnostic groups

The clinical diagnosis of dementia was established following criteria outlined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [9]. First, a comprehensive neuropsychological evaluation revealed evidence of significant cognitive decline, defined as a consistent pattern of performance-based test scores ≥ 2 or more standard deviations below the mean in an appropriate normative sample, on key test variables in two or more cognitive domains (attention, executive functions, learning and memory, language, and visual spatial and construction skills). Second, the cognitive impairment interfered with functional independence in one or more complex activities of daily living (coordinating transportation, medication management, financial management, meal preparation, or grocery shopping) confirmed by a knowledgeable informant. Third, the cognitive decline was not better explained by delirium, a major psychiatric disorder, or reversible causes of cognitive impairment such as uncontrolled thyroid

disease, untreated sleep apnea, a recent vitamin B12 deficiency, medication side effects, etc. All dementia patients underwent a neurological evaluation, appropriate laboratory studies and structural neuroimaging. Additional biomarkers (functional neuroimaging, EEG, CSF analysis, genetic testing) were incorporated in the diagnosis of dementia where available. The clinical diagnosis of mild neurocognitive disorder was defined as performance-based test scores ≥ 1 standard deviations below the mean in one or more cognitive domains without significant decline in complex activities of daily living and not better explained by other factors. The two remaining diagnostic groups included patients with cognitive difficulties better explained by psychiatric disorders and patients with other factors explaining their cognitive difficulties or no significant cognitive difficulties.

Statistical analysis

Descriptive statistics were computed where relevant. An independent t-test was conducted to compare ages of the attended alone and attended with informant samples. The attended alone sign was then investigated as a measure of dementia and compared with the final diagnosis. Analysis included calculations of sensitivity, specificity, positive and negative predictive values, diagnostic odds ratio, and positive and negative likelihood ratios with 95% confidence intervals.

Results

Demographic and diagnostic information are presented in Table 1. The majority of the sample was male (56%) with a mean age of 59.8 (range 16-98). The attended with an informant group was significantly older than the attended alone group, $t(273) = 5.93$, $p \leq 0.001$. Of the 275 patients, 119 attended with an informant (43%) and 156 attended alone (57%). A total of 47 patients were diagnosed with dementia (17%) and 228 were not (83%). In the dementia group, 44 patients attended with an informant (94%) and only 3 attended alone (6%). In the non-dementia group, 75 attended with an informant (33%) and 153 attended alone (67%). The non-dementia diagnostic groups included 42 patients diagnosed with mild neurocognitive disorder (15%), 87 with cognitive difficulties better explained by psychiatric disorders (32%), and 99 with other factors explaining their cognitive difficulties or no significant cognitive difficulties (36%). In the 42 patients diagnosed with mild neurocognitive disorder, and therefore at risk of progressing to dementia, 28 attended with an informant (67%) and 14 attended alone (33%).

Statistical analyses investigating the diagnostic utility of the attended alone sign in dementia are presented in Table 2. In this sample, the attended alone sign as a diagnostic tool for dementia had an overall accuracy of 0.72, sensitivity of 0.94 and specificity of 0.67. The diagnostic odds ratio was 29.92. The positive predictive value was 0.37 and the negative predictive value was 0.98. Positive and negative likelihood ratios were 2.85 and 0.10, respectively.

All 47 dementia patients completed structural neuroimaging with 31 showing abnormalities consistent with dementia such as diffuse generalized atrophy beyond expected for age, focal hippocampal atrophy, significant vascular involvement, or FTLD. Of the 12 AD cases with MRI volumetric data, 10 showed hippocampal volumes in the 1^{st}-16^{th} percentile relative to an age-appropriate normative sample. One patient had significant frontotemporal atrophy consistent with a clinical diagnosis of FTLD. Three patients completed functional neuroimaging with one suggesting LBD, one showing changes associated with FTLD, and one being inconclusive. Two patients had autopsy results with both confirming a mixed-AD pathology, with mixed vascular-AD in one patient and mixed AD-LBD in another. CSF analysis was available in six AD patients, and four were supportive of the diagnosis. One patient had autosomal dominant AD supported by genetic testing. The breakdown of dementia etiologies is presented in Figure 1. The majority of the sample showed evidence of mixed dementia, mostly AD and vascular dementia.

Table 1. Demographic variables and diagnostic classification.

N	**275**
M:F, % male	154:121, 56%
Mean age, SD (range)	59.8, 17.1 (16-98)
Attended alone, % of total sample	**156, 57%**
M:F, % male	86:70, 55%
Mean age, SD (range)	53.3, 16.3 (18-87)
Attended with informant, % of total sample	**119, 43%**
M:F, % male	68:51, 57%
Mean age, SD (range)	67.4, 14.6 (16-98)
Diagnostic Groups	
Dementia, % of total sample	**47, 17%**
M:F, % male	24:23, 52%
Mean age, SD (range)	73.3, 9.7 (53-90)
Dementia attended alone	3, 6%
Dementia attended with informant	44, 94%
Mild neurocognitive disorder, % of total sample	**42, 15%**
M:F, % male	29:13, 69%
Mean age, SD (range)	68.9, 12.5 (44-98)
Mild neurocognitive disorder attended alone	14, 33%
Mild neurocognitive disorder attended with informant	28, 67%
Primary psychiatric diagnosis, % of total sample	**87, 32%**
M:F, % male	49:38, 56%
Mean age, SD (range)	50.7, 16.3 (16-82)
Primary psychiatric diagnosis attended alone	65, 75%
Primary psychiatric diagnosis attended with informant	22, 25%
Other factors/No cognitive difficulties, % of total sample	**99, 36%**
M:F, % male	46:53, 46%
Mean age, SD (range)	56.4, 16.4 (19-88)
Other factors/No cognitive difficulties attended alone	74, 75%
Other factors/No cognitive difficulties attended with informant	25, 25%

Table 2. The diagnostic utility of the "attended alone" sign for dementia.

Test accuracy	0.72 (95% CI=0.66–0.77)
Sensitivity	0.94 (95% CI=0.82–0.99)
Specificity	0.67 (95% CI=0.61–0.73)
Positive predictive value	0.37 (95% CI=0.32–0.42)
Negative predictive value	0.98 (95% CI=0.94–0.99)
Diagnostic odds ratio	29.92 (95% CI=8.99–99.51)
Positive likelihood ratio	2.85 (95% CI=2.33–3.48)
Negative likelihood ratio	0.10 (95% CI=0.03–0.29)

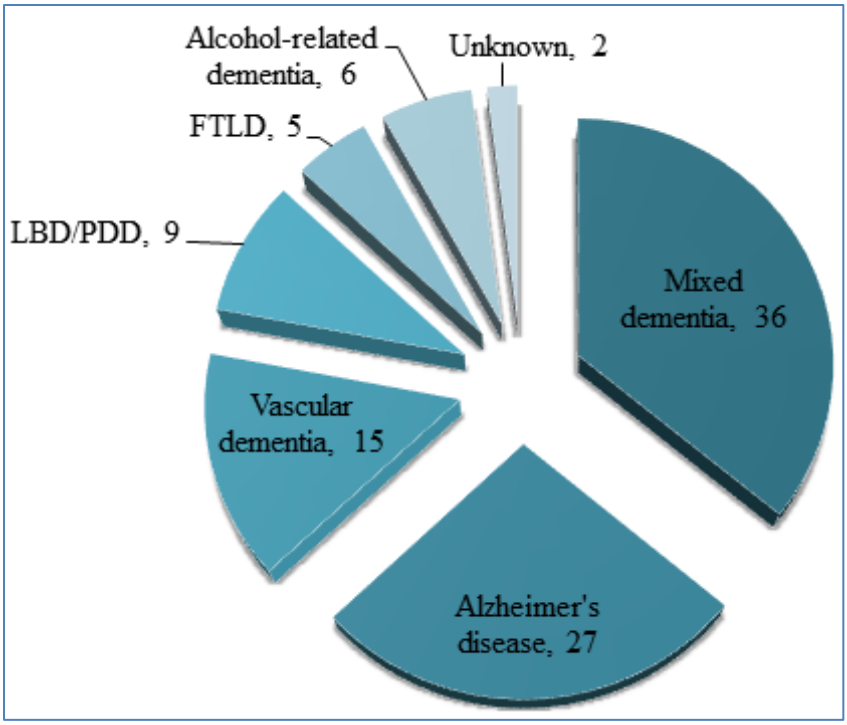

Figure 1. Percentage of dementia etiologies in the current sample.

Patients with dementia who attended alone

All three patients with dementia who attended alone had dementia onset before the age of 61 (range 56-61). All three drove themselves to the appointment. Two of three were employed and wanting to stay employed, but experiencing cognitive problems affecting work performance. Two of three had limited social or caregiving support. One patient lived with family, one lived with roommates, and one lived alone. Patient one was a male with autosomal dominant AD supported by genetic testing and an MRI with hippocampal volumes in the 1st normative percentile. Patient two demonstrated cognitive impairment across domains with severely impaired memory. Her medical history was unremarkable and structural imaging was essentially normal, though hippocampal volumes were at the 12th normative percentile. Her mother was diagnosed with probable AD with onset around the same age. Genetic testing was not available. She was diagnosed with probable AD. Patient three had a complex medical history that included diabetes, chronic obstructive pulmonary disease, obesity, obstructive sleep apnea (appropriately treated), and congestive heart failure. Brain MRI demonstrated moderate to severe small vessel ischemia and a hypoxic-ischemic etiology was suspected.

Discussion

The “attended alone” sign demonstrated very high sensitivity, which translated to both a very large negative predictive value and a small negative likelihood ratio, indicating that patients who attended a neuropsychological evaluation alone were extremely unlikely to have dementia. Therefore, the attended alone sign remains an underappreciated, yet very sensitive marker for the absence of dementia with very few false negatives, replicating previous studies [5-8]. The attended with an informant group was significantly older than the attended alone group. This finding was likely influenced by multiple factors, such as physical limitations affecting driving capacity, in addition to cognitive impairment. All three dementia patients who attended alone had dementia onset before age 61, indicating the attended alone sign is less sensitive to dementia with early onset. Two of these three had limited social support

explaining why they attended alone. Thus, the availability of social and caregiving support is another important factor to consider when interpreting the attended alone sign. A third of patients diagnosed with mild neurocognitive disorder attended alone, indicating the attended alone sign has far less utility in identifying this patient population. However, follow-up may reveal these patients represent the subset of individuals diagnosed with mild neurocognitive disorder that never progress to dementia.

There are several important differences between the current study and prior research in this area. The most important distinction is that all patients underwent comprehensive neuropsychological testing in the current study. A specific dementia diagnostic criteria was used, requiring significant decline in at least two different cognitive domains with functional decline confirmed by an informant. These criteria helped ensure the purity of the dementia group, limiting false positive dementia diagnoses at the potential cost of false negative diagnoses. Also contrasting with previous research, the patient was encouraged, yet not required to attend the evaluation with an informant. This resulted from the diverse nature of the referral base. Patients were referred for a variety of neurologic, psychiatric, and general medical problems, not just suspicion of dementia. Therefore, not all required an informant. Finally, this study was conducted at a general psychology clinic, rather than a memory disorders clinic or general hospital setting. These subtle differences in research methodology might explain why the proportion of dementia cases in the current study was smaller than reported in previous research [8].

Given the simplicity and diagnostic gain associated with the attended alone sign in the exclusion of dementia in this and previous studies, further investigations of associated variables in larger data sets is recommended. The attended alone sign could ultimately be incorporated into dementia prediction models and classification schemes to enhance clinical diagnosis.

Conflict of Interest

The authors declare no potential conflict of interest.

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