PAIN & AGING SECTION

Original Research Article

Chronic Pain in "Probable" Vascular Dementia: Preliminary Findings

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Abstract

Background. In a previous study, the levels of pain reported by patients with "possible" vascular dementia (VaD) were higher than those reported by older individuals without dementia.

Objective. To examine experienced pain in patients with "probable" VaD, confirmed by brain imaging.

Study Design. Observational, cross sectional.

Setting. Nursing home.

Methods. The participants were 20 nursing home residents (14 females, 6 males) who met the NINDS-AIREN criteria for "probable" VaD and 22 nursing home residents with a normal mental status (18 females, 4 males). The patients were in a mild to moderate stage of dementia. All of the participants were suffering from arthritis/arthrosis or osteoporosis. Global cognitive functioning was measured by the Mini-Mental State Examination. Pain was assessed by the Coloured Analogue Scale (CAS: original and modified version) and the Faces Pain Scale. The Geriatric Depression Scale and the Symptom Checklist-90 were used to assess mood.

Results. The main finding was that, after controlling for mood, the pain levels indicated by patients with "probable" VaD (M = 102.32; standard deviation [SD] = 53.42) were significantly higher than those indicated by the control group (M = 59.17; SD = 38.75), only according to the CAS modified version ($F[1,29]) = 5.62$, $P = 0.01$, $\eta^2 = 0.16$).

Conclusion. As VaD patients may experience greater pain than controls, it is essential for prescribers to be aware of the presence of this neuropathology if these patients are to receive adequate treatment.

Key Words: Pain Intensity; Pain Affect; Probable Vascular Dementia; Pain Treatment; Central Neuropathic Pain; White Matter Lesions

Introduction

Age is a risk factor for dementia [1]. More specifically, an increase in life expectancy coincides with a higher prevalence of Alzheimer's disease (AD) [2]. Age also enhances the risk of pain [3], such as musculoskeletal pain [4]. As life expectancy is expected to increase still further in the years ahead [5], we argue that the number of dementia patients suffering from pain will increase in the near future.

Most studies on pain in dementia focus on patients with "dementia," with no further specification of the diagnosis, for example, AD, Lewy Body disease, vascular dementia (VaD), combined AD and VaD, or frontotemporal dementia (FTD). These are the most prevalent subtypes of dementia [6,7]. The majority of clinical and experimental studies on pain that did distinguish between subtypes of dementia focused on patients with AD. In these studies, the pain levels reported by AD patients were lower than those reported by controls [8,9,10]. Indeed, a reduction in the

use of analgesics was also found, particularly in the treatment of chronic pain in AD patients [11]. It has been suggested that in patients with AD, cortical atrophy (including the hippocampus, for example) may cause a decrease in experienced pain [12]. The hippocampus is involved in the processing of pain, specifically its motivational–affective and cognitive–evaluative aspects [12]. In contrast, Cole and colleagues [13] found that brain regions involved in pain processing show even higher levels of activity in mild stage AD, which suggests that they experience greater distress than those without dementia. An increase in experienced pain in AD might also be due to white matter lesions [14, 15]. White matter lesions may cause an increase in experienced pain [16,17] by damaging ascending pathways to the thalamus, for example, such as the spinothalamic tract [18]. This is known as central neuropathic pain, which can also affect stroke patients [19]. However, white matter lesions are a neuropathological hallmark of patients with VaD, much more so than in AD. This may account for the fact that VaD patients have the highest risk of suffering an increase in experienced pain [12].

As far as the authors are aware, there has only been a single study into the experience of clinical chronic pain in patients with VaD [16]. The results of that study suggest that VaD patients indicate higher levels of experienced chronic pain. However, a serious limitation of this study was that participants did not meet the diagnostic criteria for "probable" VaD [20], the strictest diagnosis in living patients. A diagnosis of "probable" VaD can only be made if the presence of white matter lesions is confirmed by brain imaging (CT or MRI) [20]. No such data were available in that study [16] as brain imaging is not a standard procedure in nursing homes in the Netherlands. The most feasible diagnosis in that study was "possible" VaD, according to the criteria developed by Román and coworkers [20].

The goal of the present study was, therefore, to take the next logical step and refine the diagnosis. As a result, the study only includes VaD patients who have had a CT scan or MRI confirming a diagnosis of "probable" VaD [20]. Based on studies of poststroke pain [19] and on the study of pain in patients with "possible" VaD [16], it was hypothesized that pain levels (from chronic painful conditions such as arthrosis/arthritis) indicated by patients with "probable" VaD would exceed those indicated by older individuals without dementia.

Methods

Subjects

The sample consisted of two groups of participants who lived in three nursing homes belonging to one large nursing home organization in the Netherlands. One group consisted of 20 patients (14 females, 6 males) in a mild to moderate stage of dementia (see Results, Global cognitive functioning) who met the NINDS-AIREN criteria for "prob-

able" VaD [20]; the other consisted of 22 elderly individuals without a cognitive impairment (18 females, 4 males).

Inclusion Criteria

First, the diagnosis of VaD was confirmed by the nursing home physician and/or neurologist. Subsequently, to be included in the study, our patients had to meet the following NINDS-AIREN criteria for the diagnosis of "probable" VaD [20]: 1) cognitive decline: an impairment in episodic memory (word list learning) and in two or more other cognitive domains; 2) a confirmation of the diagnosis of VaD using a CT scan. More specifically, four patients were found to have a lacunar infarction (basal ganglia, caudate nucleus, 2× capsula interna), two patients had an intracerebral hemorrhage (subarachnoid space), and five patients had leuko-araiosis (periventricular). In the remaining five patients, CT scans revealed only a single lesion (e.g., frontal, fronto-parietal). Concerning the remaining three patients, no detailed information was available in the medical records except for the diagnosis VaD; and 3) executive dysfunction. In addition, the scores on recognition memory must be higher than the scores on active retrieval after learning of a word list (Table 1); this finding would further support the diagnosis of VaD [21]. For a detailed description of the various neuropsychological tests, see next section. A final inclusion criterion for both groups was the presence of one chronic painful condition (i.e., arthritis/arthrosis or osteoporosis). This information was registered in the medical record and supported by the treating nursing home physician specialist [22].

Exclusion Criteria

Individuals were excluded from participation if they had a psychiatric history (e.g., depressive, bipolar disorder), alcohol abuse, other neurodegenerative diseases (e.g., M. Parkinson, a decline in consciousness, a stroke, and a brain tumor). In addition, none of the patients had a diagnosis of AD or mixed dementia, which is indicative of concurrent VaD and AD.

Education

Level of education was rated with an ordinal 7-point rating scale [23]. Elementary school not finished: 1; elementary school finished: 2; elementary school finished with additional education of less than 2 years: 3; lower level secondary school: 4; secondary school: 5; higher level secondary school: 6; and preuniversity education: 7.

Comorbidity

All participants suffered from a chronic painful condition (i.e., arthritis/arthrosis or osteoporosis). Other comorbidities such as disorders of the circulatory tract (coronary disease, heart disease, peripheral vascular disease), gastrointestinal tract, and urinary tract, lung disease (e.g., chronic obstructive pulmonary disease), endocrine diseases (e.g., diabetes mellitus), and disorders of the sensori-motor system were extracted from the medical records.

Table 1 Means (M), SDs, and *t*-tests concerning the scores on the various neuropsychological tests by the group of patients with vascular dementia and the control group

	Patients with Vascular Dementia		Control Group		t-Tests		
	M	SD	M	SD	t	df	P<
Verbal memory							
Eight-word test							
Direct recall	18.65	7.39	25.36	5.28	3.41	40	0.001**
Delayed recall	1.10	1.45	3.77	2.16	4.66	40	0.001**
Recognition	12.65	2.32	14.86	1.70	3.55	40	0.001**
Digit span forward	9.85	2.35	11.09	1.85	1.91	40	0.07
Visual memory							
Face recognition	6.80	4.37	9.27	4.30	1.85	40	0.08
Picture recognition	17.65	9.92	26.09	8.52	2.97	40	0.006
Visuospatial memory							
Knox Cube Test	8.22	1.67	9.23	1.15	2.25	38	0.04
Executive functions							
Digit span backward	5.65	2.46	7.14	1.52	2.38	40	0.03
Rule shift cards	6.56	3.19	2.91	3.18	3.61	38	0.001**
Key search test	4.68	2.85	7.68	3.09	3.21	39	0.002**
Verbal fluency							
Animals	8.60	3.86	16.55	6.22	4.92	40	0.001**
Professions	6.20	2.78	11.55	5.29	4.04	40	0.001**

** Level of significance was set at $P < 0.005$ to correct for multiple tests; one-tailed.
SD = standard deviations

Depression and Anxiety

It is known that a close relationship exists between depression, anxiety, and pain [24,25]. Therefore, the Geriatric Depression Scale (30 items) [26], Dutch version [27], and the subscales depression (15 items) and anxiety (10 items) of the Symptom Checklist-90 [28], Dutch version [29], were administered. To strive for data reduction, *z* scores of the three scales were added to compose a mood domain: Cronbach's alpha: 0.85.

Medication

The prescription of the following medication was registered during the period spanning the two pain assessments (see Procedure): acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and morphine. The medication was prescribed on an "only-if-needed" basis.

Informed Consent

The participants and their legal representatives were extensively informed about the aim and procedure of the study. Subsequently, participants in the control group and the patients were asked to participate and to fill in a written informed consent. Concerning the patients, the legal representatives were also asked for permission to include the patient in the study and were requested to fill in a written informed consent. The local medical ethical committee approved the study.

Material and Procedure

Measures

Neuropsychological Assessment of VaD

Assessment of Global Cognitive Functioning. Global cognitive functioning was assessed by the Mini-Mental State Examination (MMSE) [30]. Maximum score is 30.

Assessment of Specific Cognitive Functions for the Diagnosis of "Probable" VaD. A variety of neuropsychological tests, assessing specific cognitive functions, was administered to meet all the NINDS-AIREN criteria of Román and coworkers [20]. The cognitive domains included verbal and visual short- and long-term memory, visuospatial attention, and executive functions.

Verbal Long-Term Memory. The eight-word test of the Amsterdam Dementia Screening [31] assesses verbal long-term memory, that is, direct recall (max. score: 40), delayed recall (max. score: 8), and recognition score (maximum score: 16).

Attention and Verbal Short-Term Memory. Digit span forward is a subtest of the Wechsler Adult Intelligence Scale (WAIS, Dutch version; maximum score: 14) [32] and is meant to assess attention and short-term verbal memory.

Visual Long-Term Memory. Face and picture recognition are subtests of the Rivermead Behavioural Memory test [33] assessing nonverbal long-term recognition memory (max. score face recognition: 20; maximum score picture recognition: 40).

Visuospatial Attention. The Knox Cube test [34] is meant to assess visuospatial, nonverbal immediate attention, with a maximum score of 18.

Executive Functions. Digit span backward is a subtest of the WAIS [32] measuring verbal working memory. Maximum score is 21. Rule Shift Card Test is a subtest of the Behavioural Assessment of Dysexecutive Syndrome (BADS) [35] which measures mental flexibility and impulse control (maximum score: 21). The key search test is another subtest of the BADS and measures planning ability (maximum score: 16). Verbal fluency is a subtest of the Groninger Intelligence Test (the maximum score depends on how many words the participant is able to mention) [36].

Vital and Gnostic Sensitivity

To assess whether the afferent pathways that mediate sensory stimuli to the central nervous system, including nociceptive stimuli, are intact, vital and gnostic sensitivity were tested by a standard neurological examination.

Vital sensitivity included 1) touch, tested by touching the forearm and the hand on different places by means of a cotton wool; 2) temperature, assessed by applying two plastic tubes, one filled with lukewarm water, one filled with cold water, to the skin of the forearm and the hand in random order; the participant was asked to indicate whether the temperature was warm or cold; and 3) sense of pain, tested by a pinprick, that is, applying a needle with a sharp and a blunt side to the forearm and hand in random order. During these tests, the participants had to close their eyes and indicate whether they felt the sharp or the blunt side. *Gnostic sensitivity* was assessed by placing a finger of the patient in a certain position (e.g., bent or stretched). With the eyes closed, the patient has to indicate which finger has been placed in which position (e.g., index finger, bent).

Pain

In assessing pain, a vertical visual analogue scale and a Faces Pain scale were administered. The vertical visual analogue scale is in fact a pain "thermometer," and such a pain assessment instrument is preferred by cognitively impaired older persons [37]. These scales have been shown to have high intrarater and interrater reliability, as measured by intraclass correlation coefficients (ICCs). The ICC between the two assessments were 0.87 for the vertical visual analogue scale, and 0.71 for the Faces Pain Scale. The ICC between two different raters were 0.94 and 0.97, respectively [38].

The *Coloured Analogue Scale (CAS) original version* [39] is a kind of vertical pain "thermometer" with a plastic slide

that can be moved upwards ("most pain"; dark red color; score 100) and downwards ("no pain"; white/pink color; score 0). We used the CAS original version to assess particularly the intensity of pain.

Comprehension of the scale. First, we assessed whether the participant understood the concept of the scale by asking: "suppose someone, not you, has a lot of pain, in what direction would you move the plastic slide, upwards or downwards"? If the participant understood the concept of the scale, we subsequently asked to indicate how much pain they experience themselves.

Modified CAS was administered to assess the more affective aspects of pain: The label "worst pain" was replaced by "worst suffering" (score 100) and the label "no pain" by "no suffering" (score 0).

Comprehension of the scale. We used the same procedure as with the CAS original version; however, we replaced "has a lot of pain" by "suffers from a lot of pain."

Faces Pain Scale [40] is a 7-point scale consisting of seven different faces expressing no pain (one face) and various intensities of pain (six faces). The scale is primarily meant to assess the intensity of pain [40]. Scores range from 0 (no pain) to 6 (most severe pain).

Comprehension of the scale. To assess whether the participant understood the concept of the scale, we showed all the faces to the participant and asked the participant to indicate which face represented no pain at all and which face represented the most severe pain. After a correct response, we asked the participants to indicate how much pain they experience themselves.

Procedure

As pain caused by arthrosis/arthritis and osteoporosis might change (less or more) over a period of time, each pain scale was administered twice, with an interval of, on average, 2 months. For each participant, the two pain scores were summed up (maximum score of 200 for the CAS original and maximum score of 200 for the Modified CAS). Subsequently the two scores of the CAS original version and the Modified CAS were summed up into one pain score (maximum score: 400). The tests for vital and gnostic sensitivity, the neuropsychological tests, and the scales for depression and anxiety were administered only once. The order in which the tests were administered was as follows: first, the pain scales and tests for vital and gnostic sensitivity, followed by the neuropsychological tests. Finally, the depression and anxiety questionnaires were administered.

Six well-trained master students, studying Clinical Neuropsychology, collected the data. The administration of the tests took place in a private room at the nursing home (e.g., the nursing station). This ensured that participants would not be distracted during the tests. Rest periods were, of course, allowed, if requested by the participants.

Data Analyses

Data were analyzed by means of Mann–Whitney *U*-tests, *t*-tests, chi-squared tests, and analyses of variance with mood as a covariate (ANCOVA) (SPSS version 20.0, SPSS Inc., Chicago, IL, USA). Analgesics appeared not to correlate with pain experience, as assessed by the various pain instruments. Accordingly, analgesics were not included as a covariate in the data analyses. Concerning cognition, level of significance was set at $P < 0.005$ to control for multiple tests. For the remaining dependent variables, level of significance was set at $P < 0.05$, one-tailed. Effect sizes $\eta2$ were small, 0.1; moderate, 0.6; and large, 0.14 [41].

Results

Demographics

The mean age of the VaD group (M = 80.85, standard deviation [SD] = 4.91) differed significantly from the age of the control group (M = 85.59, SD = 5.60) ($t[40] = 2.90$, $P = 0.006$). Gender did not differ significantly between both groups ($\chi^2 = 0.81$, df = 2, $P = 0.37$). Furthermore, the level of education of the VaD group (median = 3; IQR: 2) and the control group (median 4; IQR: 3) did not differ significantly (Mann–Whitney *U*: $Z = 1.36$, $P = 0.19$).

Comorbidity

The presence/absence of these disorders, expressed in percentages, did not differ significantly between both groups (results from data analyses by chi-squared are not shown). Consequently, the percentage of total comorbidity did not differ between both groups ($\chi^2 = 15.09$, df = 12, $P = 0.24$).

Analgesics

Patients with VaD and participants of the control group did not differ significantly concerning the use of acetaminophen (paracetamol [acetaminophen]), NSAIDs, and morphine (see Table 2). Similarly, concerning the overall use of

Table 2 Percentages and chi-squared tests relating to the use of paracetamol, NSAIDs, and morphine in the group of patients with vascular dementia and in the control group

Analgesics	Patients with Vascular Dementia %	Control Group %	Chi-Squared Tests		
			χ^2	df	*P*
Paracetamol	18.2	31.6	0.26	1	0.61
NSAIDs	27.3	10.5	1.41	1	0.24
Morphine	9.1	10.5	0.02	1	1.00
Overall use	45.5	42.1	0.08	2	0.96

NSAID = non-steroidal anti-inflammatory drug.

analgesics, both groups did not show a significant difference.

Mood

Both groups did not differ significantly concerning depression and anxiety (see Table 3 for means, SDs, and *t*-tests).

Global Cognitive Functioning

As expected, the MMSE scores differed significantly between the VaD group (M = 19.50, range: 11–24) and the control group (M = 26.95, range: 25–29) ($t[40] = 9.02$, $P < 0.001$).

Specific Cognitive Functions

Data analyses by means of *t*-tests show that, compared with the control group, patients with VaD perform significantly worse on tests appealing to verbal memory (eight-word test) and executive functions (rule shift cards, key search test, and verbal fluency). Furthermore, the difference between both groups concerning picture recognition showed a trend; the mean score on Picture recognition of patients with VaD was lower than that of the control group. For means, SDs, and *t*-tests, see Table 1.

Vital and Gnostic Sensitivity

Vital Sensitivity

Temperature did not differ significantly between both groups ($\chi^2 = 0.01$, df = 1, $P = 0.95$). Similar findings were observed concerning sense of pain ($\chi^2 = 1.67$, df = 1, $P = 0.20$). The participants of both groups correctly reported each time they were touched by a cotton wool.

Gnostic Sensitivity

No significant difference was observed between both groups ($\chi^2 = 0.31$, df = 1, $P = 0.58$).

Pain

CAS Original

An analysis of variance with anxiety/depression as a covariate showed that the VaD patients (M = 103.75; SD = 59.41) did not differ significantly from the control group (M = 74.14; SD = 43.20) ($F[1,29] = 1.56$, $P = 0.11$, $\eta^2 = 0.05$).

CAS Modified

An analysis of variance with anxiety/depression as a covariate showed that the VaD patients had a significantly higher mean pain score (M = 102.32; SD = 53.42) than the control group (M = 59.17; SD = 38.75) ($F[1,29] = 5.62$, $P = 0.01$, $\eta^2 = 0.16$).

Table 3 Means (M), SDs, and *t*-tests concerning the depression and anxiety scores of the group of patients with vascular dementia and the control group

	Patients with Vascular Dementia		Control Group		*t*-Tests		
	M	SD	M	SD	*t*	df	*P*
GDS	10.06	6.42	8.23	5.42	0.98	38	0.34
SCL-90 anxiety	15.47	7.20	13.71	5.06	0.90	38	0.37
SCL-90 depression	25.53	9.78	24.43	7.89	0.39	38	0.70

GDS = Geriatric Depression Scale; SCL-90 = Symptom Check List-90; SD = standard deviation.

Faces Pain Scale

The VaD group (M = 4.00; SD = 2.30) and the control group (M = 3.11; SD = 2.70) did not show a significant difference concerning the Faces Pain Scale ($F[1,27] = 0.94$, $P = 0.17$, $\eta^2 = 0.04$).

Discussion

Key Finding

To our knowledge, this is the first study to examine experienced pain in patients with "probable" VaD. It is difficult to make this diagnosis in nursing homes as brain imaging is not a standard procedure in these institutions. However, this affects millions of people with dementia throughout the world. The key finding in the present study is that patients in a mild to moderate stage of "probable" VaD report experiencing significantly more chronic pain than do older individuals without dementia. A large effect size was involved. This finding confirms the results of our previous study, which focused on patients with "possible" VaD [16].

Chronic Pain in VaD

The hypothesis that an increase in pain in patients with "probable" VaD who are also suffering from conditions such as arthrosis/arthritis or osteoporosis that might be caused by white matter damage (due to deafferentiation) is only partly supported by the present study. White matter lesions were explicitly reported in about half of the patients. On the other hand, in those with a single lesion, hypertension was observed, and a close relationship between hypertension and white matter lesions is well known [42]. The clinical relevance of the finding reported here is that because patients with white matter lesions exhibit a combination of increased pain and decreased cognition, they are at risk of being undertreated for pain [43]. In the present study, there is only indirect support for the latter suggestion. There were no reliable details about the dosages of analgesics given, but although the number of participants for whom analgesics were prescribed on an "only if needed" basis was the same in both groups, the patients with "probable" VaD reported more severe pain. We argue that the presence of white matter lesions in AD [44] and FTD [45] should alert attending physicians to the fact that their patients may be experiencing increased pain and that the doses of pain medication should be adjusted accordingly.

Central Neuropathic Pain

The rationale for testing vital and gnostic sensitivity was that VaD patients exhibit decreased glucose metabolism in regions such as the thalamus [46]. The thalamus is known to transmit somatosensory information to the cortex [47], and any dysfunction in this process can cause central neuropathic pain [48]. This pain, in turn, might be reflected by either hypoalgesia or hyperalgesia to a pin-prick (sense of pain), for example [49]. However, there was no significant difference between these groups in terms of their responses to the tests for temperature sensitivity, sense of pain, and gnostic sensitivity. This part of the study was affected by the limitation that vital and gnostic sensory testing was restricted to the participants' fore-arms, rather than using several different parts of the body. It is essential for the attending physician to know whether or not their patient's pain is of central origin as this type of pain does not respond to acetaminophen. In such cases, antidepressants and antiepileptic drugs might be more effective [50].

Diagnosis of "Probable" Subcortical Ischaemic VaD

Our cognitive data meet the NINDS-AIRENS criteria on which the diagnosis of "probable" VaD is based [20], that is, a cognitive decline in episodic memory (eight-word test) and in two or more other cognitive domains, that is, visual memory (picture recognition) and executive functions (rule shift cards, key search test, and verbal fluency). Although a decline in executive functioning supports a diagnosis of "probable" VaD [51,52], there is some evidence to suggest that the impairment in verbal fluency observed here might instead be an indication of AD. Indeed, in some studies comparing VaD patients with AD patients, the latter achieved poorer verbal fluency scores than VaD patients [53]. However, the verbal fluency scores of VaD patients were still significantly lower than those of the control group [53], which corresponds to our own findings. Yet AD patients were not always outperformed by VaD patients in terms of verbal fluency scores. In one study, they performed this task better than VaD patients, although the difference involved was not significant [54].

The diagnosis of VaD is further supported by the fact that the patients in the present study scored higher on the recognition test than on the delayed recall subtest of the eight-word test (see Table 1). The latter requires the active retrieval of information from a memory store, a process that has been found to be particularly severely impaired in VaD patients [21].

On the other hand, the NINDS-AIREN criteria are known to exhibit relatively low sensitivity. Gold et al. [55] report a sensitivity of 58% and a specificity of 80%. However, in another study, the psychometric qualities of NINDS-AIREN criteria were compared with three other diagnostic "schemes," that is, the ADDTC criteria (AD Diagnostic and Treatment Center's criteria for ischemic vascular dementia), Bennett's criteria for Binswanger's disease, and the ICD-10 criteria for VaD [56]. It was concluded that a diagnosis of VaD made by using one of these schemes was not always confirmed by the others [56]. According to the authors, the heterogeneous nature of VaD tends to undermine the usefulness of these schemes. Instead, they emphasize the diagnostic value of factors such as these patients' neuropsychological functioning (e.g., a more severe decline in executive functions compared with recognition memory).

Additional Limitations

One of the inclusion criteria was that VaD had to be confirmed by a neurologist who performed brain imaging. However, a visit to a neurologist who performs brain imaging is not a standard procedure in nursing homes in the Netherlands. A second criterion was that the patient's medical status had to indicate the presence of arthrosis/arthritis or osteoporosis. The third criterion was that the individual had to be willing to participate. Together, these three inclusion criteria greatly limited the number of participants that were able to meet the inclusion requirements for the present study. As a result, it took approximately 6 years to complete the study. Nevertheless, it would be feasible to carry out a large-scale study, particularly if the patients in question were at a relatively early stage of the disease. Such patients still live at home and are referred to a university hospital for a one-day screening that includes CT/MRI, a neuropsychological examination, and a blood test. A large-scale study would also address a second limitation, that is, VaD has a heterogeneous etiology, so it would have been useful to subdivide the groups and analyze the data per subgroup. However, given the limited number of participants in the present study, there would be too few individuals in each subgroup to carry out subgroup analyses of this kind. A third limitation is that we assume that if the patient understands the concept of a pain scale, then their understanding of the concept of "pain" (in the sense of somatic pain) is also intact. However, it is possible that the patient is suffering from grief (due to the loss of a child, for example) and that they translate this as "pain." A fourth limitation is the use of the Geriatric Depression Scale as a means of assessing depression in a group of patients with dementia. The validity of this instrument in this specific population has

been questioned [57], at least for those with an MMSE score below 14. A final limitation is that we have no information on the subjects' medication use during the 24 hours immediately preceding the pain assessment procedure.

Clinical and Research Implications

As VaD patients appear to experience more pain than controls, it is essential for prescribers to be aware of the presence of this neuropathology if these patients are to receive adequate pain treatment. Larger-scale brain imaging studies, confirming the present findings, will reduce the risk that millions of patients suffering from VaD will be undertreated for pain.

Finally, given the number of patients involved, together with other limitations, it should be noted that these findings are preliminary in nature and that they need to be validated by future studies.

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