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# Performance and complications of lumbar puncture in memory clinics: results of the multicenter LP feasibility study

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**ABSTRACT**

**INTRODUCTION:** Lumbar puncture (LP) is increasingly performed in memory clinics. We investigated patient-acceptance of LP, incidence of and risk factors for post-LP complications in memory clinic populations.

**METHODS:** We prospectively enrolled 3868 patients (50% women, age 66±11 years, MMSE 25±5) at 23 memory clinics. We used logistic regression analysis using generalized estimated equations to investigate risk factors for post-LP complications, such as typical post lumbar puncture headache (PLDH) and back pain.

**RESULTS:** 1065 patients (31%) reported post-LP complaints; 589 patients (17%) reported back pain, 649 (19%) headache, of which 296 (9%) reported typical PLPH. Only few patients needed medical intervention: 11 (0.3%) received a blood patch, 23 (0.7%) were hospitalized. The most important risk factor for PLPH was medical history of headache. An atraumatic needle and age >65 years were preventive. Gender, rest after LP or volume of CSF had no effect.

**CONCLUSIONS:** The overall risk of complications is relatively low. If risk factors shown in this study are taken into account, LPs can be safely performed in memory clinics.

**Key words:** lumbar puncture; cognitive disorders; Alzheimer's disease; memory clinic; post-LP complications; post-LP headache; multi-center study on LP feasibility.

**Abbreviations:** AD: Alzheimer's disease; CRF: case report form; CSF: cerebrospinal fluid; G: gauge; GEE: generalized estimated equations; ICHD: International Classification of Headache Disorders; LP: lumbar puncture; MCI: mild cognitive impairment; MMSE: mini mental state examination; MRI: magnetic resonance imaging; OR: odds ratio; PET: positron emission tomography; PLPH: post-LP headache; SD: standard deviation.

## 1. Introduction

Numerous studies have shown high diagnostic accuracy of cerebrospinal fluid (CSF) biomarkers for diagnosing Alzheimer's disease (AD) [1-3]. This has resulted in inclusion of CSF biomarkers as evidence for AD pathology in the research diagnostic guidelines for AD and mild cognitive impairment (MCI) [4-6]. As a result, CSF collection by means of lumbar puncture (LP) is being performed in a growing number of memory clinics [7-9]. Factors that may hamper widespread implementation of CSF biomarkers in diagnostic routine are however the attitude towards LP among clinicians (need of training and time constraints) and patient expectations (fear of pain and complications) [10]. In addition, the procedure itself is debated because of its invasive nature, which entails complaints following LP in a proportion of patients.

The most frequent post-LP complication is post-LP headache (PLPH) [11]. The reported incidence varies widely however; even when performed in comparable memory clinic populations the proportion ranged from <1% to as high as 25% [12-15]. Lower incidence of PLPH has been reported when using a needle with a smaller diameter, or an atraumatic (pen-point) instead of a cutting-edge needle tip [16-19]. In addition, younger age and female gender are regarded risk factors for PLPH [20-22]. Most of these risk factors have been studied in a much younger population than that of a memory clinic. Consequently, they may be less relevant in mostly elderly memory clinic populations. Moreover, many studies had relatively small sample sizes ($n$<500), with insufficient power to simultaneously evaluate several risk factors.

In this largest to date, prospective multicenter study, including data from 22 memory clinics across Europe and one in Brazil, we aimed to evaluate acceptance rate of LP, incidence of post-LP complications, and patient- and LP-related risk factors for post-LP complications in the memory clinic population.

## 2. Methods

### *2.1 Patients*

Patients were consecutively enrolled from November 2010 until March 2014 in 23 centers participating the JPND project BIOMARKAPD, resulting in 3868 patients. All patients presenting at the memory clinics were enrolled whenever an LP was considered by the physician, either for research purposes, a clinical trial or diagnostic routine. Patients refusing the LP were also enrolled, to be able to estimate acceptance rate. Patients with contra-indications for LP, such as an intracerebral mass or anticoagulant treatment that could not be interrupted, were not included. As 310 patients (8%) refused to undergo the LP, and 102 patients (3%) could not be contacted for follow-up, post-LP complications could be assessed in 3456 patients (89%). Figure 1 shows the flow chart of the study, supplementary table 1 shows patient number per center. Approval for the study was given by the local ethical review boards. In 19 centers patients gave written informed consent for the use of their CSF and clinical data for research purposes. Four centers considered the study as part of normal patient care and therefore no such consent was needed

### *2.2 Report forms*

Patient characteristics, LP procedure and follow-up details were reported on case report forms (CRFs) developed at the Clinical Neurochemistry Laboratory, Sahlgrenska University, Mölndal (Sweden)(Supplementary form 1). The CRFs were distributed to the participating centers, and all items were uploaded in a central digital database. The report forms were completed by physicians and researchers within one week after the LP.

#### *2.2.1 Patient characteristics*

Prior to LP, patients were questioned regarding headache (e.g. tension headache or migraine) and pain in their medical history (none, mild/sometimes, severe/chronic pain), prior knowledge of what

the LP procedure entails (yes or no) and opinion on LP (standard medical or invasive/fearful procedure), fear for post-LP complications (no, slightly worried, very worried), and attitude towards the procedure (i.e. calm, reluctant or refusal to undergo the LP). In addition, clinical characteristics including age, gender, diagnosis, and MMSE (when performed) were recorded.

*2.2.2 LP details*

LPs were performed by neurologists, geriatricians, or residents, who were all trained in the procedure. The following details were reported: needle type (cutting-edge or atraumatic), needle diameter (in Gauge), whether the LP was performed in the morning or afternoon, whether the patient was in sitting or supine position, difficulty of the procedure (one attempt, 2-4 attempts or >4 attempts), volume of CSF collected (<5 mL, 5-12 mL, or >12 mL), blood contamination of CSF (no, mild, or marked), and whether the patient rested after LP (no/yes: <one hour, 1-2 hours, >2 hours).

*2.2.3 Post-LP complications*

Follow-up was performed within two weeks after LP, by a research nurse, assistant or physician, using the form in Supplementary form 2. Patients were asked about their complaints after LP, either by phone or during their return visit to the clinic. Post-LP complications – headache, local back pain, and any other complication – were recorded in detail. Headache was specified as typical PLPH or non-specific headache. Typical PLPH was defined according to the International Classification of Headache Disorders (ICHD): 1) onset within 5 days of LP, 2) worsens within 15 minutes of assuming upright position and disappears or lessens within 30 minutes of resuming recumbent position, and 3) disappears within 14 days after LP, or within 48 hours after effective treatment [11]. Detailed questions were included for onset (<2 hours, 2-24 hours, 1-2 days, or >2 days after LP), duration (<1 day, 1-2 days, 2-4 days, or >4 days), severity (mild, moderate or severe) and treatment (none, analgesics, caffeine, and/or blood patch) of headache. Severe complications were defined as

complaints serious enough to require medical intervention other than analgesics only, i.e. hospitalization or blood patch.

*2.3 Statistical analysis*

SPSS 21.0 (IBM for Windows) was used for statistical analysis. Because of the multicenter design, the data – especially the LP-procedure characteristics – were assumed to be correlated within centers. We therefore not only calculated frequencies of LP-procedure details for the total population, but also assessed how many centers had standardized procedures, i.e. performed the LP as such in >90% of cases. In addition, we analyzed all risk factors for post-LP complaints using generalized estimated equations (GEE) with an exchangeable correlation structure, to account for within center correlation. Within this model we performed multivariable logistic regression to simultaneously investigate associations of patient and LP-procedure characteristics (all predictors entered as dummy variables in one model) with occurrence of typical PLPH, non-specific headache or local back pain (entered as dependent, dichotomous variable in separate models). Factors with p-values > 0.10 in univariate analyses were not included in the multivariate model; these were complications after previous LP and use of anesthesia during LP (results of univariate analyses are not shown). We categorized patient age (based on the population mean), diagnosis and needle diameter due to small numbers in subgroups. Due to missing values in several variables (shown in tables 1 and 2), 3053 cases (88% of all patients having undergone LP and having follow-up available) could be included in these analyses.

## 3. Results

*3.1 Patients*

Table 1 shows the patient characteristics. In total 3868 patients in 23 centers were included. There were 1932 (50%) women, age was 66±11 years (mean±SD), MMSE was 25±5 (mean±SD). 20% of the participants were healthy subjects (i.e. subjective cognitive decline, without another neurological or

psychiatric diagnosis), 25% were diagnosed with mild cognitive impairment (MCI), 40% with dementia, and the remainder with several different non-neurodegenerative disorders, shown in more detail in table 1. 417 patients (11%) indicated they were very worried to experience post-LP complications, 310 patients (8%) refused the LP. 48.2% of the LPs were performed for research purposes, 46.3% for diagnostic purposes, 2.9% for both diagnostic and research purposes and 2.6% for trial purposes. Acceptance rate was slightly lower when the LP was for research purposes compared to diagnostic use (1672/1934 [86%] vs 1608/1647 [98%]). Compared to patients who underwent LP, patients refusing the LP were more often non-demented (61% versus 34%), slightly more often female (58% versus 49%), and slightly younger (61±11 versus 66±11).

*3.2 LP procedure*

Table 2 shows details on the LP procedures within the centers and patients. Half of the LPs were performed with the patient in supine position. The majority of LPs were performed with a cutting-edge needle (2956 patients [83%]), which was the standardized procedure in 18 centers. Four centers routinely used a needle of smaller than 22G, thirteen centers a needle with a diameter of 22G or larger. In total, 2337 patients (66%) were punctured with these relatively large needles. Local anesthesia was routinely used in nine centers (in total 1451 patients (41%]), all using large size needles. Seven centers used a syringe to actively withdraw CSF in a number of patients, but only two of these centers used this method regularly. In 588 punctures (17%) there was slight to marked visible blood contamination of the CSF. Most LPs succeeded in one attempt (2527 patients [71%]), whereas in a small proportion the LP was unsuccessful and no CSF was obtained (116 patients [3%]). Most often between five and 12 mL of CSF was collected; as part of their standardized procedure, eight centers never collected more than 12 mL.

*3.3 Post-LP complications*

Table 3 shows all reported post-LP complications. There were only 33 patients (1%) with severe complications needing medical intervention; 11 patients (0.3% of total) received a blood patch, 23 patients (0.7%) needed hospitalization (partly overlapping with patients needing a blood patch), and three patients (0.1%) visited an emergency department for their post-LP complications but could be discharged without hospital admission. All patients fully recovered after treatment. One patient died two days after the LP because of an intracerebral hemorrhage. In this patient oral anticoagulant medication had been temporarily discontinued to enable performance of the LP, and the patient died shortly after restarting the medication.

Of all patients, 1065 (31%) reported complications of any kind after LP. Of the patients in whom LP was successful, 589 (17%) reported back pain, and 649 (19%) reported any type of headache, of which 296 (9%) reported typical symptoms of PLPH. In contrast, of the 116 patients in whom LP was unsuccessful 42 patients (35%) reported back pain, whereas only 9 (8%) reported headache. Headache lasting longer than 4 days was reported by 4% of the patients (*n*=137; 21% of patients with headache), moderate to severe headache by 7% (*n*=237; 37% of patients with headache). Some form of analgesic against the headache was needed in 11% (*n*=382; 69% of patients with headache). 139 patients (4%) reported other mild complications such as nausea, vomiting or dizziness. Proportions differed substantially between centers however, ranging from 2% up to 51% of patients reporting complaints in general, 1% to 33% reporting any headache, and 0% to 21% reporting typical PLPH. Supplementary figure 1 shows all proportions of headache and back pain per center. The number of included patients per center are indicated in supplementary Table 1. There was no correlation between number of patients included and frequency of complaints (data not shown).

*3.4 Risk factors for post-LP complications*

To investigate patient- and LP procedure-related factors associated with post-LP complaints, we performed multivariable logistic GEE analysis, to account for within center correlation of the

clustered data. Results are shown in table 4. An important risk factor for typical PLPH was headache in the medical history (OR [95%CI] for mild headache 1.8 [1.4-2.6], for severe headache 2.7 [1.9-3.7]). Age >65 years (0.7 [0.5-1.0]) and a diagnosis of dementia resulted in a lower risk of PLPH (0.7 [0.6-0.8]). The only significant procedure-related factor preventive for PLPH was an atraumatic needle (OR [95%CI] 0.4 [0.2-0.8]); there was a trend for an effect of smaller needle diameter (0.6 [0.4-1.1). The effects of needle characteristics are visualized in figure 2. For non-specific headache, patient characteristics were more important, especially fear of complications (OR [95%CI] slightly worried 1.6 [1.3-2.0], very worried 2.0 [1.4-2.9]). There was no effect of needle characteristics, but free flow of CSF gave a slightly lower risk for headache compared to active withdrawal.

To assess whether there were specific factors associated with moderate to severe post-LP headache, we repeated the analysis after exclusion of patients reporting mild headache. Results are shown in supplementary table 5. Age >65 years became the most important preventive factor (OR [95%CI] 0.3 [0.2-0.4]); history of headache still gave a higher risk (mild headache 1.7 [1.3-2.4], severe headache 2.9 [1.9-4.3]). In addition, free flow instead of active withdrawal of CSF (0.5 [0.3-0.8]), a smaller needle diameter (0.6 [0.4-0.9]; see figure 2) and a supine position of the patient (0.6 [0.3-0.9]) decreased the risk for moderate to severe post-LP headache. Patient characteristics associated with back pain were similar; history of headache was a risk factor (OR [95%CI] mild headache 1.4 [1.1-1.8], severe headache 2.4 [1.9-2.9]), age >65 years (0.6 [0.5-0.7]) and a diagnosis of MCI or dementia (0.7 [0.5-1.0] for MCI, 0.7 [0.6-1.0] for dementia) were preventive factors. All post-LP complaints by age are visualized in supplementary figure 2. The only procedure-related risk factor for back pain was number of attempts (2-4 attempts 2.1 [1.7-2.7], >4 attempts 5.4 [2.9-10.2]). The patient's gender, time of LP, bed rest after LP, position of the patient during the procedure, and volume of CSF withdrawn were not associated with typical PLPH or local back pain.

## 4. Discussion

In this large-scale international multicenter study on LP feasibility we showed that post-LP complaints occurred quite frequently, but typical PLPH occurred in less than 10%, and complications needing medical intervention were rare (1%). In addition, acceptance rate of LP was high (92%), even when the LP was performed for research purposes (86%), while the rate was 98% when the LP was performed for clinical indications. Patient characteristics, especially history of headache and age, were as important as LP procedure characteristics for prediction of PLPH. Patient-related risk factors for local back pain were similar to those for headache, while the only important procedure-related risk factor for back pain was number of LP attempts.

The frequency of post-LP complaints was higher than expected based on previous studies in memory clinic populations [12,14,15]. Although patients in this study were younger, a more plausible explanation is that we actively asked patients about post-LP complaints using a questionnaire. In one of the previous studies PLPH was only registered when patients reported these complaints spontaneously [14]. In another study patients were contacted once by a nurse the morning following LP [12], while in up to one third of patients PLPH starts after 48 hours [21]. Hence, the low incidence in these studies could have been an underestimation, as many patients may have had subclinical complaints, or were not yet experiencing complaints at follow-up. In addition, we used internationally accepted criteria for PLPH [11], and asked specific questions on headache as well as back pain. This gives a comprehensive and detailed overview, although it is debatable whether mild complaints, without consequences for patients, have clinical relevance. The 1% of patients with complications serious enough to require medical intervention is probably most relevant in this respect. In addition, it is important to also assess patient discomfort before, during and after procedures for other biomarker modalities than CSF analysis, and to compare patient experience between these procedures. Patients undergoing MRI or PET scans may experience anxiety, claustrophobia or other complaints of which the incidence is unknown.

During the study one patient died of an intracerebral hemorrhage shortly after anti-coagulant medication was restarted. Although it is unlikely that the hemorrhage was a direct consequence of the LP, it underscores that special attention is needed in patients using anticoagulants. Discontinuation and restarting this medication is likely accompanied with fluctuating coagulation leading to an increased risk on thrombosis [23], and should be strongly avoided if possible. We believe that an LP for diagnostic or research purposes in the context of dementia never warrants interrupting oral anticoagulant therapy.

Regarding risk factors for PLPH, we confirmed previous results that the amount of CSF drawn as well as bed rest after LP does not influence the incidence of PLPH [24,25]. In addition, we confirmed the preventive effect of aging [19,21,22]. As we found a lower incidence of all complaints with increasing age, it is perhaps a more general phenomenon of decreasing pain sensitivity in elderly individuals [26], or that elderly are less fearful. In addition, there were several remarkable findings. First, whereas PLPH has repeatedly been reported to be more common in women than men, we did not observe such a gender difference [18,21,27]. Since especially women under the age of 40 have a substantially higher risk of PLPH [27], it is plausible that gender effects disappear with increasing age, and is negligible in an average memory clinic population. Of note, a previous study of similar design did show a gender effect on prevalence of back pain[13]. However, that study was smaller in size, included fewer centers and did not account for the center effect, which is relevant given the consistence of procedures within centers. Second, a diagnosis of MCI or dementia was associated with a lower risk of post-LP complaints compared to a non-neurodegenerative diagnosis, while age was accounted for. This has been demonstrated before in a relatively small cohort [12]. It may either be due to short-term memory problems of these patients and thus reporting bias [28], or might be related to brain atrophy with increased CSF volume, although this has not yet been demonstrated experimentally. Third, LP-procedure characteristics were not as important as we hypothesized. Needle type, but not diameter, was associated with typical PLPH; needle diameter was only

associated with severe headache. Free flow of CSF seemed to give a slightly lower risk for headache compared to active withdrawal, although the effect was only significant for non-specific and severe headache. Finally, we showed that fear for complications was an important risk factor for actually experiencing post-LP complaints, except for typical PLPH. Hence, there may be psychological factors relating to more complaints, which might be influenced by personality traits. In agreement, one study found no difference in incidence of PLPH between real LP and a sham procedure [29]. In conclusion, these findings suggest that patient characteristics are as important as LP-procedure characteristics for predicting post-LP complaints.

Among the strengths of our study is the unprecedented large number of patients and the prospective nature. The large sample allowed us to simultaneously investigate many factors possibly associated with post-LP complaints, and enabled us to give representative proportions of patients willing to undergo LP, and experiencing post-LP complaints. However, there was a wide variation between centers regarding proportion of patients with complaints, suggesting differences in how questions were asked and answers interpreted, or cultural differences. All centers were participants of the BIOMARKAPD project, representing specialized memory clinics in a large proportion of European countries plus Canada. In addition, most centers used their own standardized procedures for LPs, making within-center variability regarding LP-procedure characteristics low. Factors related to the LP procedure could therefore have been somewhat obscured in this study, even though we used a model designed for clustered data to overcome the correlation within centers. Moreover, we applied self-reports and did not address the relation between perceived benefit of the procedure of both the patients and physicians, which is addressed in other studies [8]. Lastly, we used the 2004 ICHD criteria for classification of PLPH, as the most recent criteria were only published at the end of our inclusion period (2013) [30]. These new criteria are more inclusive; any headache occurring within five days after LP is characterized as PLPH. For identification of risk factors the more specific previous

criteria seem meaningful however, as effect sizes of these factors differed substantially between typical PLPH and non-specific headache.

In conclusion, LPs can be safely performed in the memory clinic. The acceptance rate for LP was high, most post-LP complaints were mild in nature, and severe complications were very rare. Patient characteristics, such as age, diagnosis and history of headache, were equally important as LP-procedure characteristics for prediction of post-LP complaints. These factors should be taken into account when performing LPs, to further decrease the risk of post-LP complaints.

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**Declaration of interests**

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Dr. Teunissen is member of international advisory boards of Fujirebio and Roche, and has performed contract research for Probiodrug, IBL, Shire. Dr. Engelborghs is / was consultant for Fujirebio Europe, ADx Neurosciences and Roche diagnostics. Dr. Scheltens serves/has served on the advisory boards of: Novartis, Pfizer, Roche, Danone, Jansen AI, Baxter and Lundbeck. He has been a speaker at symposia organized by Lundbeck, Lilly, Merz, Pfizer, Jansen AI, Danone, and Roche. He is co-editor-in-chief of Alzheimer's Research & Therapy. He is a member of the scientific advisory board of the EU Joint Programme on Neurodegenerative Disease Research (JPND) and the French National Plan Alzheimer. He acts as vice-chair of the Dutch Deltaplan Dementia. Dr. Scheltens receives no personal compensation for the activities mentioned above.

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**Table 1.** Demographic characteristics of the study population

| **Characteristics** | *Total population (n=3868)* | *Patients with LP and follow-up (n=3456)** |
|---|---|---|
| Women, *n* (%) (3855/3445) | 1932 (49.9%) | 1697 (49.1%) |
| Age, mean ± SD (3848/3439) | 66 ± 11 | 66 ± 11 |
| MMSE, mean ± SD (3438/3051) | 25 ± 5 | 25 ± 5 |
| Diagnosis, *n* (%) | | |
| Healthy subjects | 754 (19.5%) | 581 (16.8%) |
| MCI | 946 (24.5%) | 875 (25.3%) |
| AD | 1052 (27.2%) | 982 (28.4%) |
| Other dementia | 478 (12.4%) | 436 (12.6%) |
| Psychiatric disorder | 167 (4.3%) | 143 (4.1%) |
| Neurological disorder | 215 (5.6%) | 211 (6.1%) |
| Other / unclear | 256 (6.6%) | 228 (6.6%) |
| Prior knowledge about procedure, *n* (%) (3837/3428) | 1520 (39.6%) | 1374 (39.8%) |
| Headache in medical history, *n* (%) (3842/3436) | | |
| No headache | 3038 (79.1%) | 2734 (79.1%) |
| Mild / sometimes | 561 (14.6%) | 488 (14.1%) |
| Severe / chronic | 243 (6.3%) | 214 (6.2%) |
| Fear of complications, *n* (%) (3849/3440) | | |
| Not worried | 2118 (55.0%) | 2028 (58.7%) |
| A bit worried | 1314 (34.1%) | 1241 (35.9%) |
| Very worried | 417 (10.8%) | 171 (4.9%) |
| Attitude towards LP, *n* (%) (3857/3446) | | |
| Calm | 2978 (77.2%) | 2891 (83.7%) |

| | | |
|---|---|---|
| Reluctant | 569 (14.8%) | 555 (16.1%) |
| Disapproves (refused LP) | 310 (8.0%) | n/a |

* i.e. the cohort as used in the final analyses regarding risk factors for post-LP complaints.

Shown are either mean ± SD or *n* (% of total). Between parentheses behind each characteristic is the number of subjects in which the data were available, of the total population and of the group with LP and follow-up.

**Table 2.** Characteristics of LP procedure

| **Characteristics** | **Standard procedure, *n* *** | **Patients, *n* (%)** |
|---|---|---|
| Time of LP (3535) | | |
| AM | 10 | 2226 (62.6%) |
| PM | 3 | 1309 (36.8%) |
| Medication during LP (3549) | | |
| None | 10 | 2026 (57.1%) |
| Premedication | 1 | 72 (1.9%) |
| Local anesthesia | 9 | 1433 (37.0%) |
| Both premedication and local anesthesia | 0 | 18 (0.5%) |
| Position of patient (3536) | | |
| Lying | 1 | 1779 (50.0%) |
| Sitting | 8 | 1757 (49.4%) |
| Needle type (3516) | | |
| Cutting edge (e.g. Quincke) | 18 | 2956 (83.1%) |
| Atraumatic (e.g. Sprotte, Whitacre) | 3 | 560 (15.7%) |
| Needle diameter (3531) | | |
| 25G or smaller | 3 | 982 (27.6%) |
| 23-24G | 1 | 212 (6.0%) |
| 22G | 4 | 1129 (31.7%) |
| 21G | 2 | 309 (8.7%) |
| 19-20G | 7 | 899 (25.3%) |
| Method to obtain CSF (3410) | | |

| | | |
|---|---|---|
| Free flow / dripping | 19 | 2749 (77.3%)1 |
| Withdrawal with syringe | 2 | 661 (18.6%) 2 |
| Blood contamination of CSF (3536) | n/a | |
| No | | 2833 (79.6%) |
| Mild | | 526 (14.8%) |
| Marked | | 62 (1.7%) |
| Difficulty of procedure (3543) | n/a | |
| Easy (one attempt) | | 2527 (71.0%) |
| 2-4 attempts needed | | 841 (23.6%) |
| Difficult (five or more attempts) | | 59 (1.7%) |
| LP not succeeded | | 116 (3.3%) |
| Volume of CSF obtained (3541) † | n/a | |
| <5 mL | | 450 (12.6%) |
| 5-12 mL | | 1761 (49.5%) |
| >12 mL | | 1214 (34.1%) |

Total number of patients who underwent LP was 3558. Between parentheses behind each characteristic is the number of subjects in which the data were available. Percentages are displayed as percentages of the total of 3558 subjects; due to missing values they may not add up to 100%.

* Number of centers in which >90% of LPs were performed as such (i.e. as part of a standardized procedure), and therefore had very low intra-center variation regarding this specific LP characteristic. Note that numbers in this column do not always add up to the total of centers (i.e. 23), as in several centers LP procedures were performed in several (mixed) ways, hence percentages did not exceed 90%.

† As part of their standardized procedure, eight centers never collected more than 12 mL.

**Table 3.** Complications after LP procedure

| **Complications** | ***n* (%)** |
|---|---|
| Any complaint after LP | 1065 (30.8%) |
| Back pain total | 589 (17.0%) |
| Mild discomfort | 462 (13.3%) |
| Moderate / several days | 127 (3.7%) |
| Headache total | 649 (18.8%) |
| Typical post-LP headache | 296 (8.6%) |
| Non-specific headache | 353 (10.2%) |
| Duration of headache (635) | |
| < 1 day | 165 (4.8%) |
| 1-2 days | 152 (4.4%) |
| 2-4 days | 181 (5.2%) |
| > 4 days | 137 (4.0%) |
| Severity of headache (636) * | |
| Mild (patient functions normally) | 399 (11.5%) |
| Moderate (functioning impaired) | 214 (6.2%) |
| Severe (hospitalization needed) | 23 (0.7%) |
| Treatment of headache (644) † | |
| No treatment needed | 269 (7.8%) |
| Pain medication | 379 (11.0%) |
| Caffeine | 24 (0.7%) |
| Other mild complications † | 139 (4.0%) |
| Nausea and/or vomiting | 86 (2.5%) |
| Dizziness | 45 (1.3%) |

| | | |
|---|---|---|
| Vasovagal collapse | 16 (0.5%) | 1 |
| Severe complications † | 33 (1.0%) | 2 |
| Blood patch needed | 11 (0.3%) | 3 |
| Hospitalization needed | 23 (0.7%) | |
| Emergency department visited but sent home | 3 (0.1%) | |
| Died ‡ | 1 | |

The total number of patients in which post-LP complications could be assessed (i.e. patients which had undergone LP and had follow-up available) was 3456. Between parentheses behind each characteristic is the number of subjects in which the data were available, if applicable. Percentages are displayed as percentages of the total population of 3456 subjects.

* Moderate to severe headache was defined as: caused disability and impaired functioning, i.e. the patient had to stay in bed for (a period of) the day or had to be hospitalized due to severity of the headache.

† more than one answer allowed.

‡ caused by oral anticoagulant-related intracerebral hemorrhage two days after the LP. Oral anticoagulant medication had been temporarily discontinued before LP. Hemorrhage occurred shortly after restarting the medication.

**Table 4.** Factors associated with post-LP headache and back pain

| Factors | Typical PLPH * | Non-specific headache | Local back pain |
|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| **Patient-related factors** | | | |
| Age (> 65 vs ≤ 65 years) | 0.68 (0.46-1.00) | 0.42 (0.31-0.57) | 0.56 (0.48-0.65) |
| Diagnosis † | | | |
| MCI vs no dementia | 1.00 (0.76-1.32) | 0.52 (0.38-0.71) | 0.72 (0.54-0.97) |
| Dementia vs no dementia | 0.66 (0.55-0.80) | 0.59 (0.42-0.82) | 0.74 (0.56-0.99) |
| Gender (male vs female) | 0.84 (0.58-1.23) | 0.93 (0.81-1.08) | 0.86 (0.72-1.04) |
| History of headache | | | |
| Mild vs no headache | 1.76 (1.19-2.59) | 1.58 (1.13-2.20) | 1.42 (1.13-1.79) |
| Severe/chronic vs no headache | 2.65 (1.88-3.74) | 1.64 (1.11-2.42) | 2.38 (1.94-2.92) |
| History of pain | | | |
| Mild vs no pain | 1.24 (0.84-1.84) | 1.33 (1.02-1.72) | 1.10 (0.87-1.39) |
| Severe/chronic vs no pain | 1.42 (0.82-2.47) | 1.03 (0.59-1.81) | 1.49 (0.84-2.64) |
| Fear of complications | | | |
| Slightly worried vs not worried | 1.04 (0.79-1.36) | 1.60 (1.28-2.00) | 1.17 (1.02-1.35) |
| Very worried vs not worried | 1.16 (0.72-1.87) | 2.01 (1.39-2.91) | 1.41 (1.12-1.78) |
| **LP-related factors** | | | |
| Time of LP (PM vs AM) | 0.96 (0.68-1.34) | 0.97 (0.67-1.41) | 1.18 (0.85-1.63) |
| Position of patient (sitting vs lying) | 1.23 (0.78-1.64) | 1.44 (0.91-2.28) | 1.11 (0.84-1.46) |
| Needle type (non-cutting vs cutting) | 0.39 (0.20-0.75) | 0.89 (0.49-1.63) | 0.81 (0.43-1.54) |
| Needle diameter (small vs large diameter) ‡ | 0.63 (0.38-1.07) | 0.95 (0.61-1.47) | 0.99 (0.66-1.48) |

| | | | |
|---|---|---|---|
| Method to obtain CSF (free flow vs active withdrawal) | 0.77 (0.52-1.15) | 0.68 (0.50-0.92) | 1.24 (0.98-1.57) |
| Volume CSF | | | |
| 5-12 mL vs < 5 mL | 1.02 (0.67-1.57) | 0.91 (0.66-1.25) | 1.17 (0.83-1.66) |
| > 12 mL vs < 5 mL | 0.96 (0.55-1.70) | 1.00 (0.69-1.45) | 1.15 (0.80-1.63) |
| Number of attempts | | | |
| 2-4 vs one attempt | 0.71 (0.41-1.21) | 0.76 (0.51-1.13) | 2.10 (1.65-2.69) |
| ≥ 5 vs one attempt | 0.37 (0.03-5.64) | 1.10 (0.57-2.14) | 5.42 (2.87-10.24) |
| CSF ([mild] hemorrhagic vs clear) | 0.78 (0.44-1.39) | 0.72 (0.56-0.93) | 1.33 (0.99-1.79) |
| Rest after LP (rest vs no rest) | 0.60 (0.35-1.02) | 1.20 (0.81-1.80) | 1.03 (0.71-1.49) |

Data are represented as OR (95% CI). Analyses were performed with generalized estimated equations to account for within center correlations, using multivariable logistic regression analysis. All predictors were included in one model; different models were used for typical PLPH, non-specific headache and post-LP back pain (dependent variables, entered as dichotomous variables). Dichotomous predictors were compared to the reference (mentioned as second between parentheses), for categorical predictors each group was compared to the reference. Due to missing values 3053 of the 3456 cases (88%) could be included in the analyses.

* Typical PLPH as defined by ICHD: 1) onset within 7 days of the LP, 2) comes or worsens within 15 minutes of assuming upright position and disappears or lessens within 30 minutes of resuming recumbent position, and 3) disappears within 14 days after the LP [11].

† For this analysis all non-neurodegenerative disorders (i.e. healthy controls, neurological and psychiatric disorders) were pooled in a 'no dementia' group, and AD and other dementia were pooled in a 'dementia' group.

‡ Large needle diameter was defined as 22G and larger, small diameter as smaller than 22G.

**Figure 1.** Flow chart of study population.

**Figure 2.** Type of headache and severity of headache per type and diameter of LP needle

Large needle diameter was defined as 22G and larger, small diameter as smaller than 22G.