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Factors influencing successful lumbar puncture in Alzheimer research

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Abstract

Objective—Lumbar puncture (LP) is increasingly common in Alzheimer disease research; however, agreement to undergo LP varies. We sought to determine factors influencing LP consent at Alzheimer's Disease Centers (ADCs) in the United States.

Methods—A three-part survey was distributed to each ADC: 1) ADC LP Experience; 2) LP Requestor Experience; and 3) Patient LP Experience (both Initial and Follow-up). 64 LP Requestor, 579 Patient/Initial, and 404 Patient/Follow-up surveys were collected. Logistic regression analyses with generalized estimating equations were used to assess factors associated with LP agreement and post-LP complications.

Results—Asians and those viewing LP negatively were less likely to agree to LP. Three hundred and fifty-two participants had an LP; LP headache occurred in 11.9% (blood patch required in 1.4%) and 9.9% reported other complications. Younger individuals, women, those diagnosed with mild cognitive impairment, use of a Quincke needle, 20mL cerebrospinal fluid drawn, and hemorrhage during LP were associated with LP headache. Use of gravity flow during LP was associated with fewer other complications (nausea, dizziness, vasovagal response, back pain, neck stiffness, and/or nerve root pain).

Conclusions—LP in AD research is generally safe and well-tolerated. Factors influencing LP agreement potentially could be studied to advance participant acceptance of the procedure.

Keywords

Lumbar puncture (LP); biomarkers; cerebrospinal fluid; Alzheimer disease; post-LP headache; post-LP complications

The need for reliable Alzheimer disease (AD) biomarkers has driven the demand for cerebrospinal fluid (CSF) collection by lumbar puncture (LP). AD CSF biomarkers

consistently have very high diagnostic accuracy for AD, including in the earliest symptomatic stages.¹ Thus, AD CSF biomarkers are important tools for early diagnosis, which will be critical when disease-modifying treatments are clinically available.

LP agreement, however, is negatively affected by pervasive misconceptions.² Complications after LP, such as post-LP headache, may contribute to negative patient experiences. We sought to examine factors influencing agreement to undergo LP as well as factors contributing to LP complications. Building on a survey conducted at European and Canadian memory clinics through the BIOMARKAPD project,^{3,4} we prospectively surveyed and documented LP practices, perceptions, agreement rates, and complications at the National Institute on Aging (NIA)-funded Alzheimer's Disease Centers (ADCs) in the United States over a two-year period.

Methods

Design Overview

Survey forms were modified from the Patient LP Experience forms designed for the BIOMARKAPD project.³ In addition to these Patient forms, we developed ADC LP Experience and LP Requestor surveys; see Table 1 for survey design. The three-part survey was distributed to all ADCs on September 1st, 2011 (Supplemental Form 1). Data were collected prospectively through the National Alzheimer's Coordinating Center (NACC) website, requiring log-in access. The ADC LP Experience captured reasons for obtaining LP, numbers and types of LP studies, and educational practices. LP Requestor survey completion was solicited from all ADC personnel (not limited to personnel who perform LPs) who request research LP in their clinical cohorts; data collected included demographics, perceptions about LP, and personal LP experience. The following ADCs contributed LP Requestor forms: Boston University; Columbia University; Emory University; Indiana University; Johns Hopkins University; Massachusetts Alzheimer's Disease Research Center; Mount Sinai; Oregon Health & Science University; University of California, Irvine; University of California, Los Angeles; University of California, San Diego; University of California, San Francisco; University of Kansas; University of Kentucky; University of Pennsylvania; University of Southern California; University of Texas Southwestern; University of Washington; Washington University; University of Wisconsin.

Patient LP Experience-Initial survey data were collected when research participants were asked to undergo LP. Data collected included demographics, LP history, and perceptions about LP. If research participants agreed to LP, Patient LP Experience-Follow-up survey data were collected one week post-LP (if the LP was not conducted, this information was collected along with the reason for the missing LP). LPs were conducted per standard operating procedures at each ADC; there was no master protocol for CSF collection. Data collected in the Patient LP Experience-Follow-up survey included methods used to perform the LP and information about LP complications, including post-LP headache. Post-LP headache was defined according to the International Classification of Headache Disorders:⁵ 1) headache develops within seven days after an LP; 2) headache develops/worsens within 15 minutes after assuming an upright position and disappears/lessens within 30 minutes after

resuming recumbent position; and 3) headache disappears within 14 days after an LP. These criteria were written into the survey to minimize ambiguity. The following ADCs contributed Patient LP Experience (Initial and Follow-up) forms: Boston University; Emory University; Indiana University; Johns Hopkins University; Massachusetts Alzheimer's Disease Research Center; Mayo Clinic; Oregon Health & Science University; University of California, Irvine; University of California, Los Angeles; University of California, San Francisco; University of Kansas; University of Kentucky; University of Pennsylvania; University of Southern California; University of Texas Southwestern; University of Washington; Washington University; University of Wisconsin.

Participants

Patient LP Experience data were collected from individuals approached about undergoing LP (N = 579) between September 1st, 2011 and December 31st, 2013 at participating ADCs. The LP was not necessarily part of an ADC's Clinical Core operations (i.e., a funded aspect of the ADC grant), but participants were required to be enrolled in the ADC's Clinical Core, with Uniform Data Set⁶ data submitted to NACC. All activities were reviewed by each contributing ADC's Institutional Review Board; if a determination was made that the survey constituted human subjects research, a protocol was approved at that institution for survey administration and informed consent was obtained for participants at that site.

Statistical Analysis

We described the characteristics of individuals who completed the Patient LP Experience-Initial questionnaire, and compared the characteristics of those who did and did not agree to undergo LP using unadjusted logistic regression using Generalized Estimating Equations (GEE), which accounts for clustering by Center. Among those who underwent LP, we described their individual and LP characteristics and the percent of each category experiencing LP headache or other adverse events.

We then conducted unadjusted logistic regression using GEE to examine the associations between participant and LP characteristics and LP headache and other adverse events. Each outcome was considered in 2 separate models (LP headache: yes versus no; other adverse events: yes versus no). Adjusted models were used to examine the association between each participant or LP characteristic and the two outcomes of interest, while controlling for a continuous measure of participant age and sex. For example, for models with LP headache as the outcome, one model was run with participant diagnosis, age, and sex in the model, and another was run with previous LP complication, age, and sex in the model. This was repeated for all participant and LP characteristics of interest. We were unable to include multiple characteristics in the same model due to the relatively small sample size of those experiencing LP complications (N = 42 for headache; N = 35 for other adverse events). Analyses were performed in SAS v9.4, using an α -level of 0.05 to assess statistical significance.

A small subset of the participants (n=20) had more than one LP follow-up form, corresponding to having more than one LP done. In order to ensure our analyses were conducted at the unique participant level, we restricted the analyses for these participants to

their first available LP follow-up form that corresponded closely in time to an available initial form date. We also conducted a sensitivity analysis that ignored repeated data for these participants.

Results

ADC LP Experience

ADC LP Experience surveys were completed by all ADCs active at study inception (Table 1). All Centers reported collecting CSF for research, with a mean of 4.4 CSF studies per Center over the previous five years. In addition to Center-specific research, these studies included the Alzheimer's Disease Neuroimaging Initiative and clinical trials of investigational drugs. The most common CSF analytes measured were β -amyloid, tau, and 14-3-3 protein, with the last used as a marker of prion disease.⁷ Discussion of LP risks and benefits with the participant required 6–10 minutes in 48% of ADCs, >10 minutes in 28% of ADCs, and <5 minutes in 24% of ADCs. The most common educational material was a brochure (76% of ADCs), with a group participants' meeting being the second-most frequent (52% of ADCs). Other tools included video (36%) and webpages (20%).

Requestor LP Experience

Fifty-five percent of LP Requestors were physicians, 12% were nurses, and 33% were other personnel (e.g., social worker). Fifty percent were women and 81% were Caucasian; 15% were Asian, 2% were African American, and 2% listed race as "other". Only 5% of LP requestors were of Hispanic ethnicity. Only 8% of requestors had undergone LP themselves. Of those requestors who also perform LP (53.1%), the mean $\pm$ standard deviation time since last LP performed was 0.8 ± 1.5 years.

ADC LP Requestors considered LP to be both valuable for research (5.5 ± 0.5 on a six-point Likert scale with 6 as "extremely valuable") and causing and associated with a relatively low amount of discomfort (2.4 ± 0.4 on a six-point Likert scale with 1 being "no discomfort"). In comparison with colonoscopy, requestors indicated that LP causes less discomfort (2.4 ± 1.2 on a six-point Likert scale with 1 being "much less discomfort for LP") and results in fewer complications (2.2 ± 1.0 on a six-point Likert scale with 1 being "many fewer complications for LP").

Patient LP Experience

The Patient LP Experience queried factors influencing agreement to undergo LP, standard LP practice, and factors influencing LP complication, including LP headache. Demographic data from Patient LP Experience surveys are detailed in Table 2. Table 3 summarizes patient and clinical characteristics and their impact on LP agreement rates. Overall, 75.5% of research participants who were invited agreed to do LP. Race, but not ethnicity, had a significant effect on agreement. Also, patients viewing the LP procedure as a 'frightening, invasive procedure' were less likely to agree to LP.

Individuals who previously had undergone LP more often agreed to LP than individuals who had not, but this finding was not statistically significant. Furthermore, individuals with a

medical history of headache were no less likely to agree to LP than those without such a history.

Table 4 summarizes ADC LP practices and the characteristics of participants who had an LP. 83% of LP clinicians were very experienced (>100 LPs performed); the amount of experience was not significantly correlated with the incidence of LP headache (unadjusted OR: 1.03; 95% CI: 0.98–1.09) or other mild complications (unadjusted OR: 0.93; 95% CI: 0.87–1.01). LPs were completed in 88% of those participants who initially agreed and for whom follow-up data were submitted. Several factors accounted for lack of an LP in 47 participants who initially agreed, primarily refusal after initial agreement (n=13) or a medical reason (n=12); not all reasons for lack of LP completion were captured.

Analyses of LP complication were conducted considering two parameters: LP headache and other adverse events (nausea, dizziness, vasovagal response, back pain, neck stiffness, nerve root pain). Approximately 12% of all participants with LP reported LP headache and 10% reported other adverse events. LP headaches generally were mild (64%) and lasted <1 day (40%) to 1–2 days (29%). A blood patch was administered in only 5 participants (1.4% of all persons undergoing LP). Nausea, dizziness, and nerve root pain each were observed in 2% of all LPs; vasovagal response, back pain, and neck stiffness each were observed in 1% of all LPs. No person reported a severe complication (e.g., subdural hematoma or infection).

Previous reports have suggested several factors that contribute to incidence of LP headache and/or other LP complications. Table 5 summarizes our results regarding these factors. In the adjusted analysis, which controlled for continuous measure of age and sex, having a diagnosis of MCI (versus no MCI/dementia), having an LP performed with a Quincke needle (versus Sprotte), and hemorrhage (defined as “initial CSF was slightly bloody”) were associated with increased odds of LP headache. Having >20mL of CSF drawn was associated with lower odds of LP headache. Using gravity flow was associated with a lower odds of other adverse events (e.g., dizziness, nausea).

In our sensitivity analysis, in which all LP follow-ups were included for the 20 participants who had more than one LP, CSF volume >20mL was not associated with lower odds of LP headache, as it was in our main analysis. Using a 24–25G needle was associated with a lower odds of LP headache. Finally, having a diagnosis of MCI was associated with an increased odds of other (non-headache) adverse events. The correlated data for the 20 participants could not be accounted for easily in the analysis because the vast majority of the participants did not have multiple LP reported; therefore, we decided to report only one unique LP date per participant for our main findings

Discussion

Agreement to Undergo LP

Inclusion of CSF biomarkers in AD research studies, clinical trials, and clinical practice is increasingly common as their importance is accepted throughout the AD community. CSF biomarkers now are included as metrics in the NIA-Alzheimer’s Association diagnostic guidelines for AD,^{8,9} as well as the International Working Group diagnostic criteria for

AD.¹⁰ However, agreement to undergo LP, even for clinical care, is not universally accepted by either physicians or patients/research participants in the United States. We therefore explored the factors influencing agreement to undergo LP in research participants at the NIA-funded ADCs (Table 3). We found that Asian Americans agreed to LP at a lower percentage than Caucasians; this also was true for African Americans, but the result was not statistically significant. These data demonstrate that sensitivity to racial differences is critical in increasing agreement, providing an opportunity for educational intervention. Consistent with the idea that LP education could increase participation, we found that individuals who viewed LP as a “standard medical procedure” were more likely to agree to LP than those who viewed it as a “frightening, invasive procedure”. Furthermore, individuals who previously had undergone LP were more likely to agree to the current LP than those who had never undergone LP, although this did not reach statistical significance. These observations are in line with the work by Tsvetkova and colleagues who found that individuals who had an LP in the past were more likely to view LP as a standard procedure than those who had not.¹¹ Collectively, these data suggest that pervasive misperceptions or a lack of awareness about LP negatively impact agreement rates. Educational efforts designed to increase familiarity with and counter misinformation about LP therefore should be incorporated into AD research studies and clinical trials.

The agreement percentages included here are somewhat limited by the manner in which the survey was administered across ADCs. Centers were instructed to offer the survey to anyone being approached to consider LP, but after site-specific follow-up, we learned that some ADCs administered the survey only to participants who already had agreed to LP. This limitation means that overall LP agreement percentages are higher than would have been measured otherwise, and we cannot exclude the possibility that factors influencing LP agreement might have been subtly altered. In addition, all individuals queried about undergoing LP already were engaged in research to some degree; as such, their attitudes about LP are not reflective of the overall population.

LP Complications

Similar to many published reports, LP headache was less frequently observed with increasing age^{3,12–17} and male sex^{16–19} (Table 5). LP headache also was less likely with use of the atraumatic Sprotte needle versus the cutting Quincke needle; this result is consistent with many reports,^{12,143,20,21} and specifically with American Academy of Neurology recommendations.^{22,23} Even given these recommendations and the preponderance of research data, Quincke needles still were used in 45% of LPs (Table 4), reflecting a reticence to change practice, which also is well-documented.^{20,24,25} We did not find a significant effect of needle gauge or patient position on LP complications.

Other factors influencing LP complications have been more widely debated. We detected an effect of diagnosis with an increased incidence of LP headache for individuals with a diagnosis of MCI, but not AD dementia. It is possible that individuals with a MCI diagnosis had neuropsychiatric symptoms, including irritability or agitation,²⁶ thus leading to increased report of complications, but this increase was not maintained in individuals who had progressed to an AD dementia diagnosis due to decreased cognitive insight; a protective

effect against LP complications previously has been reported for a diagnosis of AD or dementia.^{3,27,28} While anecdotal reports and some published data^{29,30} suggest that individuals who experience an LP headache are likely to have a repeat headache with subsequent LP, we did not detect an effect of a prior LP complication on LP complication incidence for the current LP. Furthermore, we did not find a significant correlation between a medical history of headache with incidence of LP headache (migraine or tension headache were listed as exemplars), as has been reported elsewhere,^{3,15} but see ². Lastly, we found an effect of the volume of CSF collected on LP headache; collection of >20 mL CSF was protective (compared to ≤20 mL), consistent with the work of Monserrate and colleagues.³¹ Higher volumes of CSF may be protective against LP headache because transiently lower CSF pressure may decrease leakage through the dural puncture, facilitating dural closure.³¹ Alternatively, headache incidence may be higher in LP attempts in which complications led to early termination of the procedure, with less CSF collected.

We detected statistically significant effects of two factors that heretofore have received little attention in the field: method by which CSF was obtained and presence of hemorrhage during the LP. Although some practitioners are reticent to collect CSF by gravity drip due to time concerns, we found a significant correlation between use of aspiration and increased odds of other adverse events (e.g., nausea, dizziness, neck stiffness). This is consistent with the report by Duits and colleagues wherein gravity drip decreased the risk for moderate-to-severe LP headache.³ We also observed that the presence of hemorrhage, which was reported in 9.7% of LPs, was associated with an increased risk of LP headache, suggesting that this parameter should be closely monitored at time of LP.

Although most LP practice research focuses on post-LP headache, which was ~12% in our study, 10% of participants reported other mild complications. These included nonspecific headache, nausea, dizziness, nerve root pain, vasovagal response, back pain, neck pain, and other symptoms (examples included perspiration, fatigue, and tinnitus). Of note, the percentages of nausea, dizziness, and vasovagal response were even less than those reported for venipuncture for blood sampling at 2.9–7.0%,^{32,33} underscoring the relative safety and tolerability of LP.

The ADC LP Experience

An added benefit of the present study is that it documents LP practices across NIA-funded ADCs. These data include reasons for acquiring CSF, demographics of LP requestors and participants, and methods used to perform LP. Similar to the BIOMARKAPD survey,³ all data were acquired prospectively, allowing for detailed recording of multiple parameters potentially affecting LP agreement and LP complications. The post-LP headache incidence of 11.9% and incidence of other mild adverse events of 9.9% are higher than reported by some other studies, such as Peskind and colleagues²⁸ and Vidoni and colleagues,¹² but well within the ranges previously reported. Across participating Centers, the BIOMARKAPD survey³ reported a post-LP headache average incidence of 8.6% and an average incidence of other mild complications of 4.0%. Two factors to consider in both studies are: 1) no LP protocol was specified, allowing for variability among Centers and practitioners and evaluation of the impact of different techniques; and 2) a greater incidence of LP

complication may have been captured because participants were systematically queried one week after LP, which likely uncovered complications that otherwise would not have risen to the attention of the research team or clinic.

This prospective study at NIA-funded ADCs demonstrated that LPs were safe and well-tolerated, with low rates of complication. The frequencies of LP-associated nausea, dizziness, and vasovagal responses in this study were less than has been reported for venipuncture.^{32,33} We identified variables that can impact LP agreement rates; the observation that race and whether LP is viewed as a “standard medical procedure” affect agreement to undergo LP should caution clinicians to be sensitive to these aspects when discussing LP with patients and research participants. Given that previous LP experience increased agreement rates for subsequent LP, a ready opportunity exists to dispel LP myths and increase awareness about LP and its importance to the AD field. We also identified factors that can contribute to the incidence of LP complications. Results from this study suggest that to minimize risk of complications, including LP headache, LPs should be performed with an atraumatic (Sprotte) needle using gravity flow, with >20 ml CSF collected. Clinicians also should be aware of the greater risk of complications in individuals who are younger, female, or have a diagnosis of MCI, or when even mild hemorrhage is observed. In contrast, medical history of headache or a prior LP complication were not associated with increased incidence of LP headache or other adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Survey Design and Completion

Survey Component	Completed By:	Completed When:	# Surveys Completed
ADC LP Experience	One designated individual per ADC (limited to the Director, Administrator, or Clinical Core Leader)	<ul style="list-style-type: none"> At survey launch 	27 (All active ADCs)
LP Requestor	Any and all ADC personnel who are responsible for explaining the LP procedure to patients/research volunteers	<ul style="list-style-type: none"> At survey launch In the event of a new requestor 	64 (20 ADCs)
Patient LP Experience	One designated patient coordinator (nurse, social worker, or other health professional) per site who has knowledge of the LP procedures of patients/research volunteers	<ul style="list-style-type: none"> Just after the patient/ research volunteer is requested to undergo LP 	579 (18 ADCs) <ul style="list-style-type: none"> 437 agreed to LP 142 refused LP
Patient LP Experience – Follow-up	Same person who completed the Patient LP Experience form	<ul style="list-style-type: none"> One week after LP 	404* (18 ADCs)

* 394 forms were submitted by individuals agreeing to LP; 10 forms were submitted by individuals who initially refused LP, 5 of whom changed their refusal and did undergo LP and 5 who refused and never had LP.

Table 2

Lumbar Puncture Initial Survey Participant Demographics and Cognitive Status

Characteristic	Statistic
Sample size, n	579
Male, n (%)	275 (47.5%)
Age, mean (SD)	70.7 (10.3)
MMSE [*] , mean (SD)	27.2 (4.3)
Race, n (%)	
Caucasian	507 (87.6%)
African American	39 (6.7%)
American Indian / Alaska Native	0 (0.0%)
Native Hawaiian / Other Pacific Islander	0 (0.0%)
Asian	28 (4.8%)
Other	5 (0.9%)
Diagnosis, n (%)	
Not MCI or dementia [†]	328 (56.7%)
MCI	134 (23.1%)
AD dementia	94 (16.2%)
Non-AD dementia	23 (4.0%)

MMSE = Mini Mental State Examination; SD = standard deviation; MCI = mild cognitive impairment; AD = Alzheimer disease

^{*} Range of 0–30, with 30 being a perfect score.

[†] Includes patients with normal cognition or cognitively impaired not MCI.

Table 3

Agreement to Undergo Lumbar Puncture

Characteristic	n and % agreeing or not agreeing to LP by each row category		Unadjusted OR* (95% CI)
	Agreed	Did Not Agree	
Age			
<65 years	121 (89.6%)	14 (10.4%)	Ref
65–79 years	227 (71.8%)	89 (28.2%)	0.42 (0.14–1.28)
80 years	89 (69.5%)	39 (30.5%)	0.56 (0.10–3.11)
Sex			
Male	217 (78.9%)	58 (21.1%)	1.19 (0.76–1.88)
Female	220 (72.4%)	84 (27.6%)	Ref
Race [‡]			
White	395 (77.9%)	112 (22.1%)	Ref
African American	25 (64.1%)	14 (35.9%)	0.46 (0.12–1.77)
Asian	12 (42.9%)	16 (57.1%)	0.33 (0.19–0.58)
Ethnicity			
Hispanic	11 (68.8%)	5 (31.3%)	0.75 (0.24–2.39)
Non-Hispanic	426 (75.7%)	137 (24.3%)	Ref
Diagnosis			
Not MCI or dementia [‡]	242 (73.8%)	86 (26.2%)	Ref
MCI	93 (69.4%)	41 (30.6%)	1.42 (0.70–2.89)
AD dementia	82 (87.2%)	12 (12.8%)	2.35 (0.60–9.25)
Non-AD dementia	20 (87.0%)	3 (13.0%)	1.35 (0.39–4.73)
Previous LP experience			
Yes	108 (87.8%)	15 (12.2%)	1.68 (0.66–4.26)
No	329 (72.2%)	127 (27.9%)	Ref
Previous LP complication [§]			
Yes	26 (76.5%)	8 (23.5%)	0.37 (0.10–1.35)
No	131 (90.3%)	14 (9.7%)	Ref
Medical history of headache			
Yes	40 (81.6%)	9 (18.4%)	1.24 (0.64–2.39)
No	397 (74.9%)	133 (25.1%)	Ref
View of the LP procedure			
“Standard medical procedure”	371 (88.5%)	48 (11.5%)	Ref
“Frightening, invasive procedure”	66 (41.3%)	94 (58.8%)	0.11 (0.05–0.25)

Abbreviations: LP = lumbar puncture; MCI = mild cognitive impairment; AD = Alzheimer disease; OR = odds ratio; CI = confidence interval

* Unadjusted logistic regression using GEE to account for clustering by Center

[†] 5 participants of other race excluded from analysis

[‡] Includes patients with normal cognition or cognitively impaired not MCI

[§] 400 participants missing data on previous LP complication

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Table 4

Characteristics and Complications among Patients Receiving a Lumbar Puncture

Characteristic	Total LP, n	n and % affected by each row category	
		LP headache	Other adverse events*
Total sample	352	42	35
Age, mean (SD)	69.4 (10.5)	65.3 (10.0)	67.4 (10.9)
Sex			
Male	174	14 (8.1%)	15 (8.6%)
Female	178	28 (15.7%)	20 (11.2%)
Diagnosis [†]			
Not MCI or dementia [‡]	206	23 (11.2%)	21 (10.2%)
MCI	62	10 (16.1%)	9 (14.5%)
AD dementia	68	6 (8.8%)	4 (5.9%)
Previous LP complication [§]			
Yes	24	2 (8.3%)	2 (8.3%)
No	107	7 (6.5%)	9 (8.4%)
Medical history of headache			
Yes	39	7 (18.0%)	6 (15.4%)
No	313	35 (11.2%)	29 (9.3%)
Position during LP			
Lying down	125	12 (9.6%)	11 (8.8%)
Sitting	227	30 (13.2%)	24 (10.6%)
Needle type			
Quincke	162	21 (13.0%)	16 (9.9%)
Sprotte	190	21 (11.1%)	19 (10.0%)
Needle gauge			
20G	96	11 (11.5%)	7 (7.3%)
22G	133	16 (12.0%)	15 (11.3%)
24G	101	10 (9.9%)	8 (7.9%)
25G	22	5 (22.7%)	5 (22.7%)
Method			
Gravity flow	212	22 (10.4%)	15 (7.1%)
Negative pressure	140	20 (14.3%)	20 (14.3%)
CSF volume			
20mL	165	23 (13.9%)	21 (12.7%)
>20mL	187	19 (10.2%)	14 (7.5%)

Characteristic	Total LP, n	n and % affected by each row category	
		LP headache	Other adverse events [*]
Hemorrhage			
Yes	34	10 (29.4%)	5 (14.7%)
No	318	32 (10.1%)	30 (9.4%)
Post-LP rest			
<1 hour	215	25 (11.6%)	17 (7.9%)
1 hour	137	17 (12.4%)	18 (13.1%)
Performed LP:			
Neurologist	234	28 (12.0%)	25 (10.7%)
Nurse Practitioner/Nurse Anesthetist	62	6 (9.7%)	4 (6.5%)
Other [¶]	56	8 (14.3%)	6 (10.7%)
Time of day			
Morning	279	37 (13.3%)	27 (9.7%)
Afternoon	73	5 (6.9%)	8 (11.0%)
Fasting			
Yes	297	37 (12.5%)	31 (10.4%)
No	55	5 (9.1%)	4 (7.3%)

Abbreviations: SD = standard deviation; MCI = mild cognitive impairment; AD = Alzheimer disease; LP = lumbar puncture; CSF = cerebrospinal fluid

^{*} 1 participant missing data on Other Adverse Events (nausea, dizziness, vasovagal response, back pain, neck stiffness, nerve root pain, other)

[†] Other dementia diagnosis patients excluded (n=16)

[‡] Includes patients with normal cognition or cognitively impaired not MCI

[§] 221 patients missing previous LP complication data (previous complication includes headache and other complications)

[¶] Psychiatrist, anesthesiologist, neuroradiologist, geriatrician, fellow/resident

Table 5

Associations between Lumbar Puncture and Headache or Mild Complications (n=352 underwent LP)

Characteristic	LP headache		Other adverse events*	
	Unadjusted OR (95% CI) [†]	Adjusted OR (95% CI) ^{†,‡}	Unadjusted OR (95% CI) [†]	Adjusted OR (95% CI) ^{†,‡}
Age (years)	0.96 (0.93–0.98)	NA	0.98 (0.95–1.01)	NA
Male	0.47 (0.23–0.95)	NA	0.76 (0.37–1.56)	NA
Diagnosis				
Not MCI/dementia [§]	Ref	Ref	Ref	Ref
MCI	1.53 (0.87–2.70)	1.96 (1.01–3.82)	1.56 (0.72–3.36)	1.70 (0.79–3.62)
AD dementia	0.75 (0.26–2.18)	0.85 (0.25–2.95)	0.57 (0.15–2.15)	0.60 (0.15–2.31)
Previous LP complication	1.29 (0.25–6.72)	0.77 (0.16–3.66)	1.00 (0.31–3.22)	0.80 (0.22–2.92)
Medical history of headache	1.84 (0.67–5.07)	1.62 (0.57–4.58)	1.85 (0.76–4.48)	1.77 (0.77–4.07)
Position during LP				
Lying down	0.70 (0.40–1.19)	0.66 (0.37–1.19)	0.84 (0.36–1.97)	0.80 (0.35–1.81)
Sitting	Ref	Ref	Ref	Ref
Quincke (v Sprotte)	1.15 (0.63–2.12)	1.86 (1.08–3.20)	0.99 (0.48–2.03)	1.17 (0.59–2.32)
Needle gauge				
24G or 25G	1.10 (0.51–2.37)	0.59 (0.29–1.20)	1.62 (0.78–3.37)	1.54 (0.67–3.54)
22G	1.08 (0.57–2.05)	0.92 (0.46–1.84)	1.48 (0.60–3.61)	1.18 (0.43–3.22)
20G	Ref	Ref	Ref	Ref
Method				
Gravity flow	0.69 (0.44–1.08)	1.01 (0.63–1.61)	0.46 (0.25–0.83)	0.50 (0.25–0.98)
Negative pressure	Ref	Ref	Ref	Ref
CSF volume				
>20mL	0.71 (0.40–1.26)	0.52 (0.31–0.87)	0.55 (0.21–1.41)	0.47 (0.21–1.05)
20mL	Ref	Ref	Ref	Ref
Hemorrhage [¶]				
Yes	3.70 (1.62–8.44)	3.60 (1.63–7.93)	1.65 (0.49–5.48)	1.59 (0.48–5.21)
No	Ref	Ref	Ref	Ref
Post-LP rest				
<1 hour	1.09 (0.55–2.17)	0.98 (0.45–2.14)	1.81 (1.00–3.28)	1.75 (0.96–3.19)
1 hour	Ref	Ref	Ref	Ref
Time of day				
Morning	2.00 (0.63–6.38)	1.88 (0.53–6.63)	0.81 (0.34–1.93)	0.79 (0.36–1.77)

Characteristic	LP headache		Other adverse events [*]	
	Unadjusted OR (95% CI) [†]	Adjusted OR (95% CI) ^{†,‡}	Unadjusted OR (95% CI) [†]	Adjusted OR (95% CI) ^{†,‡}
Afternoon	Ref	Ref	Ref	Ref
Fasting				
Yes	1.38 (0.52–3.64)	1.42 (0.53–3.82)	1.47 (0.56–3.88)	1.49 (0.56–3.97)
No	Ref.	Ref	Ref	Ref

Abbreviations: MCI = mild cognitive impairment; AD = Alzheimer disease; LP = lumbar puncture; CSF = cerebrospinal fluid; NA = not applicable/calculated; OR = odds ratio; CI = confidence interval

^{*} 1 participant missing data on Other Adverse Events (nausea, dizziness, vasovagal response, back pain, neck stiffness, nerve root pain, other)

[†] Logistic regression using Generalized estimating equations

[‡] Controlling for continuous measure of age and sex

[§] Includes patients with normal cognition or cognitively impaired not MCI

[¶] Hemorrhage data queried separately from other complications