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Featured Article

Head or brain injuries and Alzheimer's disease: A nested case-control register study

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Abstract

Introduction: Many previous studies have been limited by self- or proxy-reported injury or short follow-up. We investigated whether head or brain injuries are associated with Alzheimer's disease (AD), possible modifying factors and dose-response relationship.

Methods: Nested register-based case-control study of all community dwellers who received clinically verified AD diagnosis in Finland in 2005 to 2011 (n = 70,719) and one to four matched controls for each case (n of controls = 282,862).

Results: The magnitude of association between hospital-treated head and/or brain injuries was strongly dependent on the lag time between exposure and outcome. With a 5-year lag time, head injury (adjusted odds ratio; 95% confidence interval 1.19; 1.15–1.23) or brain injury (1.23; 1.18–1.29) was associated with higher risk of AD. Dose-response relationship with number and severity of injuries was observed. Associations were stronger in those with earlier onset of AD.

Conclusions: Stronger associations with shorter lag times indicate that head and/or brain injuries may also reflect the ongoing AD disease process.

Keywords: Alzheimer's disease; Head injury; Brain injury; Case-control study

1. Introduction

Dementia, with Alzheimer's disease (AD) being the most common cause, is a key determinant of health care costs and quality of life. In 2015, there were 46.8 million people with dementia, and the number is expected to double by 2050 [1]. Thus, identification of potentially modifiable or preventable risk factors is important. Furthermore, as the evidence on strategies for improving or maintaining the cognitive function in high-risk groups is emerging [2], knowledge on these risk factors could help in targeting the preventive measures.

Association between head and brain injuries and dementia is a biologically plausible one. The consequences of these injuries (reviewed in, for example [3–5]) include axonal and cytoskeletal alterations in the brain, neuroinflammation, increased amyloid beta and tau pathology, impairment of homeostasis, disruption of blood-brain barrier and consequent neurodegeneration, and brain atrophy. Brain regions with the most prominent atrophy after traumatic brain injury (TBI), that is, hippocampus, amygdala, precuneus, and parietal and frontal cortices, overlap closely with regions of

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predominant β-amyloid deposition, decreased glucose use, and progressive atrophy in AD [6]. However, a recent study detected stronger association between TBI and neuropathologic changes related to Lewy body disease and Parkinson's disease than AD-like pathology [7].

Many studies have shown that head injury [8–15] and TBI [13,16–23] are related to higher risk of AD. Consequently, two meta-analyses concluded that head and brain injuries predispose people to higher risk of dementia and AD [24,25]. However, the association has not been replicated in individual studies, with six studies concluding with null results [7,19,20,26–28] and one showing no association between TBI and AD but higher risk of dementia among persons with TBI [27]. Some studies have suggested that the associations are stronger in men [13,15,24,29] or those with stronger genetic predisposition (apolipoprotein E ε4-allele carriers) [27], or that head injuries are related to younger age of AD onset [30], but also these findings have not been replicated in other studies [7,11,12,19]. Similarly, some studies have shown that there is a dose-response relationship with more serious injury conferring a larger risk [14,17], whereas others have not detected such relationship [19,24].

Many of these previous studies have relied on self-reported [7,8,14,16,19,27] or spouse-/proxy-reported [11–14] injury, and thus recall bias (i.e., persons with dementia or their spouses remembering or reporting previous injuries differently from those without dementia) may explain some of the differences. In addition, dementia has long latency period, but in many studies, the follow-up time has been relatively short and in most of them less than 10 years [9,14–18,22,23,26,28]. Therefore, it is possible that the injuries could actually have been consequences of dementia or undergoing disease processes.

The aim of this nationwide-nested case-control study with more than 3 decades of data on hospital-treated head and brain injuries before AD diagnosis was to assess whether (1) head or brain injuries are associated with AD; (2) the association is dependent on the lag time (i.e., time between head injury and AD diagnosis); (3) there is a dose-response relationship with the number or severity of injuries; and (4) sex or age modifies the association.

2. Participants and methods

2.1. Study population

We conducted a nested nationwide case-control study of the entire population of Finland using register-linkage approach. The Medication and Alzheimer's Disease study includes all community-dwelling persons who received a clinically verified diagnosis of AD in 2005 to 2011 (*n* of cases = 70,719) [31]. AD cases were identified from the Finnish Special Reimbursement Register maintained by the Social Insurance Institution of Finland (SII) as described previously [31]. The Special Reimbursement Register contains records of all persons who are eligible for higher reimbursement due to certain chronic diseases, including AD. To be eligible for reimbursement, the disease must be diagnosed according to specific criterion, and diagnosis statement must be submitted to the SII by a physician. The study was restricted to incident AD cases.

One to four age- (±1 year), sex-, and hospital district-matched controls for each AD case (*n* of controls 282,862) were identified from the register that contains all residents of Finland who are entitled to benefits by the SII, that is, all citizens and residents living in Finland for at least 2 years. The number of identified controls per case varied because in some hospital districts, it was not possible to obtain four controls for a case from specific age and sex stratum. The Finnish health care system is organized according to a national framework, set by the Ministry of Social Affairs and Health. All citizens/residents are covered by tax-supported public health service and have unrestricted access to health services, regardless of their socioeconomic status [32]. Each resident of Finland is assigned a unique personal identification, which was used to link the participant data to the National Hospital Discharge Register.

2.2. Standard protocol approvals, registrations, and patient consents

Data retrieval was performed by the register maintainers (SII, National Institute of Health and Welfare and Statistics Finland). All data were de-identified before submission to the research team by substituting the personal identification numbers with a study id. According to Finnish legislation, no ethics committee approval was required, as only de-identified data were used and the study participants were not contacted.

2.3. Diagnosis of AD

Persons with AD were identified from the Finnish Special Reimbursement Register maintained by the SII as described in detail previously [31]. The AD diagnosis was closely based on the NINCDS-ADRDA and DSM-IV criteria for AD [33,34]. Briefly, the specific criterion for a verified AD diagnosis is (1) symptoms consistent with mild or moderate AD, (2) a decrease in social capacity over a period of at least 3 months, (3) a computer tomography/magnetic resonance imaging scan, (4) exclusion of possible alternative diagnoses, and (5) confirmation of the diagnosis by a registered neurologist or geriatrician. The physician also has to confirm whether the patient has other dementing diseases in addition to AD. However, patients with these diseases are also entitled to reimbursed medicines if the symptoms are considered to be mainly caused by AD. Summary of anamnestic information from the patients and family, as well findings from clinical examination and all diagnostic findings, for example, magnetic resonance imaging /computer tomography, laboratory, and cognitive tests are submitted to the SII, where a geriatrician/