Postdural puncture headache in migraineurs and nonheadache subjects

A prospective study

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ABSTRACT

Objectives: To prospectively assess 1) the incidence and duration of postdural puncture headache (PDPH) in migraineurs and healthy subjects; 2) the associated risk factors; and 3) the risk of getting a migraine attack shortly before or after lumbar puncture (LP).

Methods: As part of an extensive biochemical migraine research program, we assessed the occurrence, duration, and characteristics of PDPH in 160 migraineurs and 53 age- and sex-matched healthy controls. In addition, we evaluated potential risk factors for PDPH as well as the risk of developing a migraine attack before or after LP.

Results: In total, 64 of 199 subjects (32.2%) developed PDPH. Young age, low body mass index, severe headache immediately after LP, and sitting sampling position, but not being a migraineur, increased the risk of PDPH (all $p < 0.05$). Duration of PDPH was prolonged by history of depression, sitting sampling position, high perceived stress during the LP procedure, and multiple LP efforts (all $p < 0.05$). Migraine attacks were less likely to occur before or shortly after LP.

Conclusions: Migraineurs are not at increased risk of developing PDPH. PDPH duration is similar in migraineurs and age- and sex-matched controls. LP does not trigger migraine attacks, and the stress of an upcoming LP might even have a protective effect against onset of migraine attacks.

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GLOSSARY

BMI = body mass index; **ICHD-IIR** = International Classification of Headache Disorders-II, revised; **LP** = lumbar puncture; **OR** = odds ratio; **PDPH** = postdural puncture headache.

Postdural puncture headache (PDPH) occurs in 10% to 40% of subjects after lumbar puncture (LP), usually within 5 days.^{1,2} The headache typically comes on within 15 minutes after assuming an upright position and improves again within 15 minutes after lying down.³ Frequently associated symptoms are neck stiffness, tinnitus, hyperacusis, photophobia, and nausea (table e-1 on the *Neurology*® Web site at www.neurology.org).³⁻⁵ Sometimes, patients may also experience blurred vision or diplopia.⁶ In 95% of cases, the symptoms spontaneously resolve within a week.³

Various pathophysiologic mechanisms have been hypothesized for PDPH,⁷⁻¹¹ and retrospective observational studies suggest young age,¹²⁻¹⁹ female sex,^{17,19-21} low body mass index (BMI),^{19,22} previous PDPH,^{7,18} and (migraine) headache before LP^{6,23-25} as risk factors. Prospective studies on the epidemiology of PDPH, however, are lacking.

As part of an extensive biochemical migraine research program, we were allowed by the Medical Ethical Committee to sample CSF from 160 well-characterized migraineurs and 53 healthy controls. All subjects gave written informed consent and were followed for at least a week after LP. This gave unique opportunity to prospectively study the risk and course of PDPH in migraine and healthy subjects. For both populations, we assessed 1) incidence and duration of PDPH; 2) possible risk factors for PDPH; 3) risk of migraine provocation by LP; and 4) whether the prospect of undergoing LP could trigger or prevent migraine attacks in the preceding days. The results of our study may call for a re-evaluation of the International Classification of Headache Disorders-II, revised (ICHD-IIR) criteria for PDPH.

Supplemental data at
www.neurology.org

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METHODS Subjects. Migraineurs and healthy controls older than 18 years were included as part of a study on biochemical changes in migraine. All subjects underwent full physical examination, including ophthalmoscopy. Exclusion criteria were 1) use of antidepressive or anticoagulation medication, 2) BMI >32 kg/m², 3) any oncologic history, and 4) any contraindication for LP. Migraineurs were diagnosed according to the ICHD-IIIR criteria³ and could have no more than 10 headache days per month. Healthy volunteers had to be free of any form of regular headaches. History of depression was scored by asking participants whether they were ever diagnosed with depression by a physician. Stress regarding the upcoming LP was assessed with a visual analog scale, ranging from 0 (no stress at all) to 10 (most stressful event ever). This score was assessed 10 to 15 minutes before the LP. None of the participants reported to have undergone an LP in the past in the setting of a scientific study. The exclusion criterion of any other neurologic disease has led to the inclusion of LP-naïve subjects, since use of the LP procedure is limited to a neurologic diagnostic setting. A very small proportion of subjects might have had epidural anesthesia in the past, but we have no reason to believe this proportion would differ between migraineurs and controls. We therefore consider the study population LP naïve.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Medical Ethical Committee. All subjects gave written informed consent and received a small financial compensation according to standard guidelines of the Center for Human Drug Research, Leiden, the Netherlands.

Study design. All LPs were performed between 9:00 AM and 1:00 PM by experienced neurology residents and at least 3 days after a previous migraine. Participants were subjected to overnight fasting and were only allowed to drink water before the LP. With the patient in left lateral supine, a total of 14 mL of CSF was collected using a 0.9-mm traumatic Quincke needle (Medioplast, Sweden). If a successful puncture was not possible in the left lateral supine position, the LP was performed with the subject in sitting position. Participants were mobilized after the procedure because there is no evidence that prolonged recumbent position after LP may prevent PDPH.^{26,27}

Follow-up assessment. All participants were contacted 3 days after LP, but could contact the research team at any time earlier or later. The presence and severity of PDPH and migraine were evaluated in a semistructured telephone interview using ICHD-IIIR criteria³ and, for PDPH, Lybecker's classification.⁶ Conservative treatment with bed rest, oral nonsteroidal anti-inflammatory drugs, fluids, antiemetics, and caffeine was recommended to all subjects with mild to moderate PDPH. Autologous epidural blood patch was offered to all subjects with severe or PDPH not improving with conservative treatment.

Statistics. General characteristics were compared between the groups with and without PDPH using a Student *t* test for continuous variables, and a χ^2 test for categorical data. To assess risk factors for PDPH, binary logistic regression was performed with migraine status as independent variable, adjusted for age, sex, and BMI. Additional risk factors were also analyzed with the regression model, both uni- and multivariate. Multivariate analyses were performed in 2 ways: 1) adjusted for age, BMI, and sex; and 2) with significantly associated ($p < 0.05$) variables from the univariate analysis. To identify factors for PDPH duration, a multiple linear regression (uni- and multivariate) was performed, adjusted for age, sex, and BMI. Variables were selected based on literature or because they were considered relevant. All data

analyses were performed using SPSS 17.0 (SPSS Inc., IBM, Armonk, NY); p values <0.05 were considered significant.

To assess whether 1) LP could trigger migraine attacks, or 2) (the stress of) the prospect of undergoing LP, or the mere participation in the study, could trigger or actually prevent the occurrence of a migraine attack in the days preceding a *scheduled* LP, we conducted 2 separate analyses. For the first objective, we compared the proportion of migraineurs who developed an attack within the 3 days after LP with the proportion of migraineurs in a separate headache diary study, who had not had a migraine in the first 3 days of the diary study but who subsequently did develop an attack in the following 3 days. The diary study was previously conducted at our centre in 700 migraineurs who kept a headache diary for a month. Of these, 41 later also participated in the present LP study. To test significance, a logistic regression model was fit with a dummy variable encoding LP (yes/no) as the only covariate. A random-patient effect was also included to account for the fact that some subjects participated in both studies. In a secondary analysis, we only included the 41 subjects who had participated in both studies, using the McNemar test.

To address the second objective, we compared the proportion of migraineurs with an attack in the 3 days preceding a *scheduled* LP in the LP study with the proportion of migraineurs who had an attack in the first 3 days of the diary study. We fit a logistic regression model, including a random-patient effect. Again, we repeated the analysis also for the subgroup that had participated in both studies, using the McNemar test.

RESULTS Study population. Between January 2008 and September 2010, 160 migraineurs and 53 healthy controls ($n = 213$; 131 females) were included in the study (figure e-1). LP was unsuccessful in 13 of 213 subjects (6.1%), of whom 9 were migraineurs, leaving 200 subjects at risk for PDPH. After LP, 1 subject developed headache that could not reliably be attributed to either PDPH or episodic migraine. Retrospectively, this patient had chronic migraine that started months before the study and should not have been included in our study. Therefore, the patient was excluded from the analysis. The baseline characteristics of the remaining 199 study participants ($n = 49$ controls; $n = 84$ with migraine with aura, of whom 19 had hemiplegic migraine; $n = 66$ with migraine without aura) are described in table e-2. Migraineurs had a higher mean age (44.0 ± 13.3 years vs 36.3 ± 15.3 years, $p = 0.001$), were more frequently female (98/150 [65.3%] vs 24/49 [49.0%]; $p = 0.041$), and were less likely to consume alcohol (44/150 [29.3%] vs 42/49 [85.7%]; $p = 0.036$) than controls.

PDPH incidence and characteristics. Sixty-four of 199 subjects (32.2%) developed PDPH, which was mild in 27 of 64 (42.2%), moderate in 18 of 64 (28.1%), and severe in 14 of 64 (21.9%). In 59 of 64 subjects (92.2%), the PDPH had started within 2 days and in 63 of 64 (98.4%) within 3 days. The median time to onset was 20 hours (range 1–76; figure 1). The overall median duration of PDPH was 5.1 days (range 1–18) and tended to be shorter in migraineurs (mean $\pm$ SD: 4.6 ± 2.4 days compared with controls 5.9 ± 3.6 days;

Figure 1 Cumulative onset of postdural puncture headache (PDPH) in 64 subjects

Fifty-nine of 64 subjects (92.2%) reported PDPH <48 hours and 63 of 64 (98.4%) <72 hours after lumbar puncture (LP). Median time to onset was 20 hours.

$p = 0.098$). In the 52 subjects with a spontaneous recovery, the median duration was 4.0 days (range 1–11). In the 12 subjects who were successfully treated with a blood patch, the median duration was 6.5 days (range 3–18; figure 2). Information on associated symptoms was available for 62 of 64 subjects with

PDPH (96.9%) of whom 55 of 62 (88.7%) reported the presence of the following symptoms: vestibulocochlear symptoms (vertigo, dizziness, hypacusia, and tinnitus) in 40 of 62 (64.5%); nausea and/or vomiting in 40 of 62 (64.5%); cochlear symptoms (including hypacusia and tinnitus) in 19 of 62 (30.6%); ocular symptoms (diplopia) in 2 of 62 (3.2%); and musculoskeletal complaints (stiff neck or stiff shoulder region) in 23 of 62 (37.1%). Photophobia was reported by 3 of 62 (4.8%). PDPH was more prevalent in the subgroup that underwent LP in sitting position vs in lateral supine position: 13 of 20 (65.0%) vs 51 of 179 (28.5%); $p = 0.001$ (odds ratio [OR] 3.5, 95% confidence interval 1.2–10.1; $p = 0.022$ when adjusted for number of LP efforts, age, sex, and BMI).

Differences between subjects with and without PDPH.

Table 1 compares the baseline characteristics of the participants who developed PDPH and those who did not. Subjects with PDPH were younger, had a lower BMI, and reported higher scores on immediate post-LP headache severity. CSF opening pressure did not differ between subjects who developed PDPH (18.3 ± 4.6 cm H₂O) vs those who did not (17.4 ± 4.2 cm H₂O; $p = 0.18$) (see table 1). Fewer migraine subjects (42/150; 28.0%) reported PDPH than did controls (22/49; 44.9%; $p = 0.028$). There was no difference in PDPH incidence between migraineurs with and without aura (data not shown). PDPH difference also did not differ between patients with hemiplegic migraine (2/19; 10.5%) vs nonhemiplegic migraineurs (40/131;

Figure 2 Duration (days) of postdural puncture headache (PDPH) in 64 subjects with PDPH

Table 1 Baseline characteristics of study population^a

Variable	Total (n = 199)	PDPH (n = 64)	Non-PDPH (n = 135)	p
Age, y, mean (SD)	42.1 (14.1)	37.9 (13.2)	44.1 (14.2)	0.004 ^b
Female, n (%)	122 (61.3)	37 (57.8)	85 (63.0)	0.486
Migraine, n (%)	150 (75.4)	42 (65.6)	108 (80.0)	0.028 ^b
BMI, kg/m ²	24.2 (3.0)	23.4 (3.0)	24.5 (2.9)	0.022 ^b
Education level, n (%)				
Low	17 (13.6)	4 (8.9)	13 (9.6)	0.173
Middle	69 (34.6)	22 (48.9)	47 (34.8)	
High	94 (47.2)	19 (42.2)	75 (55.6)	
Comorbidity, n (%)				
None	189 (95.0)	61 (95.3)	128 (94.8)	0.952
History of depression	6 (3.0)	2 (3.1)	4 (3.0)	
Epilepsy	4 (2.0)	1 (1.6)	3 (2.2)	
Family history migraine, ^c n (%)	108 (54.3)	34 (53.1)	74 (54.8)	0.823
Intoxications, n (%)				
Alcohol	148 (74.4)	49 (76.6)	99 (73.3)	0.626
Smoking	37 (18.6)	13 (20.3)	24 (17.8)	0.668
Drugs	4 (2.0)	3 (4.7)	1 (<0.1)	0.064
Caffeine	188 (94.5)	62 (96.9)	126 (93.3)	0.307
Hours sober, mean (SD)	11.3 (2.3)	11.8 (2.1)	11.1 (2.3)	0.052
LP efforts, mean (SD)	1.4 (1.0)	1.7 (1.1)	1.3 (1.0)	0.042 ^b
Puncture traumatic, n (%)	16 (8.0)	6 (9.3)	10 (7.4)	0.655
CSF opening pressure, mean (SD)	17.7 (4.3)	18.3 (4.6)	17.4 (4.2)	0.184
Sitting position, n (%)	23 (11.6)	13 (20.3)	10 (7.4)	0.008 ^b
VAS scores				
Pain during LP	3.3 (2.4)	3.4 (2.5)	3.2 (2.4)	0.548
Stress before LP	2.4 (2.7)	2.1 (3.1)	2.5 (2.5)	0.284
Stress during LP	3.2 (2.8)	3.0 (2.7)	3.3 (2.9)	0.547
Headache directly after LP	1.0 (1.6)	1.5 (2.0)	0.7 (1.4)	0.009 ^b

Abbreviations: BMI = body mass index; LP = lumbar puncture; PDPH = postdural puncture headache; VAS = visual analog scale (range 1–10: 1 = no stress/pain; 10 = most stressful/painful imaginable).

^aBaseline characteristics of subjects who developed PDPH (PDPH, n = 64) vs subjects without PDPH (non-PDPH; n = 135) of participants with successful LP (n = 199).

^bSignificant differences ($p < 0.05$) using independent samples t tests and χ^2 tests, as appropriate.

^cFirst-degree relative with migraine.

30.5%; $p = 0.07$). Excluding hemiplegic migraine cases in a post hoc analysis did not change the significant lower incidence of PDPH in the migraine group compared with controls.

Risk factors for occurrence and long duration of PDPH.

Several risk factors were identified that significantly enhanced the risk of PDPH (table 2). In a univariate analysis, young age and low BMI increased the risk of PDPH. The risk of PDPH was also increased in subjects who reported high headache severity immediately after LP and sitting sampling position. In a multivariate analysis (adjusted for age, sex, and BMI), young age, low BMI, sitting position, and high headache score after LP proved significant

predictors. In a second multivariate analysis (using variables with $p < 0.05$ association from univariate analysis), severe headache after LP and sitting position were confirmed as predicting factors. Table 3 indicates risk factors for longer PDPH duration. Both univariate and multivariate (adjusted for age, sex, and BMI) analyses show that sitting sampling position, history of depression, multiple LP effort, and high perceived stress during the procedure were associated with a longer duration of PDPH. Lower level of education and absence of migraine family history showed a similar but nonsignificant trend. A second multivariate analysis (using variables with $p < 0.05$) confirmed sitting position as an important risk factor.

Table 2 Risk factors for PDPH onset^a

Variable	1. Univariate OR (95% CI)	p	2. Multivariate OR (95% CI)	p	3. Multivariate OR (95% CI)	p
Age, y	0.972 (0.951-0.993)	0.010 ^b	0.976 (0.955-0.998)	0.033 ^b	0.977 (0.954-1.000)	0.051
Sex, F	0.787 (0.433-1.432)	0.433	0.701 (0.376-1.306)	0.263		
BMI, kg/m ²	0.877 (0.793-0.971)	0.011 ^b	0.892 (0.803-0.990)	0.032 ^b	0.912 (0.816-1.019)	0.102
Migraine diagnosis	0.506 (0.264-0.969)	0.040 ^b	0.618 (0.306-1.248)	0.180	0.557 (0.274-1.134)	0.107
Education level						
Middle vs low	2.531 (0.774-8.272)	0.124	2.143 (0.626-7.338)	0.225		
High vs middle	1.398 (0.576-4.523)	0.576	0.812 (0.232-2.839)	0.744		
History of depression	0.760 (0.199-2.903)	0.688	0.740 (0.183-2.984)	0.672		
Family history migraine	0.963 (0.535-1.734)	0.901	1.147 (0.614-2.143)	0.667		
Alcohol, yes/no	1.169 (0.590-2.317)	0.655	0.849 (0.407-1.770)	0.663		
Smoking, yes/no	1.046 (0.503-2.174)	0.904	1.096 (0.513-2.344)	0.813		
Drugs, yes/no	7.230 (0.737-70.87)	0.089	4.011 (0.384-41.92)	0.246		
Caffeine, yes/no	2.007 (0.421-9.563)	0.382	1.800 (0.371-8.730)	0.466		
Sober, h	1.136 (0.997-1.294)	0.056	1.138 (0.996-1.300)	0.057		
LP effort, 1 vs >1	0.553 (0.281-1.090)	0.087	0.579 (0.286-1.172)	0.129		
Puncture traumatic, yes/no	1.407 (0.489-4.052)	0.527	1.591 (0.532-4.755)	0.406		
CSF opening pressure, cm H ₂ O	1.054 (0.975-1.138)	0.184	1.057 (0.969-1.153)	0.209		
Sitting position, vs supine	3.186 (1.313-7.731)	0.010 ^b	3.321 (1.323-8.338)	0.011 ^b	3.210 (1.287-8.006)	0.012 ^b
VAS 1-10						
Pain during LP	1.005 (0.893-1.132)	0.931	0.990 (0.872-1.125)	0.883		
Stress before LP	0.946 (0.840-1.066)	0.363	0.957 (0.845-1.083)	0.485		
Stress during LP	0.960 (0.863-1.069)	0.458	0.948 (0.846-1.062)	0.356		
Headache after LP	1.322 (1.103-1.583)	0.002 ^b	1.377 (1.139-1.664)	0.001 ^b	1.443 (1.169-1.782)	0.001 ^b

Abbreviations: BMI = body mass index; CI = confidence interval; LP = lumbar puncture; OR = odds ratio; PDPH = postdural puncture headache; VAS = visual analog scale.

^aOR (1: univariate; 2: multivariate, adjusted for age, sex, and BMI; and 3: multivariate with variables $p < 0.05$ in univariate analysis) for the risk of developing PDPH using a logistic model ($n = 199$).

^bSignificant differences ($p < 0.05$).

Migraine after LP. In total, 25 of 150 migraineurs (12.0%) experienced a migraine attack between 0 and 10 days after LP (median: 2 days), the majority (18/25; 72%) within 3 days. In the subgroup of migraineurs in whom the LP was performed on the first scheduled appointment, thus who did not have an attack on days -3 to 0 before the LP, the risk of experiencing a migraine attack within 3 days after LP was 13 of 94 (14%). This was substantially lower than the risk of experiencing a migraine attack on days $+4$ to $+7$ in the diary study for those migraineurs who had not had an attack on the first 3 or 4 days of the study (111/257; 43.2%; OR 0.74; $p < 0.0001$). A similar trend for reduced risk of a migraine attack after LP was observed for the subgroup of 41 migraineurs who had participated in both the LP and diary study: 14 of 41 (34.1%) vs 24 of 41 (58.5%; OR 0.25; $p = 0.37$).

Perceived stress levels immediately before LP tended to be higher in migraineurs who did not

experience an attack ≤ 3 days after LP (2.6 ± 3.0) than those in migraineurs who did experience an attack (1.6 ± 1.6 ; $p = 0.19$). Stress levels during the LP procedure were very similar in migraineurs with (2.9 ± 2.4) and without an attack (3.2 ± 2.9 ; $p = 0.72$). None of the controls experienced a migraine attack after LP.

Migraine preceding LP. Fewer migraineurs had an attack in the 3 days preceding LP (37/131; 28.2%) than in the first 3 days of the diary study (388/645; 60.2%; $p < 0.0001$). This was also true for the subset of migraineurs who had participated in both the LP (21/41; 51.2%) and diary study (24/41; 58.5%; $p = 0.04$).

DISCUSSION This is the first prospective evaluation of the risk of PDPH and migraine after LP in migraineurs and healthy subjects. We carefully assessed and compared 2 large populations of well-characterized

Table 3 Risk factors for longer PDPH duration^a

Variable	1. Univariate B (95% CI)	p	2. Multivariate B (95% CI)	p	3. Multivariate B (95% CI)	p
Age, y	−0.016 (−0.067 to 0.034)	0.520	−0.017 (−0.075 to 0.041)	0.551		
Sex, F	0.788 (−0.531 to 2.107)	0.236	0.807 (−0.600 to 2.214)	0.254		
BMI, kg/m ²	−0.043 (−0.262 to 0.176)	0.692	0.031 (−0.231 to 0.292)	0.815		
Migraine diagnosis	−0.946 (−2.317 to 0.425)	0.172	−0.926 (−2.422 to 0.570)	0.219		
Education level						
Middle vs low	2.667 (−0.159 to 5.492)	0.064	2.548 (−0.358 to 5.454)	0.084		
High vs middle	2.667 (−0.942 to 4.799)	0.183	1.749 (−1.210 to 4.708)	0.240		
History of depression	6.578 (2.115– 11.042)	0.005 ^b	7.598 (2.929–12.267)	0.002 ^b	−0.279 (−1.851 to 1.293)	0.722
Family history migraine	−1.149 (−2.441 to 0.144)	0.080	−1.182 (−2.587 to 0.223)	0.097		
Alcohol, yes/no	0.945 (−0.528 to 2.419)	0.204	0.922 (−0.637 to 2.481)	0.240		
Smoking, yes/no	0.436 (−1.246 to 2.117)	0.605	0.738 (−1.029 to 2.505)	0.405		
Drugs, yes/no	1.187 (−1.643 to 4.017)	0.404	1.723 (−1.429 to 4.876)	0.277		
Caffeine, yes/no	1.090 (−2.352 to 4.532)	0.528	0.961 (−2.548 to 4.471)	0.584		
Sober, h	0.053 (−0.261 to 0.368)	0.735	0.060 (−0.263 to 0.382)	0.712		
LP effort, 1 vs >1	−1.718 (−3.155 to −0.281)	0.020 ^b	−1.629 (−3.173 to −0.085)	0.039 ^b	−0.268 (−0.968 to 0.432)	0.444
Puncture traumatic, yes/no	0.721 (−1.524 to 2.966)	0.522	0.760 (−1.531 to 3.052)	0.508		
CSF opening pressure, cm H ₂ O	−0.023 (−0.149 to 0.103)	0.718	−0.013 (−0.151 to 0.125)	0.852		
Sitting position, vs supine	2.750 (1.082–4.418)	0.002 ^b	3.003 (1.192–4.814)	0.002 ^b	2.534 (0.632–4.435)	0.010 ^b
VAS 1–10						
Pain during LP	0.161 (−0.111 to 0.433)	0.239	0.141 (−0.138 to 0.421)	0.314		
Stress before LP	0.030 (−0.172 to 0.231)	0.770	0.057 (−0.153 to 0.268)	0.587		
Stress during LP	0.369 (0.149–0.588)	0.001 ^b	0.356 (0.120–0.592)	0.004 ^b	0.345 (0.076–0.614)	0.013 ^b
Headache after LP	0.189 (−0.152 to 0.531)	0.271	0.148 (−0.217 to 0.512)	0.419		

Abbreviations: BMI = body mass index; CI = confidence interval; LP = lumbar puncture; PDPH = postdural puncture headache; VAS = visual analog scale.

^aRegression coefficients (1: univariate; 2: multivariate, adjusted for age, sex, and BMI; and 3: multivariate with variables $p < 0.05$ in univariate analysis) for the duration of PDPH using a linear regression model ($n = 52$ PDPH cases with spontaneous recovery).

^bSignificant differences ($p < 0.05$).

migraine patients with episodic migraine and age- and sex-matched healthy subjects, using in all subjects the same standardized LP procedure, pre- and post-LP detailed clinical characterization, and 1 week proactive follow-up.

Contrary to common belief,^{6,28} but in line with an earlier, small, retrospective study,²⁹ migraine patients did not have increased risk or longer duration of PDPH. In fact, we found a remarkably lower incidence of PDPH in migraineurs also when excluding the hemiplegic migraine cases. Notably, chronic migraineurs were not included in this study as well as migraineurs with active comorbid depression wherefore treatment was required. The finding that migraineurs were not at increased risk prompted us to further investigate and compare the underlying mechanisms for PDPH and migraine. In contrast to what is believed by some, LP did not trigger attacks in migraine patients. Interestingly, pre-LP stress levels tended to be higher in those participants who did not have an attack after LP, which would suggest a protective rather than a provoking effect of acute stress.^{30,31}

In our study, we confirmed previously found risk factors for PDPH (young age and low BMI^{18,21,32}) and identified headache immediately after LP and sitting sampling position as previously unrecognized additional risk factors. Moreover, we showed that sitting sampling position, history of depression, multiple LP efforts, and higher perceived stress during the LP procedure were associated with a longer duration of PDPH. Sitting position seemed to have a larger effect than the number of LP efforts, although we believe these factors are strongly related. Higher levels of neuroticism or anxiety have been described before as risk factors for PDPH³³ but not for a longer duration of PDPH.

One might argue that using smaller sized atraumatic needles^{34,35} and parallel bevel insertion, rather than perpendicular,^{18,36} could have potentially reduced the risk of PDPH. However, after careful consideration, we decided to use traditional procedures and needles, for several reasons. First, because the present study was primarily a “CSF biochemical profiling

study,” it was crucial to limit the sampling time to preclude ex vivo metabolization.³⁷ Using larger sized needles and the simplest available procedure allowed for higher CSF flow rates and briefer overall sampling times. An alternative could have been the use of 20-gauge atraumatic needles.³⁸ However, atraumatic needles are more difficult to use, often leading to higher failure rates,³⁵ and at that time, there was no experience in our department with atraumatic needles. Furthermore, comparability with previously collected samples required us to use the same needles because it is unknown what the effect of type of needle and consequent CSF sampling rate and flow velocity is on CSF metabolites. Finally, we wanted to compare our results with those obtained in previous studies using standard LP procedures. Indeed, our results for PDPH incidence,^{1,2} duration,^{17,39} and lag time^{6,40} are all well in line with findings in previous retrospective studies, supporting the external validity of our data. In future studies, however, the use of atraumatic needles should be considered.

Finally, despite clearly showing postural dependency of the headache, more than one-tenth of the subjects with PDPH did not have any of the associated symptoms as mandated by the ICHD-IIIR classification criteria.³ This finding would call for a re-evaluation of these criteria.

AUTHOR CONTRIBUTIONS

Dr. W.P. van Oosterhout: study concept and design, data acquisition, analysis and interpretation, drafting and revising the manuscript. Dr. A.A. van der Plas: data acquisition, conceptualization of the study, revising the manuscript. Dr. E.W. Van Zwet: study design, data analysis and interpretation, drafting the manuscript. Dr. R. Zielman: data acquisition, conceptualization of the study, revising the manuscript. Prof.dr. M.D. Ferrari and Dr. G.M. Terwindt: study concept and design, data interpretation, revising the manuscript, study supervision.

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DISCLOSURE

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