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RESEARCH ARTICLE

Safety and tolerability of lumbar puncture for the evaluation of Alzheimer's disease

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Abstract

Introduction: Lumbar puncture (LP) to collect and examine cerebrospinal fluid (CSF) is an important option for the evaluation of Alzheimer's disease (AD) biomarkers but it is not routinely performed due to its invasiveness and link to adverse effects (AE).

Methods: We include all participants who received at least one LP in the Alzheimer's Disease Neuroimaging Initiative (ADNI) Study. For comparison between groups, two-sample *t*-tests for continuous, and Pearson's chi-square test for categorical variables were performed.

Results: Two hundred twenty-seven LP-related AEs were reported by 172 participants after 1702 LPs (13.3%). The mean age of participants who reported at least one AE was 69.79 (standard deviation (SD) 6.3) versus none 72.44 (7.17) years ($p < 0.001$) with female predominance (115/172 = 67.4% vs 435/913 = 48%), and had greater entorhinal cortical thickness and hippocampal volume (3.903 (0.782) vs 3.684 (0.775) mm, $p = 0.002$; 7.38 (1.06) vs 7.05 (1.15) mm^3, $p < 0.001$), respectively.

Discussion: We found that younger age, female sex, and greater thickness of the entorhinal cortex were associated with a higher rate of LP-related AE reports.

KEYWORDS
adverse effects, Alzheimer's disease, biomarker, brain volume, cerebrospinal fluid, lumbar puncture, pain relief medication

1 | INTRODUCTION

The current definition of Alzheimer's disease (AD) as a biological construct is enhancing the importance of confirming biological evidence of the three core AD biomarkers: amyloid plaques, neurofibrillary tangles, and neurodegeneration in addition to established clinical signs and symptoms.[1]

This development increases the role of their detection in asymptomatic individuals at the preclinical stage, which will allow such individuals to be included in prevention trials.

At present, there are a number of options to detect the status of these three parameters in vivo. These include cerebrospinal fluid (CSF) analyses, magnetic resonance imaging (MRI), and positron emission tomography (PET) imaging. Both CSF biomarkers obtained by lumbar puncture and imaging biomarkers obtained by PET imaging are recognized in the diagnostic criteria for dementia due to Alzheimer's disease (DAD). PET imaging remains the most widely utilized method for detecting AD pathology but has limited availability and much higher cost.

The value of these biomarkers should not only be seen in the research setting but also in clinical practice. Knowledge about a patient's amyloid status will increase confidence in the diagnosis and may lead to change in management including treatment.[2]

On the other hand, although not routinely performed in clinical practice at this time point, confirmation of elevated brain amyloid in cognitively normal individuals will help classify them as individuals on the AD continuum, and allow them to participate in prevention trials, at the earliest identifiable stage of disease. Additional AD biomarkers will provide even more accurate information about diagnosis, prognosis, and expected rate of decline.[3,4] The use of CSF ratios (amyloid beta [Aβ]1-42/1-40 and tau/Aβ1-42) is recommended for reliable differentiation between AD and non-AD at clinically symptomatic stages of disease but should also be preferred at the preclinical (asymptomatic) stage. CSF ratios (Aβ1-42/1-40 or Aβ1-42/1-38) demonstrate better performance as they correct for inter-individual differences in total Aβ levels.[5,6,7] Having positive results for one or for both AD biomarkers predicts a greater likelihood to progression from the preclinical stage of AD to mild cognitive impairment (MCI) due to AD. Only 3.3% of amyloid PET− (A−) and tau PET− (T−) and 8.9% of amyloid PET+ (A+) and T− cognitively normal individuals developed MCI, in contrast to 49.0% of A+ and tau PET+ (in the medial temporal lobe) or 53.3% of A+T+ (in the temporal neocortex) during an average follow-up of 41.8 $\pm$ 18.9 standard deviation (SD) months. Most recently, plasma biomarkers have demonstrated great promise in detecting AD-related changes in the brain.[9,10,11,12,13]

Moreover, with recent approval of the first two disease-modifying drugs, the confirmed evidence of AD-related amyloid abnormality in individuals in the early clinical stage of Alzheimer's disease (MCI due to AD or mild AD dementia [ADD]) will help physicians select the appropriate individuals for treatment.[14,15]

Although lumbar puncture (LP) is performed frequently in the neurology inpatient for a variety of indications, it is used less in the outpatient setting. Despite worldwide availability, it is not the preferred modality as an elective procedure in the diagnostic workup of AD. Some of the reasons for this limited use in the clinical setting are its invasiveness and link to more AEs than imaging or blood-based testing. Additional contributing factors are insufficient or general lack of reimbursement in some regions and until now the lack of significant treatment consequences.[16,17] However, this is expected to change significantly in the very near future as the use of newly approved treatments will require confirmation of elevated brain amyloid. This need of confirmation will surely trigger an increase in the frequency of LPs, as it is expected that the PET costs and lack of global availability will not change soon, and the very promising blood-based biomarkers are still in their early steps.

The existing evidence for the use of LP not only in AD but also in other slow or rapid neurodegenerative and inflammatory diseases shows that it is safe and well tolerated. The most commonly reported AEs are headaches and pain in the needle-insertion area.[18,19,20,21]

The Alzheimer's Disease Neuroimaging Initiative (ADNI), a multisite observational longitudinal study of AD progression and biomarkers, affords a unique opportunity to evaluate AE incidence in a well-characterized cohort of older adults undergoing research evaluations for AD pathophysiology.[22,23] Using this database, we asked what the predictors of LP-related AEs were, including age, sex, cognitive status, and brain volume.

2 | METHODS

Written informed consent was obtained from all participants. ADNI 2[22] and ADNI 3[23] are multi-center observational studies enrolling individuals at risk for developing AD. CSF is collected to measure concentrations of Aβ and tau proteins and storage for the development of novel biomarkers. In the context of our study, none of the participants was blinded in any way to the procedure. From the 1330 ADNI 2+3 participants (age 72.1 (SD 7.1), 650 female (50%), 10% other than White), 1085 completed at least one LP procedure resulting in a retrospective study of 1702 LPs. The ADNI study protocols include specific guidelines for LP performance but allow some flexibility in procedural variables. After the procedure, the participants were assessed for the presence of any immediate postprocedural AE following LP, after 24 h, per telephone interview and were allowed to call the study team at any time between visits. Participants were also asked

for any AE in general and AEs related to LP at the next study visit (12 months after). Such cases were included too. If an AE was reported, participants were asked about severity, duration, treatment needed, and further additional information. This information together with the assessment of relatedness between LP and AE per the site principal investigator's opinion was collected on a dedicated case report form (CRF).

In this retrospective study, we investigated three domains for an association with postprocedural AE: demographics, clinical factors, and MRI characteristics. Data on participant age, sex, race, ethnicity, apolipoprotein E (*APOE*) ε4 carrier status, level of education, ongoing and/or related to LP use of pain relief medication, positioning (seated or lateral decubitus), CSF collection method (gravity or aspiration), needle type, and insertion interspace, were obtained from the ADNI 2 and 3 study database. In addition, whole-brain volume, entorhinal cortex thickness, and hippocampal volume were included. Six LPs were excluded from the study owing to missing information or administration problems.

2.1 | MRI data

MRI examinations were performed using 3T scanners at study sites. The MRI sequences used for image analysis in the current study were acquired as described online (http://adni.loni.ucla.edu/research/protocols/mri-protocols/).

2.2 | Statistical analysis

The demographic characteristics of the participants in the analysis population (those receiving LP) were summarized according to those who reported an AE related to LP versus those who did not. Summaries included frequencies and percentages for categorical variables and mean and SD for continuous data. Comparisons between groups (if sufficient data) were performed using two-sample *t*-tests for continuous variables between the two groups and Pearson's chi-square test for categorical variables.

LP-related AEs were summarized only if there were sufficient data for a respective lowest level term (LLT). Percentages (and 95% confidence intervals [Cis]) were reported for each applicable LLT overall and for each level of the independent variables considered.

A logistic regression model was fit to the outcome "AE Related to LP" (coded as 1 if such an AE occurred at any visit, vs 0 if received LP and had no such AE at any visit). Stepwise (forward and backward) model selection will be used to determine the optimal subset of predictors based on Akaike's information criterion (AIC) from among age, needle method, needle type, patient position, gender, ADNI protocol/wave, baseline diagnosis, *APOE* ε4 carriage, whole brain volume, entorhinal thickness, and hippocampal volume. All analyses are conducted using R version 4.0.4 (2021-02-15).

RESEARCH IN CONTEXT

1. **Systematic Review**: The incidence of adverse events (AEs) related to lumbar puncture in the literature (PubMed) differs due to use of heterogeneous definitions of some AEs and analyzed cohorts. However, the literature is supportive of the general opinion that this is a safe method but does not provide sufficient information on predictors for AEs.
2. **Interpretation**: Our findings demonstrate that younger age, female sex, and greater thickness of the entorhinal cortex are associated with a greater rate of lumbar-puncture–related AEs but are not influenced by ongoing use of pain-relieving medication or dementia diagnosis.
3. **Future Directions**: Bringing the available magnetic resonance imaging (MRI) brain volume data and pain-relieving medication use into the analysis opened the field for further investigation on the role of brain volume and pain experience in the context of AE reporting in Alzheimer's disease studies. In addition, we hope that our findings will support clinicians during the risk–benefit discussion with patients, especially now as the use of newly approved treatments for Alzheimer's disease will require confirmation of elevated brain amyloid.

3 | RESULTS

From the 1330 ADNI 2 and ADNI 3 participants, 1085 underwent at least one LP, and in total, 1702 LPs were completed. One hundred forty-two participants (PT) had three or more LPs during the period of interest. In total, 172 participants reported a total of 227 AEs related to LP procedure. Thirty-three participants reported two or more AEs for a given LP (Table 1). The majority of AEs were back pain (95 (5.6%)) and headaches (91 (5.3%)) (Table 2). Medication was needed for 82 (36.12%) of the AEs (Table 3).

Regarding participants' characteristics, the group of participants who reported an AE related to LP was younger than the group without AEs (mean [SD] 69.79 [6.34] vs 72.44 (7.17], $p < 0.001$) with greater representation of women in the first group (67% vs 48%, $p < 0.001$). Ongoing pain relief medication was used by more participants in the group with AE than without AE (20% vs 4%, $p < 0.001$). In the group with AE related to LP, the values for entorhinal cortical thickness and hippocampal volume were greater than in the group without such AEs (903 [0.782] vs 3.684 [0.775], $p = 0.002$ for entorhinal thickness; 7.38 [1.06] vs 7.05 [1.15], $p < 0.001$ for hippocampal volume), respectively (Table 1).

AIC selected age group, gender, entorhinal thickness, and diagnosis for the final logistic model, although the effect of baseline diagnosis was not significant. Younger age (<75 years) (odds ratio [OR] 2.1, 95%

TABLE 1 Participant and LP characteristics for participants who reported an AE following any LP versus those who did not report an AE.

	Ever Reported AE Related to LP (*N* = 172)	All LPs without AE (*N* = 913)	Total (*N* = 1085)	*p* value
Age				< 0.001
Mean (SD)	69.787 (6.337)	72.442 (7.168)	72.023 (7.107)	
Gender				< 0.001
Female	115 (66.9%)	435 (47.6%)	550 (50.7%)	
Male	57 (33.1%)	478 (52.4%)	535 (49.3%)	
DX.bl				0.022
CN	90 (52.3%)	392 (43.0%)	482 (44.5%)	
MCI	65 (37.8%)	365 (40.0%)	430 (39.7%)	
AD	17 (9.9%)	155 (17.0%)	172 (15.9%)	
Education				0.996
Mean (SD)	16.453 (2.502)	16.452 (2.532)	16.453 (2.526)	
Ethnicity				0.965
Unknown	1 (0.6%)	4 (0.4%)	5 (0.5%)	
Not Hispanic/Latino	164 (95.3%)	873 (95.6%)	1037 (95.6%)	
Hispanic/Latino	7 (4.1%)	36 (3.9%)	43 (4.0%)	
Race				0.291
American Indian/Alaska Native	0 (0.0%)	2 (0.2%)	2 (0.2%)	
Asian	2 (1.2%)	17 (1.9%)	19 (1.8%)	
Hawaiian/Other Pacific Islander	0 (0.0%)	2 (0.2%)	2 (0.2%)	
Black	13 (7.6%)	32 (3.5%)	45 (4.1%)	
White	154 (89.5%)	846 (92.7%)	1000 (92.2%)	
More than one	3 (1.7%)	13 (1.4%)	16 (1.5%)	
Unknown	0 (0.0%)	1 (0.1%)	1 (0.1%)	
***APOE ε4* carrier status**				0.431
Carrier	80 (47.1%)	391 (43.8%)	471 (44.3%)	
Non-carrier	90 (52.9%)	502 (56.2%)	592 (55.7%)	
Ever on painkiller prior to LP				0.983
Ever on painkiller	116 (67%)	615 (67%)	731 (67%)	
Never on painkiller	56 (33%)	298 (33%)	354 (33%)	
Blood Patch				< 0.001
No blood patch	166 (96.5%)	911 (99.8%)	1077 (99.3%)	
Lumbar puncture blood patch	6 (3.5%)	2 (0.2%)	8 (0.7%)	
Needle Type				0.969
Atraumatic	98 (58.3%)	522 (58.1%)	620 (58.2%)	
Other	6 (3.6%)	29 (3.2%)	35 (3.3%)	
Sharp beveled	64 (38.1%)	347 (38.6%)	411 (38.6%)	
Needle Method				0.413
Syringe suction	61 (35.7%)	278 (30.6%)	339 (31.4%)	
Gravity	96 (56.1%)	555 (61.1%)	651 (60.3%)	
More than one	14 (8.2%)	76 (8.4%)	90 (8.3%)	

Mean (standard deviation (SD)) and *t*-test are used for continuous data. Counts, percentages, and Pearson's chi-square test are used for categorical data. *N* is the number of non-missing values. Tests used: (1) *t*-test; (2) Pearson test. AD, Alzheimer's disease; AE, adverse effect; CN, cognitively normal; DX. bl, Diagnose at baseline; LP, lumbar puncture; MCI, Mild cognitive impairment.

TABLE 2 Counts and percentages of top preferred terms reported in participants who reported LP-related AE.

Preferred term	Events	Individuals
Back pain	95 (5.58%)	87 (8.02%)
Headache	91 (5.35%)	87 (8.02%)
Nausea	9 (0.53%)	9 (0.83%)
Syncope	7 (0.41%)	7 (0.65%)
Dizziness	4 (0.24%)	4 (0.37%)
Fatigue	4 (0.24%)	4 (0.37%)
Vomiting	4 (0.24%)	4 (0.37%)
Swelling at LP site	3 (0.18%)	3 (0.28%)
Sciatica	2 (0.12%)	2 (0.18%)
Stiff neck	2 (0.12%)	2 (0.18%)
Buttock pain	1 (0.06%)	1 (0.09%)
Ear discomfort	1 (0.06%)	1 (0.09%)
Hot flush	1 (0.06%)	1 (0.09%)
RBC in CSF	1 (0.06%)	1 (0.09%)
Shoulder pain	1 (0.06%)	1 (0.09%)
Subdural hematoma	1 (0.06%)	1 (0.09%)

The first column reports the number of events divided by the total number of LPs conducted ($N = 1702$). Second column reports the number of individuals divided by the total number of individuals receiving LP ($N = 1085$). RBC, red blood sells; CSF, cerebrospinal fluid; LP, lumbar puncture.

TABLE 3 Medication needed for adverse event related to LP.

Needed Medication for Adverse Event	N (participants)
No	118 (63.78%)
Yes	67 (36.22%)

CI 1.3 to 3.5), female gender (2.3, 95% CI 1.5 to 3.6), and greater thickness of the entorhinal cortex (1.5 per mm, 95% CI 1.1 to 2.0) were associated with increased odds of LP-related AE (Table 4).

4 | DISCUSSION

In total, 1702 LPs were conducted in 1085 participants. Only 16% reported an AE, of them 36.12% required medications and five required blood patches (0.3%). The group that reported AEs was on average 2 years younger and predominantly female. Using the MRI volumetric data, we found that participants who reported an AE related to LP had greater entorhinal cortical thickness and hippocampal volume. Of the 58 participants receiving pain relief medication prior to LP only 18 reported AE. Back pain and headache were the most common complaints (with 82% of all events).

In the literature, there is great heterogeneity in the process of collecting adverse effects. For example, some investigations analyzed only spontaneously reported AE by patients, whereas in contrast, other investigations, such as ADNI, interviewed the participants systematically after the procedure and 24–48 h after by phone interview, which may lead to an increase of reported AEs.

In general our findings are in agreement with the existing literature that LP is a safe and well-tolerated procedure.[18,19,20,21,24,25] If an AE occurs, it is very likely to be transient headache or back pain.[18,19,20] The likelihood of reporting some symptoms increases with younger age and female gender. Of interest, in our study, it was not influenced by memory status, ongoing use of pain relief medication, or needle type but by the thickness of the entorhinal cortex and the volume of the hippocampus. Larger brain volume, which is less atrophy, was related to a greater risk of reported AEs, particularly headache.

Compared to the results of our colleagues from Spain,[19] which reported on a similar cohort of 689 (age 62.41 [SD 9.11]), we detected fewer AEs related to LP (36% and 16%, respectively). Any headache (24.8%) and back pain (16.1%) were the most frequently reported. Our result could be explained with the older population (age 72 [SD 7.1] vs 62.4 [SD 9.11]). Although at least one LP was performed with a sharp, beveled needle in 40% (491) of our participants (Table 1), we could not confirm that the type of needles used was associated with different incidences of complications. This could be due to extensive experience in the performance of LP in mostly academic sites participating in ADNI. An additional reason for this finding could be that we report on all kind of AEs and not only on headache meeting the criteria outlined by the Headache Classification Committee of the International Headache Society for post-lumbar puncture headache (PLPH) like in the study by Duits et al.[25]

In another single center (academic Hospital) study with profiles of patients and average age similar to our cohort (age 72 [SD 9.7]), only 2.6% of 1089 reported headaches.[20] This very low incidence could be explained with the focus of their report. The colleges reported only on headaches that clearly fulfilled the criteria for PLPH. Such a difference is reported also by Duits et al.[25] This abbreviation is not always used in line with the prior mentioned definition, for example, if defined as any headache after LP it rises to the incidence from 9% to 19%[24] or to 5.3%.[26] Information regarding the definition of the headaches and their incidence is important for the physician. This will allow them to provide sufficiant information to the participant as well as to stress out that there is therapeutic consequence depending on the type of headache. This will allow the participant to recognize any compliance and report them accordingly.

Similar findings are reported on LP-related AEs in other neurodegenerative diseases, for example, Parkinson's disease (PD).[18] Six hundred eighty-three participants (age 61.66 [SD 9.7]) were included in their study, and 22.5% of them reported an AE, mainly headache and back pain. In addition, in this population, it was confirmed that the factors associated with a higher incidence of AEs across the cohorts included female gender and younger age. An additional finding was that younger age was associated with greater AE severity. Nevertheless, they detected that the use of traumatic needles with a larger diameter is also associated with AE. As this study was able to compare between PD, subjects without evidence of dopaminergic deficiency

TABLE 4 Logistic final model results $N = 838$.

Predictor	Level	Estimate	Std. Error	Odds Ratio	95% CI	*p*-Value
Age group	<75	0.753	0.240	2.123	(1.346-3.459)	0.002
Gender	Male	−0.844	0.215	0.430	(0.28-0.652)	< 0.001
Entorhinal.bl		0.386	0.148	1.471	(1.102-1.969)	0.009
Baseline diagnosis	MCI	−0.062	0.216	0.940	(0.614-1.432)	0.775
Baseline diagnosis	Dementia	0.094	0.357	1.098	(0.531-2.169)	0.792

(SWEDDs) and healthy volunteers (HC), they reported that both types of AE, headache, and low back pain, occurred more commonly in HC and SWEDDs compared to PD participants. In our study, the frequency of reporting AE was not influenced by cognition status, defined as diagnose (cognitively normal [CN], MCI, and AD), as well as *APOE* ε4 status.

Khlebtovsky at al. looked for the reporting frequency in a younger (age 44.6 years) and heterogenous cohort of individuals admitted to their department of neurology.[24] Also in their study, the reporting of AE was higher in the younger group. In addition, they were able to report that body mass index (BMI) and opening pressure did not influence the incidence of AE.

In summary, regardless of the mean age of the study population and the underlying reason for the LP, the younger portion of the participants always reports more AEs.

We assumed that one reason for this finding could be the ongoing use of pain relief medication. In our study the proportion of participants taking ongoing pain relief therapy was 67% in each group. The use of this medication was heterogenous and not related to the LP. This finding does not support the assumption that such medication will change the reporting behavior due to a higher threshold for new pain experience or that the new pain does not meet the individual threshold to report and that the ongoing pain relief therapy could prevent the new pain. However, in our study, medication to treat an AE related to LP was needed only in 36% and additional blood patch in 3.24% of the AE cases.

Furthermore, we used the available MRI data to look for a link between AE and brain volume. The data showed that the greater hippocampus volume and entorhinal thickness, but not the whole brain volume, are associated with a higher frequency of reporting AEs. The role of the hippocampus/entorhinal complex in pain perception is described in the literature.[27] The hippocampus may have a direct role in the processing of nociceptive information such as pain intensity encoding. Areas within the hippocampus/entorhinal complex are involved in the comparison between actual and expected nociceptive stimuli and play a role in anxiety-driven hyperalgesia. Much more, the entorhinal thickness is one of the structures allowing a highly accurate classification of individuals as having chronic migraine or being a healthy control.[28]

Our findings suggest that the preservation of the hippocampus/entorhinal complex and not the whole brain volume is predictive for reporting AEs, most likely pain, linked to LP.

Some of the limitations of our work are the lack of accurate data to allow classification and duration of the headache. This information could allow comparison between our and other studies. Our results are limited as we report on retrospective analysis of data only of participants who had undergone at least one LP. The latter could represent bias, and both could influence the generalizability of the data. In addition, the time to contact the participant was too short after the procedure, leading to insufficient collection of AEs. To reduce this, participants were informed to report any new symptoms in the time between visits. The number of non-White individuals was insufficient to analyze reporting behavior based on ethnicity.

5 | CONCLUSION

In summary, younger age, female gender, and greater volume of the hippocampus/entorhinal complex play a role in reporting AEs after LP. In our study, the ongoing use of pain relief medication, type of needle, positioning, and cognitive status did not differ between groups. Due to the not only confirmatory (having AD pathology) and informative (progression) but now clear therapeutic value of the confirmation of elevated brain amyloid we hope that our report will provide additional confidence for the rational to perform LP and also to help the clinician performing the LP to stratify/assess the risk for each individual and provide more intensive and informative communication with the participants about this, in general, well-tolerated procedure.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts to disclose. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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