The onset of the migraine attack

Oosterhout, W.P.J. van

Chapter 5.

Postdural puncture headache in migraineurs and nonheadache subjects: a prospective study

van Oosterhout WPJ[1]
van der Plas AA[1]
van Zwet EW[2]
Zielman R[1]
Ferrari MD[1]
Terwindt GM[1]

[1]Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
[2]Department of Medical Statistics, Leiden University Medical Center, Leiden, the Netherlands

Neurology 2013; 80(10):941-948

Abstract

Objectives

To prospectively assess (i) the incidence and duration of post-dural puncture headache (PDPH) in migraineurs and healthy subjects; (ii) the associated risk factors; (iii) 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 a 160 migraineurs and 53 age- and gender 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 64/199 (32.2%) subjects 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 gender matched controls. Lumbar puncture does not trigger migraine attacks, and the stress of an upcoming LP might even have a protective effect against onset of migraine attacks.

Introduction

Postdural puncture headache (PDPH) occurs in 10-40% of subjects after lumbar puncture (LP), usually within five 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) [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 pathophysiological mechanisms have been hypothesized for PDPH [7-11] and retrospective observational studies suggest young age [12-19], female gender [17, 19-21], low BMI [19, 22], previous PDPH [7, 18], and (migraine) headache prior to 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 cerebrospinal fluid (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: (i) incidence and duration of PDPH; (ii) possible risk factors for PDPH; (iii) risk of migraine provocation by LP; and (iv) 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 ICHD-IIR criteria for PDPH.

Material and methods

Subjects

Migraineurs and healthy controls over 18 years of age were included as part of a study on biochemical changes in migraine. All subjects underwent full physical examination, including ophthalmoscopy. Exclusion criteria were: (i) use of anti-depressive or anti-coagulation medication; (ii) BMI>32; (iii) any oncological history; and (iv) any contra-indication for LP. Migraineurs were diagnosed according to the ICHD-IIR criteria[3] and could have no more than ten 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 ever were diagnosed with depression by a physician. Stress was assessed with a visual analogue scale, ranging from 0 (no stress at all) to 10 (most stressful event ever) regarding the upcoming LP. This score was assessed 10-15 minutes prior to 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 lead 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 anaesthesia 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 patients 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 09:00 a.m. and 01:00 p.m. by experienced neurology-residents and at least three days after a previous migraine. Participants were subjected to overnight fastening and were only allowed to drink water prior to 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 (Mediplast, Sweden). If a successful puncture was not possible in the left lateral supine position, LP was performed with the subject in sitting position. Participants were mobilized after the procedure, since there is no evidence that prolonged recumbent position after LP may prevent PDPH[26, 27].

Follow up assessment

All participants were standard contacted three 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 semi-structured telephone interview using ICHD-IIR criteria [3] and, for PDPH, Lybecker's classification [6]. Conservative treatment with bed-rest and oral NSAIDs, fluids, anti-emetics, 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's t-test for continuous variables, and a Chi square test for categorical data. To assess risk factors for PDPH, binary logistic regression was performed with migraine status as independent variable, adjusted for age, gender, and BMI. Additional risk factors were also analysed with the regression model, both uni- and multivariate. Multivariate analyses were performed in two ways: (i) adjusted for age, BMI and gender; and (ii) 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, gender, 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, USA). *P* values less than 0.05 were considered significant.

To assess (i) whether LP could trigger migraine attacks or (ii) whether (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 two 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 three days of the diary study but who subsequently did develop an attack in the following three days. The diary study was previously carried out 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 McNemar's test.

To address the second question, we compared the proportion of migraineurs with an attack in the three days preceding a *scheduled* LP in the LP study with the proportion of migraineurs who had an attack in the first three 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 McNemar's 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 13/213 (6.1%) subjects (of which nine were migraineurs), leaving 200 subjects at risk for PDPH. After LP, one subject developed headache which could not reliably be attributed to either PDPH or episodic migraine. Retrospectively, this patient suffered from chronic migraine which started months prior to 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 with hemiplegic migraine; n=66 with migraine without aura) are described in table e-2. Migraineurs had a higher mean age (44.0±13.3 vs. 36.3±15.3, 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

A total of 64/199 subjects (32.2%) developed PDPH, which was mild in 27/64 (42.2%), moderate in 18/64 (28.1%) and severe in 14/64 (21.9%). In 59/64 (92.2%) subjects the PDPH had started within two days and in 63/64 (98.4%) within three days. The median time to onset was 20.0 hours (range: 1.0 – 76.0; Figure 1). The overall median duration of PDPH was 5.1 days (range 1-18) and tended to be shorter in migraineurs (mean ± SD: 4.6 ± 2.4 days compared to controls (5.9 ± 3.6 days; 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 62/64 (96.9%) subjects with PDPH of whom 55/62 (88.7%) reported the presence of such symptoms: vestibulo-cochlear symptoms (vertigo, dizziness, hypacusis and tinnitus) in 40/62 (64.5%); nausea and/ or vomiting in 40/62 (64.5%); cochlear symptoms (including hypacusis and tinnitus) in 19/62 (30.6%), ocular symptoms (diplopia) in 2/62 (3.2%) and musculoskeletal complaints (stiff neck or stiff shoulder region) in 23/62 (37.1%). Photophobia was reported by 3/62 (4.8%). PDPH was more prevalent in the subgroup that underwent LP in sitting position vs.

in lateral supine position: 13/20 (65.0%) vs. 51/179 (28.5%); *p*=0.001 (OR 3.5, 95%C.I. 1.2-10.1; *p*=0.022 when adjusted for number of LP efforts, age, gender, BMI).

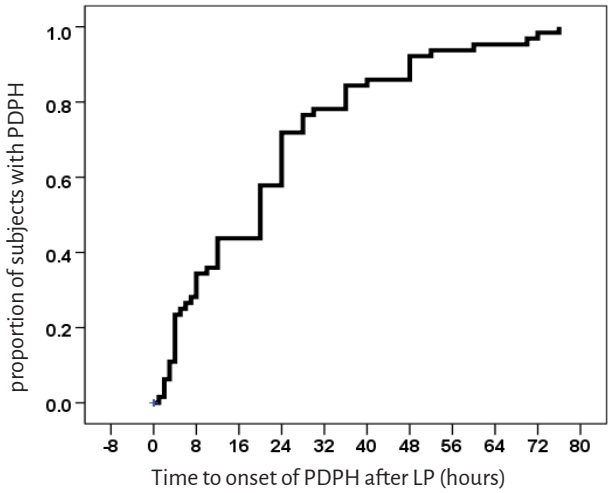

Figure 1. Cumulative onset of post-dural puncture headache in 64 subjects. 59/64 (92.2%) reported PDPH <48 hours and 63/64 (98.4%) <72 hours. Median time to onset was 20 hrs.

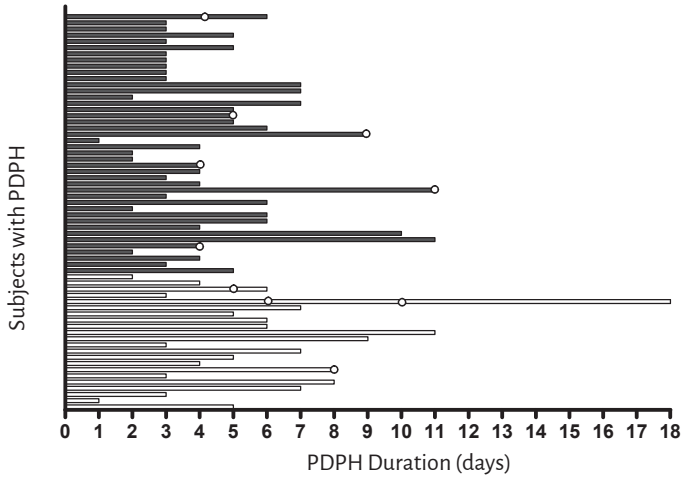

Figure 2. Duration (days) of PDPH in 64 subjects with PDPH. O = timepoint of autologous epidural blood patch; grey coloured bars = migraine patients; open bars = controls.

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 cmH_2O) vs. those who did not (17.4±4.2 cmH_2O; 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 did also not differ between patients with hemiplegic migraine (2/19; 10.5%) vs. non-hemiplegic migraineurs (40/131; 30.5%; p=0.07). Excluding HM cases in a post-hoc analysis did not change the significant lower incidence of PDPH in the migraine group compared to 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, gender and BMI) low 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 factor. Table 3 indicates risk factors for longer PDPH duration. Both univariate and multivariate (adjusted for age, gender 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 though non-significant trend. A second multivariate analysis (using variables with p<0.05) confirmed sitting position as an important risk factor.

Migraine after LP

In total 25/150 (12.0%) migraineurs 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 had an attack in days -3 to 0 prior to the LP, the risk of experiencing a migraine attack within three days after LP was 13/94 (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 suffered an attack on the first three/four days of the study (111/257; 43.2%; odds ratio = 0.74; p<0.0001). A similar trend for reduced risk of a migraine attack after LP was seen for the subgroup of 41 migraineurs who had participated in both the LP and diary study: 14/41 (34.1%) vs. 24/41 (58.5%; odds ratio = 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 three days preceding LP (37/131; 28.2%) than in the first three 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%; $p=0.04$).

Table 1; Baseline characteristics of study population. Baseline characteristics of subjects who developed PDPH (PDPH, n=64) versus subjects without PDPH (non-PDPH; n=135) of participants with successful LP (n=199). *p*-values depicted in bold indicate significant differences ($p<0.05$), using independent-samples t-tests and χ^2 tests appropriately. M = Migraine; LP = lumbar puncture; CSF = cerebrospinal fluid; VAS = visual analogous scale with range 1-10 (no stress/ pain – most stressful/ painful imaginable).

Variable	Total (n=199)	PDPH (n=64)	Non-PDPH (n=135)	*p*
Age; mean (SD)	42.1 (14.1)	37.9 (13.2)	44.1 (14.2)	**0.004**
Female (%)	122 (61.3%)	37 (57.8 %)	85 (63.0%)	0.486
Migraine (%)	150 (75.4%)	42 (65.6%)	108 (80.0%)	**0.028**
BMI	24.2 (3.0)	23.4 (3.0)	24.5 (2.9)	**0.022**
Education level (%)				
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				
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 M.* (%)	108 (54.3%)	34 (53.1%)	74 (54.8%)	0.823
Intoxications				
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 effort; mean (SD)	1.4 (1.0)	1.7 (1.1)	1.3 (1.0)	**0.042**
Puncture traumatic (%)	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	23 (11.6%)	13 (20.3%)	10 (7.4%)	**0.008**
Pain during LP (VAS)	3.3 (2.4)	3.4 (2.5)	3.2 (2.4)	0.548
Stress prior to LP (VAS)	2.4 (2.7)	2.1 (3.1)	2.5 (2.5)	0.284
Stress during LP (VAS)	3.2 (2.8)	3.0 (2.7)	3.3 (2.9)	0.547
Headache directly after LP (VAS)	1.0 (1.6)	1.5 (2.0)	0.7 (1.4)	**0.009**

Table 2; Risk factors for PDPH onset. Odds Ratios (1: univariate; 2: multivariate, adjusted for age, gender 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). *p*-values depicted in bold indicate significant differences ($p<0.05$).

Variable	1. Univariate OR [95% CI]	*p*	2. Multivariate OR [95% CI]	*p*	3. Multivariate OR [95% CI]	*p*
Age (years)	0.972 [0.951-0.993]	**0.010**	0.976 [0.955-0.998]	**0.033**	0.977 [0.954-1.000]	0.051
Gender (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**	0.892 [0.803-0.990]	**0.032**	0.912 [0.816-1.019]	0.102
Migraine diagnosis	0.506 [0.264-0.969]	**0.040**	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 (hours)	1.136 [0.997-1.294]	0.056	1.138 [0.996-1.300]	0.057		
LP effort (1x 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_2O)	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**	3.321 [1.323-8.338]	**0.011**	3.210 [1.287-8.006]	**0.012**
Pain during LP (VAS 1-10)	1.005 [0.893-1.132]	0.931	0.990 [0.872-1.125]	0.883		
Stress prior to LP (VAS 1-10)	0.946 [0.840-1.066]	0.363	0.957 [0.845-1.083]	0.485		
Stress during LP (VAS 1-10)	0.960 [0.863-1.069]	0.458	0.948 [0.846-1.062]	0.356		
Headache after LP (VAS 1-10)	1.322 [1.103-1.583]	**0.002**	1.377 [1.139-1.664]	**0.001**	1.443 [1.169-1.782]	**0.001**

Table 3; Risk factors for longer PDPH duration. Regression coefficients (1: univariate; 2: multivariate, adjusted for age, gender 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). *p*-values depicted in bold indicate significant differences ($p<0.05$).

Variable	1. Univariate B [95% CI]	*p*	2. Multivariate B [95% CI]	*p*	3. Multivariate B [95% CI]	*p*
Age (years)	-0.016 [-0.067;0.034]	0.520	-0.017 [-0.075;0.041]	0.551		
Gender (F)	0.788 [-0.531;2.107]	0.236	0.807 [-0.600;2.214]	0.254		
BMI (kg/m^2)	-0.043 [-0.262;0.176]	0.692	0.031 [-0.231;0.292]	0.815		
Migraine diagnosis	-0.946 [-2.317;0.425]	0.172	-0.926 [-2.422;0.570]	0.219		
Education level						
Middle vs. low	2.667 [-0.159;5.492]	0.064	2.548 [-0.358;5.454]	0.084		
High vs. middle	2.667 [-0.942;4.799]	0.183	1.749 [-1.210;4.708]	0.240		
History of depression	6.578 [2.115;11.042]	**0.005**	7.598 [2.929;12.267]	**0.002**	-0.279 [-1.851;1.293]	0.722
Family History Migraine	-1.149 [-2.441;0.144]	0.080	-1.182 [-2.587;0.223]	0.097		
Alcohol (yes/ no)	0.945 [-0.528;2.419]	0.204	0.922 [-0.637;2.481]	0.240		
Smoking (yes/ no)	0.436 [-1.246;2.117]	0.605	0.738 [-1.029;2.505]	0.405		
Drugs (yes/ no)	1.187 [-1.643;4.017]	0.404	1.723 [-1.429;4.876]	0.277		
Caffeine (yes/ no)	1.090 [-2.352;4.532]	0.528	0.961 [-2.548;4.471]	0.584		
Sober (hours)	0.053 [-0.261;0.368]	0.735	0.060 [-0.263;0.382]	0.712		
LP effort (1x vs. >1)	-1.718 [-3.155;-0.281]	**0.020**	-1.629 [-3.173;-0.085]	**0.039**	-0.268 [-0.968;0.432]	0.444
Puncture traumatic (yes/ no)	0.721 [-1.524;2.966]	0.522	0.760 [-1.531;3.052]	0.508		
CSF opening pressure (cm H_2O)	-0.023 [-0.149;0.103]	0.718	-0.013 [-0.151;0.125]	0.852		
Sitting position (vs. supine)	2.750 [1.082-4.418]	**0.002**	3.003 [1.192-4.814]	**0.002**	2.534 [0.632-4.435]	**0.010**
Pain during LP (VAS 1-10)	0.161 [-0.111;0.433]	0.239	0.141 [-0.138;0.421]	0.314		
Stress prior to LP (VAS 1-10)	0.030 [-0.172;0.231]	0.770	0.057 [-0.153;0.268]	0.587		
Stress during LP (VAS 1-10)	0.369 [0.149;0.588]	**0.001**	0.356 [0.120;0.592]	**0.004**	0.345 [0.076-0.614]	**0.013**
Headache-after-LP (VAS 1-10)	0.189 [-0.152;0.531]	0.271	0.148 [-0.217;0.512]	0.419		

Discussion

This is the first prospective evaluation of the risk of PDHP and migraine after LP in migraineurs and healthy subjects. We carefully assessed and compared two large populations of well-characterized 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 one-week pro-active 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 get 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 a previously unrecognized additional risk factor. 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 feel these factors are strongly related. Higher levels of neuroticism or anxiety have been described before as risk factors for PDPH[33] but not for a longer duration of PDPH.

One might argue that using smaller sized a-traumatic 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, as the present study primarily was a "CSF biochemical profiling study", it was crucial to limit the sampling time to preclude *ex vivo* metabolisation [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, a-traumatic needles are more difficult to use, often leading to higher failure rates [35], and 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, since 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, over one tenth of the subjects with PDPH did not have any of the associated symptoms as mandated by the ICHD-IIR classification criteria[3]. This finding would call for a re-evaluation of these criteria.

Acknowledgements

This work was supported by grants of the Netherlands Organization for Scientific Research (NWO) (903-52-291, M.D.F.; Vici 918.56.602, M.D.F; 907-00-217 GMT; Vidi 917-11-319 GMT), and by a grant from the Centre for Medical Systems Biology (CMSB) established by the Netherlands Genomic Initiative/ Netherlands Organisation for Scientific Research (NGI/ NWO).

References

1. Evans RW, Armon C, Frohman EM, Goodin DS. Assessment: prevention of post-lumbar puncture headaches: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology* 2000; 55(7):909-914.
2. Olsen KS. Epidural blood patch in the treatment of post-lumbar puncture headache. *Pain* 1987; 30(3):293-301.
3. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004; 24 Suppl 1:9-160.
4. Weeks SK. Spinal headache--prevention and treatment. *Can J Anaesth* 1990; 37(4 Pt 2):Sliii-Slxiii.
5. Fog J, Wang LP, Sundberg A, Mucchiano C. Hearing loss after spinal anesthesia is related to needle size. *Anesth Analg* 1990; 70(5):517-522.
6. Lybecker H, Djernes M, Schmidt JF. Postdural puncture headache (PDPH): onset, duration, severity, and associated symptoms. An analysis of 75 consecutive patients with PDPH. *Acta Anaesthesiol Scand* 1995; 39(5):605-612.
7. Amorim JA, Valenca MM. Postdural puncture headache is a risk factor for new postdural puncture headache. *Cephalalgia* 2008; 28(1):5-8.
8. Frank RL. Lumbar puncture and post-dural puncture headaches: implications for the emergency physician. *J Emerg Med* 2008; 35(2):149-157.
9. Evans RW, Mokri B. Spontaneous intracranial hypotension resulting in coma. *Headache* 2002; 42(2):159-160.
10. Vandam L. Neurological sequelae of spinal and epidural anesthesia. *Int Anesthesiol Clin* 1986; 24(4):231-255.
11. Clark JW, Solomon GD, Senanayake PD, Gallagher C. Substance P concentration and history of headache in relation to postlumbar puncture headache: towards prevention. *J Neurol Neurosurg Psychiatry* 1996; 60(6):681-683.
12. Flaatten H, Rodt S, Rosland J, Vamnes J. Postoperative headache in young patients after spinal anaesthesia. *Anaesthesia* 1987; 42(2):202-205.
13. Leibold RA, Yealy DM, Coppola M, Cantees KK. Post-dural-puncture headache: characteristics, management, and prevention. *Ann Emerg Med* 1993; 22(12):1863-1870.
14. Solomon GD, Clark JW, deSenanayake P, Kunkel RS. Hypersensitivity to substance P in the etiology of postlumbar puncture headache. *Headache* 1995; 35(1):25-28.
15. Bolder PM. Postlumbar puncture headache in pediatric oncology patients. *Anesthesiology* 1986; 65(6):696-698.
16. Vilming ST, Schrader H, Monstad I. The significance of age, sex, and cerebrospinal fluid pressure in post-lumbar-puncture headache. *Cephalalgia* 1989; 9(2):99-106.
17. VANDAM LD, Dripps RD. Long-term follow-up of patients who received 10,098 spinal anesthetics; syndrome of decreased intracranial pressure (headache and ocular and auditory difficulties). *J Am Med Assoc* 1956; 161(7):586-591.
18. Lybecker H, Moller JT, May O, Nielsen HK. Incidence and prediction of postdural puncture headache. A prospective study of 1021 spinal anesthesias. *Anesth Analg* 1990; 70(4):389-394.
19. Kuntz KM, Kokmen E, Stevens JC, Miller P, Offord KP, Ho MM. Post-lumbar puncture headaches: experience in 501 consecutive procedures. *Neurology* 1992; 42(10):1884-1887.
20. Dripps RD, VANDAM LD. Hazards of lumbar puncture. *J Am Med Assoc* 1951; 147(12):1118-1121.
21. Tourtellotte WW, Henderson WG, Tucker RP, Gilland O, Walker JE, Kokman E. A randomized,

double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post-lumbar puncture syndrome in normal individuals. *Headache* 1972; 12(2):73-78.
22. Lynch J, Krings-Ernst I, Strick K, Topalidis K, Schaaf H, Fiebig M. Use of a 25-gauge Whitacre needle to reduce the incidence of postdural puncture headache. *Br J Anaesth* 1991; 67(6):690-693.
23. Gielen M. Post dural puncture headache (PDPH): a review. *Reg Anesth* 1989; 14(3):101-106.
24. Kortum K, Rossler B, Nolte H. [Morbidity following spinal anaesthesia (author's transl)]. *Anaesthesist* 1979; 28(1):5-11.
25. Oomura M, Yamawaki T, Miyashita K, Yamagami H, Naritomi H. Disappearance of migraine attacks during long-lasting postdural puncture headache: a case report. *Headache* 2002; 42(5):356-358.
26. Carbaat PA, van CH. Lumbar puncture headache: controlled study on the preventive effect of 24 hours' bed rest. *Lancet* 1981; 2(8256):1133-1135.
27. Hafer J, Rupp D, Wollbruck M, Engel J, Hempelmann G. The effect of needle type and immobilization on postspinal headache. *Anaesthesist* 1997; 46(10):860-866.
28. Janssens E, Aerssens P, Alliet P, Gillis P, Raes M. Post-dural puncture headaches in children. A literature review. *Eur J Pediatr* 2003; 162(3):117-121.
29. Munts AG, Voormolen JH, Marinus J, Delhaas EM, van Hilten JJ. Postdural puncture headache in complex regional pain syndrome: a retrospective observational study. *Pain Med* 2009; 10(8):1469-1475.
30. Schoonman GG, Evers DJ, Ballieux BE, de Geus EJ, de Kloet ER, Terwindt GM et al. Is stress a trigger factor for migraine? *Psychoneuroendocrinology* 2007; 32(5):532-538.
31. Leistad RB, Stovner LJ, White LR, Nilsen KB, Westgaard RH, Sand T. Noradrenaline and cortisol changes in response to low-grade cognitive stress differ in migraine and tension-type headache. *J Headache Pain* 2007; 8(3):157-166.
32. Vandam LD, Dripps RD. A long-term follow-up of 10,098 spinal anesthetics. II. Incidence and analysis of minor sensory neurological defects. *Surgery* 1955; 38(3):463-469.
33. Lange HU. [Anxiety and neuroticism in the development of post lumbar puncture headache (author's transl)]. *Nervenarzt* 1978; 49(1):47-49.
34. Halpern S, Preston R. Postdural puncture headache and spinal needle design. Metaanalyses. *Anesthesiology* 1994; 81(6):1376-1383.
35. Arendt K, Demaerschalk BM, Wingerchuk DM, Camann W. Atraumatic lumbar puncture needles: after all these years, are we still missing the point? *Neurologist* 2009; 15(1):17-20.
36. Strupp M, Brandt T, Muller A. Incidence of post-lumbar puncture syndrome reduced by reinserting the stylet: a randomized prospective study of 600 patients. *J Neurol* 1998; 245(9):589-592.
37. Rosenling T, Slim CL, Christin C, Coulier L, Shi S, Stoop MP et al. The effect of preanalytical factors on stability of the proteome and selected metabolites in cerebrospinal fluid (CSF). *J Proteome Res* 2009; 8(12):5511-5522.
38. Carson D, Serpell M. Choosing the best needle for diagnostic lumbar puncture. *Neurology* 1996; 47(1):33-37.
39. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. *Br J Anaesth* 2003; 91(5):718-729.
40. Poukkula E. The problem of post-spinal headache. *Ann Chir Gynaecol* 1984; 73(3):139-142.

Supplementary material

Table e-1; Diagnostic criteria for post-dural (post-lumbar) puncture headache (PDPH) as set by the Headache Classification Subcommittee of the International Headache Society[3].

Diagnostic criteria		
A.	Headache that worsens within 15 minutes after sitting or standing, and improves within 15 minutes after lying, with at least one of the following (see 1 to 5) and fulfilling criteria C and D:	1. Neck stiffness 2. Tinnitus 3. Hypacusia 4. Photophobia 5. Nausea
B.	Dural puncture has been performed	
C.	Headache develops within 5 days after dural puncture	
D.	Headache resolves either*:	1. Spontaneously within 1 week 2. Within 48 hours after effective treatment of the spinal fluid leak (usually by epidural blood patch).

* Note: in 95% of cases this is so. When headache persists, causation is in doubt.

Table e-2; Baseline characteristics of migraineurs (n=150) and healthy controls (n=49). *p*-values depicted in bold indicate significant differences ($p<0.05$), using independent-samples t-tests and χ^2 tests appropriately. M = Migraine; LP = lumbar puncture; CSF = cerebrospinal fluid.

Variable	Total (n=199)	Migraineurs (n=150)	Controls (n=49)	*P*
Age; mean (SD)	42.1 (14.1)	44.0 (13.3)	36.3 (15.3)	**0.001**
Female (%)	122 (61.3%)	98 (65.3%)	24 (49.0%)	**0.041**
BMI	24.2 (3.0)	24.3 (2.9)	24.1 (3.3)	0.746
Education level (%)				
Low	17 (13.6%)			
Middle	69 (34.6%)			
High	94 (47.2%)			
Comorbidity				
None	189 (95.0%)	140 (93.3%)	49 (100%)	0.179
Depressive	6 (3.0%)	6 (4.0%)	-	
Epilepsy	4 (2.0%)	4 (2.7%)	-	
Family History M.* (%)	108 (54.3%)	102 (68%)	6 (12.2%)	**<0.001**
Migraine subtype MO (%)	-	66 (44%)	-	
Intoxications				
Alcohol (%)	148 (74.4%)	44 (29.3%)	42 (85.7%)	**0.036**
Smoking (%)	37 (18.6%)	24 (16.0%)	13 (26.5%)	0.100
Drugs (%)	4 (2.0%)	1 (0.7%)	3 (6.1%)	**0.018**
Caffeine (%)	188 (94.5%)	142 (94.7%)	46 (93.9%)	0.834
Hours sober; mean (SD)	11.3 (2.3)	11.3 (2.1)	11.4 (2.8)	0.871
LP effort; mean (SD)	1.4 (1.0)	1.5 (1.1)	1.3 (0.8)	0.189
Puncture traumatic (%)	16 (8.0%)			
CSF pressure; mean (SD)	17.7 (4.3)	17.7 (4.5)	17.4 (3.8)	0.716
PDPH (%)	64 (32.2%)	42 (28.0%)	22 (44.8%)	**0.028**
Pain during LP	3.3 (2.4)	3.3 (2.3)	3.2 (2.6)	0.829
Stress prior to LP	2.4 (2.7)	2.4 (2.9)	2.1 (2.3)	0.544
Stress during LP	3.2 (2.8)	3.2 (2.8)	3.2 (2.9)	0.958
Headache immediately after LP	1.0 (1.6)	1.0 (1.6)	1.0 (1.6)	0.762

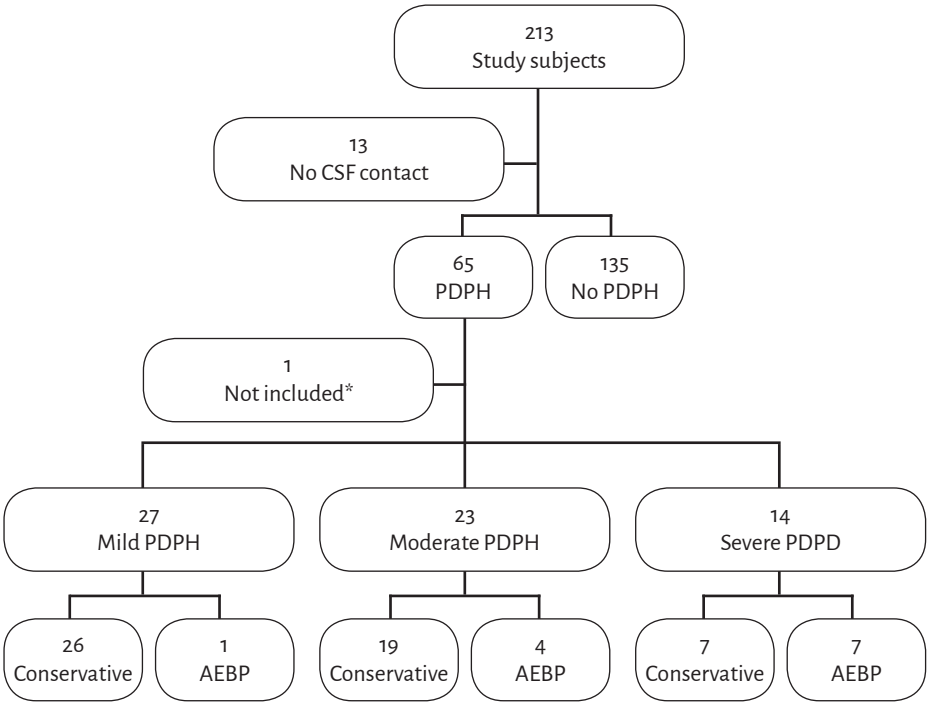

Figure e-1; Flowchart showing distribution of study subjects in relation to PDPH and selected treatment. AEBP = autologous epidural bloodpatch; Conservative = conservative treatment. *One female subject was excluded from the PDPH analysis due to headache symptoms that could be attributed to neither PDPH nor migraine, and were suggestive for chronification of migraine.