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Quantitative sensory testing and pain tolerance in patients with mild to moderate Alzheimer disease compared to healthy control subjects

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ABSTRACT

Patients with Alzheimer disease (AD) report pain less frequently than their cognitively intact peers. It has been hypothesized that pain processing is altered in AD. The aim of this study was to investigate agreement and reliability of 3 pain sensitivity tests and to examine pain threshold and tolerance in patients with AD. We examined 29 patients with mild to moderate AD and 29 age- and gender-matched healthy control subjects with quantitative sensory testing, ie, assessments of detection threshold (warmth detection threshold [WDT]) and pain threshold (heat pain threshold [HPT], pressure algometry, cold pressor test), and assessments of tolerance (pressure algometry, cold pressor test). All procedures were done twice on day 1, 1 hour apart, and repeated on day 2. We found no difference between groups for WDT (patient vs control subjects: mean [95% confidence interval]: 35.5°C [33.4°C to 37.6°C] vs 35.4°C [34.3°C to 36.5°C], $P = .8$) or HPT (41.2°C [40.0°C to 42.4°C] vs 42.3°C [41.1°C to 43.5°C], $P = .24$). We observed comparable thresholds for pressure algometry (median [25% to 75% interquartile range]: 120 kPa [100 to 142 kPa] vs 131 kPa [113 to 192 kPa], $P = .10$), but significantly lower tolerance in AD patients (213 kPa [188 to 306 kPa] vs 289 kPa [262 to 360 kPa], $P = .008$). No differences were found for the cold pressor test. The study demonstrated good replicability of the sensory testing data with comparable data variability, for both groups, which supports the use of these methods in studies of patients with mild to moderate AD. Contrary to previous studies, we observed a reduced pain tolerance in patients with mild to moderate AD, which suggests that the reduced report of pain cannot be explained by reduced processing of painful stimuli.

1. Introduction

Epidemiological studies have described a reduced report of pain [1,18,34] and lower analgesic consumption in patients with dementia [17,23,27]. One study reported that patients with early Alzheimer disease (AD) report less intense pain compared to cognitively intact elderly people [35], suggesting that pain perception or pain reporting is disturbed already in the early stages of the disease. These findings have raised the question of whether AD leads to a change in pain experience due to an altered pain processing related to neurodegenerative changes [36]. This issue has only been studied in a handful of experimental studies, and so far no consistent findings have been demonstrated. Benedetti et al. did not identify any differences in pain threshold between AD patients and healthy control subjects using electric and ischemic stimuli, but the tolerance to pain was increased [4]. Cole et al. used pressure pain stimuli and found an increased threshold for just noticeable pain [9,10]. These contradictory findings might be attributable to methodological differences in regard to pain induction, pain assessment, and severity of AD. Another explanation is that it is unclear whether the methods are appropriate in patients with AD. Patients with AD have impairment of short-term memory and may have difficulties understanding simple instructions. Consequently, some of the discrepancies found in the literature in regard to pain perception in AD patients may be due to unintentional use of assessment methods that are not reliable in patients

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with AD. Only 1 study has evaluated some aspects of reliability (ie, coefficient of variation) [15], and at present it is unknown whether the methods used in prior studies were appropriate as no studies have thoroughly investigated the reliability or agreement of the methods used. In order to bring this research forward, it is essential to thoroughly examine test-retest reliability and agreement to clarify whether the methods used are appropriate. Second, in order to be able to compare with other studies, it is important to use methods for which standardized protocols have been published [32,43]. The primary aim of our study was to estimate test-retest reliability and agreement of different pain sensitivity models using quantitative sensory testing, ie, assessments of thermal and mechanical thresholds, and assessments of tolerance to cold and pressure stimuli, in patients with AD. If the reliability and agreement of 1 or several of the models were judged to be acceptable, the secondary aim was to investigate the effects of mild to moderate AD on pain processing.

2. Patients and methods

2.1. Subjects

The protocol was approved by the Regional Committees on Health Research Ethics of the Capital Region of Denmark (protocol: H-4-2010-099) and the Data Protection Agency (journal number: 2007-58-0015/30-0862).

Twenty-nine patients were recruited among outpatients from the Memory Clinic at Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. All patients fulfilled the 10th revision of the International Statistical Classification of Diseases and Related Health Problems and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia and had a diagnosis of probable AD according to the McKhann criteria [25], which was given as a consensus diagnosis by a group of dementia specialists. The patients included were examined with a cranial computed tomography or magnetic resonance imaging (MRI), blood sample screening, and cognitive tests as part of their initial workup. Patients were able to give informed consent, and all had a caregiver who was willing to participate. We choose patients with a Mini Mental State Examination (MMSE, see description later) score between 16 and 26 points (both limits included) and a Clinical Dementia Rating (see description below) of 0.5 to 2 (both limits included), which is equal to mild to moderate dementia. The MMSE limits had been chosen as the authors believed that patients within this range would be able to cooperate with the tests and give informed consent (for further information see description of MMSE later).

We included 29 age- and gender-matched healthy control subjects. The control subjects were recruited from a group of elderly people who had previously participated in studies at the memory clinic, where they had been cognitively tested and had been found not to have dementia or mild cognitive impairment. All participants gave informed consent to the study protocol. Both patients and control subjects were excluded if they had significant psychiatric comorbidity, prior or present alcohol abuse, used daily analgesics (ie, paracetamol, nonsteroidal anti-inflammatory drugs, opioids, gabapentin/pregabalin, or tricyclic antidepressants) or had a disorder that would interfere with pain perception and pain report, such as diabetes, peripheral or central neuropathy, a chronic pain disorder, or current pain condition. They also were excluded if they had significant medical comorbidity or previously had a transient ischemic attack or stroke. Patients with a mixed diagnosis of vascular dementia and AD were excluded. At baseline, both patients and control subjects had a neurological examination and were excluded if they had any symptoms or signs of any neurological or inflammatory disease that could interfere with pain perception.

2.2. Measures

2.2.1. Evaluation of global cognitive function

To evaluate the participants' cognitive status, an MMSE was used. The MMSE is a screening instrument that is a brief standardized method to assess mental status. The score ranges from 0 to 30, with higher scores indicating better cognitive performance [14]. The MMSE is highly dependent on educational level [11], and in Denmark, where there is generally a high level of education, the optimal cutoff for dementia in population-based studies has been determined to 26 [19]. To further evaluate the patients, we also administered the Addenbrookes Cognitive Examination (ACE). The ACE is a brief test battery that includes the MMSE, but expands on cognitive domains such as memory, language, and visuospatial function, and includes a test of verbal fluency [24]. It takes 10 minutes to administer and requires no specialized equipment. ACE has been validated in Danish with an optimal cutoff of 85 of 86 for dementia [40]. The Clinical Dementia Rating is a numeric scale used to quantify the severity of dementia (ie, its stage). It uses a structured interview protocol to assess the patient's cognitive and functional performance in 6 areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scores in each of these are combined to obtain a composite score ranging from 0 through 3, with 3 indicating a severe stage of dementia [5].

2.2.2. Activities of Daily Living (ADL) function

The ADL function was assessed using the Functional Activities Questionnaire and the Instrumental Activities of Daily Living Scale [30], which is a questionnaire evaluating 10 different activities of daily living with a maximum score of 30 (dependent on help).

2.2.3. Depressive symptoms

The participants were screened for signs of a major depression with the Geriatric Depression Scale, 15 items. The Geriatric Depression Scale is a self-reported questionnaire specifically developed as a screening instrument for the presence of depressive symptoms in older populations [45]. The maximum possible score is 15. As most of the patients were unable to complete the questionnaire on their own, it was completed as an interview.

2.2.4. Reaction time

Reaction time was measured using: http://getyourwebsite-here.com/jswb/rttest01.html, showing a traffic light. The subject was instructed to press the button when the light changed from red to green. The light changed with a random interval (up to 7 seconds). The participants were allowed to try the test before recording the reaction time, in order for them to feel comfortable using the test. Ten measurements were made, and a mean value was presented.

2.3. Quantitative sensory testing

We used important elements from the standardized protocol for quantitative sensory testing published by the German Research Network on Neuropathic Pain [32] and the cold pressor test, for which guidelines for use in children have been published [43]. We chose to use only part of the protocol as patients with AD are not able to cooperate with long testing sessions, and we wished to be able to repeat the test. We chose methods that were easy to understand and to cooperate with, as this is crucial in doing any kind of examination on patients with AD. Additionally, we were interested in examining different pain modalities induced by either mechanical or thermal stimuli, and we considered the test stimuli suited for demonstrating activation of a range of nociceptors.

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