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Understanding hallucinations in probable Alzheimer's disease: Very low prevalence rates in a tertiary memory clinic

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Abstract

Current literature reports varying prevalence rates of hallucinations in patients with probable Alzheimer's disease (AD), averaging at 13.4%. This study assessed the prevalence and characteristics of hallucinations in 1227 patients with probable AD from a tertiary memory clinic specialized in early diagnosis of dementia. With 4.5% (n = 55/1227) affected patients, hallucination prevalence was very low. Hallucinations were mostly visual (n = 40/55) or auditory (n = 12/55). Comorbid delusions were present in over one-third of cases (n = 23/55). The presence of hallucinations, based on Neuropsychiatric Inventory-assessment, was associated with increased dementia severity, other neuropsychiatric symptoms, and a lifetime history of hallucination-evoking disease (such as depression and sensory impairment) but not with age or gender. In the largest sample thus far, we report a low prevalence of hallucinations in probable AD patients, comparable to rates in nondemented elderly. Our results suggest that hallucinations are uncommon in early stage AD. Clinicians who encounter hallucinations in patients with early AD should be sensitive to the hallucination-evoking comorbidity.

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Keywords: Alzheimer's disease; Hallucinations; Low prevalence; Comorbidity; Dementia severity

1. Introduction

Hallucinations occur in a variety of psychiatric, neurologic, and somatic disorders, as well as in the general population [1]. Their presence can induce distress and impair daily functioning toward a stage that professional help is necessary [2]. Better understanding of hallucinations can improve both clinical assessment and treatment [1,2].

Reported prevalence rates of hallucinations in patients with probable Alzheimer's disease (AD) vary widely from

7% to 35% [3], averaging at 13.4% ("Research in context"; [Supplementary Fig. 1](#), [Supplementary Tables 1ab](#)). Their presence has been repeatedly associated with more severe cognitive and functional decline, earlier institutionalization, higher burden of disease, and increased mortality [4]. It is therefore essential to better understand hallucinations in AD.

However, heterogeneity between studies on hallucinations in probable AD is large and complicates comparability of study results [3]. As such, current literature is not conclusive on potentially contributive factors, such as dementia severity [3]. Also, the possibility of other diagnoses and medication use as alternative contributing factors to hallucinations in patients with probable AD is often underexposed.

The present study tries to improve the understanding of these uncertainties by studying hallucinations in a large sample of patients with probable AD, derived from a tertiary

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research memory clinic specialized in early detection of dementia [5]. We assessed the prevalence and phenomenology of hallucinations and studied potentially associated factors by comparing hallucinating and nonhallucinating participants on demographics, dementia stage and severity, other neuropsychiatric symptoms, and medical history and use of medication that can trigger hallucinations.

2. Methods

We retrospectively included all patients with probable AD from the Amsterdam Dementia Cohort [5], seen between January 2005 and January 2018, studied with the Neuropsychiatric Inventory (NPI) [6] during baseline diagnostic assessment of cognitive complaints. All participants fulfilled criteria for probable AD as formulated by the National Institute for Neurological and Communicative Disorders/Alzheimer's Disease and Related Disorders Association [7] and had been diagnosed within 30 days from their initial visit. Diagnosis was based on standardized multidisciplinary assessment, including patients' history, neurological examination, vital functions, neuropsychological assessment, whole-brain magnetic resonance imaging, electroencephalography, and routine serum laboratory, and cerebrospinal fluid sampling in a subsample [5].

NPI assessment was conducted with patients' caregivers, by a specialized dementia research nurse during the study day. A participant was considered "hallucinating" if he/she had a frequency score of ≥ 1 on the NPI hallucination subscale. Further details on hallucination phenomenology were retrieved with hallucination items of the NPI, and, if necessary, by reviewing patients' charts. The overall presence and severity of neuropsychiatric symptoms were based on total NPI scores.

Subjects' medical history was dichotomously marked as relevant if one or more diagnoses had ever been present, in which hallucinations are reportedly part of the associated symptomatology, as stated by recent overview articles [1,8] (listed in Table 1). Similar dichotomization was applied if patients used one or more drugs with hallucinations listed as a side effect [9], referred to as hallucination-inducing medication (Table 1). Ranking of relevant history and medication was performed independently by two authors (M.D. and M.M.J.L.); discrepancies were solved by consensus. Dementia severity was based on scores from the Mini-Mental State Examination (MMSE) (27–30 no dementia, 20–26 mild dementia, 10–19 moderate, and 0–9 severe) [10] and the Clinical Dementia Rating (CDR) [11].

Confidence intervals (95%) for prevalence rates of hallucinations were calculated using Clopper-Pearson's exact method in R, version 3.2.0, package PropCIs. Hallucinating and nonhallucinating subjects were compared using chi-square tests for categorical variables and Mann-Whitney U-tests for continuous variables, using IBM SPSS Statistics, version 22. The level of two-tailed significance was set at $P < .05$.

3. Results

Out of 1545 patients diagnosed with probable AD during baseline screening between January 2005 and January 2018, 1227 subjects (79.4%) had NPI data available, with a mean age of 66.6 (SD 7.9) (Supplementary Fig. 2). Supplementary Table 3 shows basic characteristics of the included sample ($n = 1227$). There were no substantial differences between the group with and without NPI data (Supplementary Table 2).

Hallucinations occurred in 55 out of 1227 participants (4.5%; 95% confidence interval 3.4%–5.8%).

The 55 hallucinating subjects mainly reported experiences in the visual ($n = 40$; 73%) or auditory modality ($n = 12$; 22%). A smaller group reported olfactory ($n = 5$; 9%) and tactile hallucinations ($n = 3$; 5%); hallucination modality was unknown in 10 participants (18%). According to the NPI, delusions were present in 23 hallucinating participants (42%), of which paranoia ($n = 9$), home intruders ($n = 10$) and theft ($n = 12$) were reported most frequently.

3.1. Associated factors

Hallucinating subjects showed significantly higher percentages of comorbid delusions than nonhallucinating subjects and had higher total NPI scores (Table 1). The percentage of subjects with a history of hallucination-associated disease was higher in those with hallucinations. At trend level significance, the percentage of hallucination-inducing medication use appeared higher in the hallucinating group.

Hallucinating subjects had significantly lower MMSE scores and a significantly increased CDR in comparison with the nonhallucinating subjects (Table 1). Stratification for severity of dementia resulted in statistically significant distributions for both MMSE ($\chi^2 12.3$, $P .006$, $df 3$) and CDR ($\chi^2 11.7$, $P .020$, $df 4$) and an increasing percentage of hallucination prevalence with dementia severity (Fig. 1, Supplementary Fig. 3). No differences were observed with regard to age or gender (Table 1).

4. Discussion

In the largest sample of patients with probable AD to date, consisting predominantly of patients with early stage disease and relatively young age, we observed a remarkably low prevalence of hallucinations (4.5%) in comparison with existing literature (Supplementary Fig. 1). In studies from comparable research clinics, even the lowest reported prevalence (7.0%) [12] exceeded the upper bound of our 95% confidence interval (5.8%). In 188 subjects with mild probable AD, Wadsworth et al. [13] described a similar prevalence to ours (5.3%) but excluded subjects with comorbid psychiatric or neurological disorders.

The hallucination prevalence in this sample is comparable to the NPI-based prevalence of hallucinations in a non-demented population sample aged ≥ 65 years (4.5%;

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