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Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-9

Alzheimer's & Dementia

Featured Article

Midlife anticholinergic drug use, risk of Alzheimer's disease, and brain atrophy in community-dwelling older adults

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Abstract

Introduction: We examined how long-term anticholinergic (AC) drug use beginning at midlife affects risk of Alzheimer's disease (AD) and rates of brain atrophy in cognitively normal older adults.
Methods: We followed 723 individuals (mean baseline age 52.3 years; mean follow-up interval 20.1 years) in the Baltimore Longitudinal Study of Aging. The AC drug exposure was defined using the Anticholinergic Cognitive Burden Scale: Nonusers ($n = 404$), as well as participants exposed to medications with AC activity but without known clinically relevant negative cognitive effects (i.e., "possible AC users"; $n = 185$) and those exposed to AC drugs with established and clinically relevant negative cognitive effects (i.e., "definite AC users"; $n = 134$). The neuroimaging sample included 93 participants who remained cognitively normal through follow-up and underwent serial magnetic resonance imaging ($n = 93$, 724 brain scans, mean follow-up interval 8.2 years, and baseline age 68.6 years).
Results: Possible AC users, but not definite AC users, showed increased risk of incident AD compared with nonusers (hazard ratio, 1.63; 95% confidence interval, 1.02–2.61; $P = .04$) and greater rates of atrophy in total cortical gray matter volume compared with nonusers ($\beta = -0.74$, $P = .018$). Faster rates of brain atrophy were also observed among possible AC users in the right posterior cingulate, as well as right middle frontal and left superior temporal gyri. Data on frequency and duration of medication use were available in only approximately half of the sample. Among these participants, definite AC users had both shorter duration and lower frequency of medication use relative to possible AC users.
Discussion: Long-term exposure to medications with mild AC activity during midlife is associated with increased risk of AD and accelerated brain atrophy.

Keywords: Anticholinergic medication; Alzheimer's disease; Brain atrophy; Cortical thickness; Longitudinal change; Brain aging; Midlife

1. Introduction

The identification of modifiable risk factors for Alzheimer's disease (AD) is a critical public health priority. Understanding how exposure to such risk factors as early as in midlife may be associated with subsequent cognitive impairment may facilitate timely lifestyle modifications to prevent or delay the onset of AD.

Medication-related adverse health outcomes are common, costly, and preventable in older adults [1]. Several medications are known to be associated with both delirium and increased risk of dementia in the elderly [2]. Among them, anticholinergics (ACs) or medications with AC activity are well known to cause acute cognitive impairment,

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http://dx.doi.org/10.1016/j.trci.2017.06.004

which is typically transient and reversible [3–5]. More recent evidence suggests that AC drugs may also be associated with long-lasting cognitive impairment [6–10]. Medications with AC activity are widely used in the elderly, despite increasing evidence of adverse outcomes and concerns about their inappropriate use in this population [11–15].

As highlighted recently [6], most observational studies on the relationship between exposure to AC medications and long-lasting cognitive impairment in the elderly have been conducted over relatively short follow-up times. Moreover, the majority of such studies have been performed in late life when observed associations are especially susceptible to protopathic bias [16], wherein medications with AC side effects are more likely to be prescribed to treat prodromal symptoms such as depression, anxiety, and insomnia before obvious cognitive impairment when a clinical diagnosis of dementia can be made [17–19]. Whether exposure to AC drugs in midlife can cause long-lasting changes in brain structure before the onset of cognitive impairment also remains unknown.

In this study, we used data from the Baltimore Longitudinal Study of Aging (BLSA), to examine the associations between AC exposure between the ages 50 and 65 years and risk of AD or mild cognitive impairment (MCI). Using longitudinal magnetic resonance imaging (MRI) data available in the neuroimaging substudy of the BLSA (BLSA-NI) [20], we also asked whether exposure to AC drugs between the ages 50 and 65 years is associated with longitudinal changes in brain atrophy before the onset of cognitive impairment.

2. Methods

2.1. Study sample overview

The BLSA began in 1958 and is an ongoing, prospective cohort study of community-dwelling volunteer participants in Baltimore [21,22]. Detailed examinations, including neuropsychological assessment and neurological, laboratory, and radiological evaluations, were conducted every 2 years. Since 2003, participants older than 80 years have received yearly assessments. Written informed consent was obtained from participants at each visit, and the study was approved by the local Institutional Review Board and the National Institute on Aging. As of 2013, BLSA has recruited 3194 participants (Fig. 1).

The BLSA-NI [20], beginning in 1994, includes a subset of BLSA participants who agreed to annual neuroimaging assessment and were free of central nervous system disease (dementia, stroke, bipolar illness, and epilepsy), severe cardiac disease (myocardial infarction, coronary artery disease requiring angioplasty or coronary artery bypass surgery), or metastatic cancer [23]. Because structural brain changes can occur several years before onset of cognitive impairment, to preserve better temporal relationship between anticholinergic cognitive burden (ACB) drug use and preclinical changes in brain volumes, only participants who remained cognitively normal over the follow-up interval of MRI imaging were included in the analysis (n = 93, 724 brain scans).

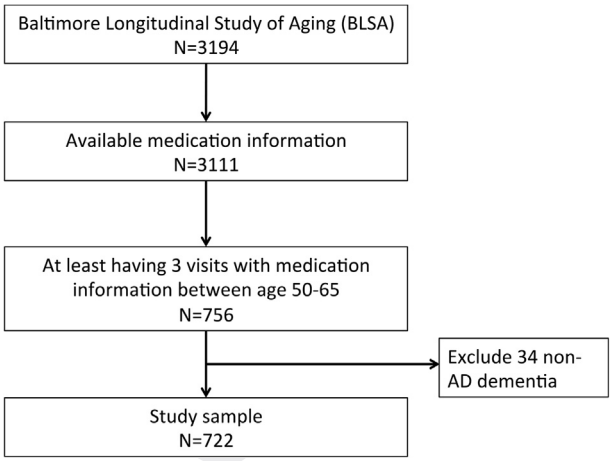

Fig. 1. Flow chart of study sample selection from the Baltimore Longitudinal Study of Aging.

2.2. Use of AC medications

Information about medication use was obtained at each visit by study nurse practitioners or physician assistants, who visually inspected the medication charts or medications that participants brought to the study unit. All medication records were entered by experienced nurse practitioners using a structured form according to the Anatomical Therapeutic Chemical classification system. Eighty-three participants in the current analyses had no available medication information (Fig. 1).

The Anticholinergic Cognitive Burden (ACB) Scale [4,12] captured a participant's AC burden due to drug exposure at each visit. Medications were categorized as having "no/absent", "possible" (ACB score = 1), or "definite" (ACB score = 2 or 3) AC activities. Drugs with possible AC effects were defined as having serum AC activity or in vitro affinity to muscarinic receptors but no known clinically relevant negative cognitive effects, whereas drugs with definite AC activities were those with established and clinically relevant negative cognitive effects. The ACB scale has been validated in diverse populations [24,25].

We characterized the exposure to AC drugs based on the longitudinal pattern of AC drug use between midlife and early late life, defined as age 50 to 65 years. Only participants with information on medication use over at least three visits between ages 50 and 65 years were included in the analysis (n = 756) (Fig. 1). The mean of follow-up visits for medication information was 6.1 ± 1.7, spanning over 11.1 ± 2.5 years. Three groups of longitudinal AC drug exposure were identified as nonusers, possible AC users, and definite AC users (Fig. 2). Nonusers had not used any ACs during the follow-up interval. Possible AC users had used only drugs with an ACB score = 1 during follow-up,