THE IMPACT OF ANXIETY ON POST-DURAL PUNCTURE HEADACHE IN ROUTINE NEUROLOGY PRACTICE

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ABSTRACT

Background: The post-dural puncture headache (PDPH) is the most common complication of lumbar puncture in neurological practice. Although the comorbidity of a headache and psychiatric symptoms is well-recognized, the data about the relationship between PDPH and symptoms of anxiety and depression are limited. The aim of the present study was to determine the influence of anxiety symptoms on the risk for PDPH. Methods: Diagnostic lumbar puncture was performed to thirty-nine neurological patients, submitted by 26 women and 13 men. All subjects completed the Hospital Anxiety and Depression Scale (HADS) before the procedure. Information about the clinical characteristic of a headache - quality, location, severity, postural nature, duration and associated symptoms (nausea, vomiting, and tinnitus) was collected. Results: Fifteen of the patients (38.5%) developed PDPH. According to the presence of PDPH the patients were divided into two groups – with (group 1) and without a headache (group 2). Women with headache were significantly younger (mean age 34,00±11,22 years) compared to females in group 2 (average age 45,07±12,36 years) (p=0,028). Patients in group 1 had significantly higher levels of reported anxiety symptoms compared to group 2 (p= 0,045). A significant positive correlation was observed between anxiety and PDPH (Spearman’s rho = 0,412, p=0,009). Conclusion: Younger female patients with anxiety had a considerably increased rate of PDPH. It could be of practical benefit in devising an additional treatment strategy for patients with PDPH.

KEYWORDS headache, anxiety, lumbar puncture, depression

Introduction

Lumbar puncture (LP) is a diagnostic and therapeutic medical procedure. Although it is regarded as a safe procedure, post-dural-puncture headache (PDPH) is common. Spinal headaches occur in between 30 to 50 percent of those who undergo diagnostic or therapeutic lumbar puncture or spinal anesthesia [1]. According to the International Classification of Headache Disorders, of the International Headache Society (IHS) [2] PDPH is described as a headache that occurs within five days of an LP. It caused by cerebrospinal fluid (CSF) leakage through the dural puncture and usually accompanied by neck stiffness and/or subjective hearing symptoms.

It remits spontaneously within two weeks, or after sealing of
The leak with the lumbar epidural patch.

The reported patient-related risk factors for PHDP in recent studies are female gender [3], age between 18 to 40 years [4-6] and a history of a chronic headache [7]. Conversely, individuals over the age of 60 have a lower risk to suffer from PHDP [4-6]. It was reported that patients with a lower body mass index (BMI) had the highest risk of developing PDPH [3,8], whereas other authors found no effect of BMI [9]. Also, it was determined that patients with a history of chronic or recurrent headaches or a recent headache (within the last seven days) before an LP be more likely to report PDPH [8,10]. Interestingly, smokers had a lower incidence of PDPH than non-smokers [11].

Modifiable clinician-controlled risk factors for PDPH are needle shape, needle size, bevel orientation and insertion angle, stylet replacement [9,12,13]. The incidence is partially dependent on the skill and experience of the person performing the lumbar puncture [14]. Patient’s position during the procedure is also one of the contributing factors [15]. Recently Monserrate AE et al.[16] reported that factors that acutely lower CSF pressure (e.g., seated positioning or extracting very high volumes of CSF) may be associated with transient post-lumbar puncture headache, without increasing rates of persistent PDPH or necessity of therapeutic blood patch. Other studies reported that CSF opening pressure, cells, protein, patient’s position during LP, the duration of recumbency following LP, and the amount of CSF removed at the time of LP did not influence the occurrence of headache [8,17].

The clinical diagnosis was also reported to be a predictive factor of PDPH. Healthy controls had a higher incidence of PDPH than patients with Alzheimer disease [18], or post-traumatic stress disorder (PTSD) [11]. Patients with anxiety and depression, but without PTSD had a higher, but the insignificant incidence of PDPH than those with PTSD [11]. It was found that the fear of the procedure (the patients’ anxiety before the procedure) does not predispose the occurrence of a post-up headache [10].

Psychiatric comorbidity, especially depression and anxiety, on the other hand, has been well documented in patients with primary headaches. The results from these longitudinal studies among adults suggest that the association between depression and headache may be bi-directional [19,20]. The early identification of psychiatric problems in patients with a headache is crucial for headache treatment and prognosis. Several recent investigations suggested that patients with headaches should receive at least brief screenings for psychiatric disorders [21,22].

Since the comorbidity of a headache and psychiatric symptoms is well-recognized, but there are only limited data regarding the relationship between PDPH and symptoms of anxiety and depression, the aim of the present study was to assess the risk factors leading to PDPH, focusing on psychiatric symptoms evaluation.

Materials & Methods

Diagnostic LP was performed in thirty-nine neurological patients (26 women and 13 men (p=0.000) with mean age 39.95 ± 13.32 years. All patients were examined at the Department of Neurology of “St. George” Hospital between January 2010 and January 2014. All participants gave their written informed consent to take part in the investigation, which was approved by the Ethics Committee of Medical University—Plovdiv, conformity with Declaration of Helsinki.

They were diagnosed with multiple sclerosis (74.4%), peripheral nerve disorders (20.8%) or other (5.1%) based on the patient’s history, detailed neurological, laboratory and instrumental examination during their hospitalization. None of the patients had a history of chronic or recurrent headaches or a recent headache (within seven days) before LP.

The LPs were performed by experienced operators in a midline approach in sitting position, between L3-L4 lumbar vertebrae. A traumatic 22G type (Quinke type point needle) was used during all procedures.

All subjects completed the Hospital Anxiety and Depression Scale (HADS) before the procedure. HADS is a 14-item self-reported instrument designed to screen for the presence and severity of symptoms of depression and anxiety over the past week. It is a brief and useful screening tool for symptoms of depression and anxiety. The items in HADS are scored on a 0–3 scale: HADS-D (depression) and HADS-A (anxiety) subscale scores (range 0–21) are derived by adding the seven items on each scale. For both subscales, scores in the range of 0–7 are considered normal; 8–10 - mild and 11–14 are moderate; and 15–21 are severe.

Data about patients’ demographic characteristics (age, sex, height, weight) were collected from medical files, and body mass index (BMI) was calculated. Procedure-related data, including indications for the test, cerebrospinal fluid (CSF) content (cells, glucose, protein and others) were collected from hospital records. Information about the clinical characteristic of the headache was evaluated according quality, location, severity (rated on a Visual Analog Scale (VAS) from 1 to 10), postural nature, duration and associated symptoms (nausea, vomiting, tinnitus).

Data Processing and Analysis.

The score for the HADS was obtained from the two subscales for anxiety and depression on 0–3 scale. The statistical analyzes were performed with SPSS and statistical significance was set at p<0.05. A descriptive statistic for demographic data was applied. Differences between patients with and without post-LP a headache were analyzed by two-sample t-tests and Mann-Whitney U test (for continuous variables), Pearson chi-square test or Fisher exact test (for binary and nominal variables). To evaluate the differences between variables in the groups comparison was done with Wilcoxon Signed-Rank Test.

Spearman’s correlation coefficients were used to measure the strength of association between the variables. Factors found to be associated with PDPH were entered into a logistic regression model to identify independent associations with a post-LP headache.

Results

According to the presence of PDPH, the patients were divided into two groups – group 1 - with a headache and group 2 - without a headache. The characteristics of the patients are shown in Table 1.

Fifteen of the patients (38.50%) developed PDPH. More women compared to men were examined in both groups (p = 0.000), without statistically significant difference according to age within the groups (group 1 - p = 0.492; group 2 - p = 0.309).

The group 1 was characterized by a lower mean age (35.33±11.88 vs. 42.83±13.59 years, (p=0.112) and a higher proportion of women (73.33% vs. 62.50% (p=0.578)), without reaching significance. The women with headache were significantly younger (mean age 34.00±11.22 years) than those without headache (mean age 45.07±12.36 years) (p=0.028) (table 1). There was no statistically significant difference between the groups

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Table 1: Characteristics of the patients. BMI - body mass index; SD - standard deviation.

| Characteristics | Female | Male  | Total   | Female | Male  | Total   |
|-----------------|--------|-------|---------|--------|-------|---------|
| Number of patients (%) | 11 (73.3%) | 4 (26.7%) | 15 (38.5%) | 15 (62.5%) | 9 (37.5%) | 24 (61.5%) |
| Age (yr), (mean ± SD) | 34.0±11.2 | 39.0±14.7 | 35.3±11.9 | 45.1±12.4 | 39.1±15.4 | 42.8±13.6 |
| BMI (kg/m²), (mean ± SD) | 24.1±3.5 | 27.8±2.9 | 25.1±3.7 | 24.5±2.5 | 25.6±3.3 | 24.9±2.8 |

Table 2: Comparison of CSF content between patients with and without PDPH. Independent-Samples T Test; Mann-Whitney U test; CSF- cerebrospinal fluid; Q1–first quartile; Q3-third quartile.

| CSF content | PDPH (n = 15) | NO PDPH (n = 24) | p VALUE |
|-------------|---------------|------------------|---------|
| Glucose (mmol/l) | 3.38 ± 0.69 | 3.30 (2.80 - 3.65) | 3.78 ± 0.95 | 3.55 (3.20 - 3.90) | 0.197 |
| Protein (g/l) | 0.57 ± 0.41 | 0.38 (0.33 - 0.63) | 0.53 ± 0.21 | 0.53 (0.33 - 0.68) | 0.672 |
| Leukocyte (x10 (6)/l) | 0.75 ± 1.25 | 0.00 (0.00 - 1.00) | 1.55 ± 1.59 | 1 (0.00 - 2.00) | 0.169 |
| Erythrocyte (x10 (9)/l) | 0.48 ± 1.08 | 0.002 (0.00 - 0.01) | 0.02 ± 0.62 | 0.00 (0.00 - 0.01) | 0.441 |
| Potassium (mmol/l) | 2.87 ± 0.15 | 2.9 (2.78 - 2.90) | 2.93 ± 0.24 | 2.9 (2.83 - 2.98) | 0.468 |
| Sodium (mmol/l) | 143.67 ± 5.65 | 145 (142.75 - 147.00) | 146.18 ± 4.32 | 147.00 (144.00 - 149.00) | 0.156 |
| IgA (mg/l) | 7.4 ± 15.7 | 2.4 (1.34 - 4.80) | 3.44 ± 3.86 | 1.7 (0.98 - 5.03) | 0.672 |
| IgG (mg/l) | 64.93 ± 57.1 | 47.41 (41.55 - 71.62) | 59.25 ± 23.3 | 48.41 (30.80 - 62.45) | 0.863 |
| IgM (mg/l) | 4.51 ± 5.69 | 1.56 (1.08 - 8.19) | 2.02 ± 2.27 | 1.23 (0.9 - 2.12) | 0.292 |

Only seven patients (17.9%) had abnormal results for the HADS-D subscale: 26.7% in group 1 compared to 12% in group 2 (p = 0.268). The subscale for depression (HADS-D) ranged from 0 to 15 (median 6, IQR 9) in group 1 and from 0 to 11 (median 3, IQR 4) in group 2 (Figure 1). There was no significant difference between both groups for the HADS-D score results (p = 0.054). Sixteen (41%) of all 39 patients showed abnormal results for the HADS-A scale, but in the PDPH group those with elevated level of anxiety reached 66.7% compared to 28% in group 2 (Table 3) and the difference was statistically significant (p = 0.011).

There was a significant difference between both groups according BMI values (Table 1; p = 0.583) and CSF content (Table 2).

Demographic variables and factors associated with PDPH were entered into a logistic regression model. The selected variables were sex, age, BMI, HADS-A score, HADS-D score and presence of anxiety and depression (patients with elevated scores were cut-off 8+). Anxiety and age were the only variables found to be significant in the model, with Nagelkerke R Square value of 0.488.

Age was found to correlate with PDPH incidence (p = 0.014, odds ratio (OR) 0.907 per year, with a 95% confidence interval for the Odds Ratio of 0.839 – 0.989). The presence of anxiety also was associated with PDPH incidence, and patients with anxiety were more likely to develop PDPH than patients with depression (p = 0.036, OR 0.013 with a 95% confidence interval for the Odds Ratio of 0.000 – 0.745).
The major finding of our study is that anxiety symptoms predominated in patients with PDPH. We found that the HADS-A score was significantly higher in PDPH group compared to group 2, and a significant positive correlation was estimated between the elevated levels of anxiety and PDPH. Unlike another study [10], we found that elevated level of anxiety can lead to PDPH. The reason for these discrepancies may be searched in different study design and methods used. Previous reports have determined the presence of anxiety just by asking a simple question about the fear of the procedure [10]. Khlebtovsky et al. [10] proposed the possibility that patient’s anxiety can lead to excessive CSF leak and as a result to PDPH, because incomplete sealing of the dural hole, with attendant CSF leakage, is an important pathophysiological factor in PDPH. They ruled out this possibility and reported that the level of fear of the procedure was similar in patients who had PDPH and those who did not. Also, no differences were found between patients with a high and low level of fear.

An explanation of the possible connection between a headache (PDPH) and anxiety could be found at neurotransmitters level and the anxiety related neurochemical effects. The expression of anxiety involves a coordinated activity of numerous brain pathways involving different neurotransmitters, all of which interact with and are modulated by local and distant synaptic connections. The most important neurotransmitters involved in modulation of anxiety responses are inhibitory neurotransmitter GABA, serotonin, norepinephrine, opioid peptides, endocannabinoids, neuropeptide Y, oxytocin, and corticotropin-releasing hormone[25]. However, extensive data support the role of monoamine neurotransmitters, serotonin, and norepinephrine, also in the modulation of pain. The serotonin-norepinephrine reuptake inhibitors (SNRIs) have shown to be efficient and generally well-tolerated treatment in patients with anxiety disorders, but currently available preclinical and clinical data indicate that SNRIs may be the most promising agents for the modulation of pain symptoms [26].

Furthermore, it was reported that mirtazapine - an antidepressant that refines the specificity of effects on noradrenergic and serotonergic systems, relieves the PDPH, probably by activation of 5-HT 1 receptors (notably 5-HT 1B/1D) [27]. Mirtazapine could treat PDPH by constriction of dilated cerebral vessels, especially through 5-HT1A receptors. Also, mirtazapine might act as a 5-HT 2/3 receptor antagonist, and can potentiate the endogenous opioid systems. Also, it has a net positive effect on noradrenergic neurotransmission [28], and the vasoconstricting actions of norepinephrine may also be a factor in limiting PDPH.

These data allow to postulate the hypothesis that, if antidepressants relieve the PDPH and chronic pain, then the opposite can be expected: the anxiety can lead to PDPH and can increase the perception of pain. Our results support the suggestion that anxiety can be a risk factor for PDPH although the exact mechanism remains unclear, and a review of this area is beyond the boundaries of the current report. We should mention the small sample size of our subjects, group, which is a limitation of the study and should, at this point, accounts for preliminary conclusions only. Keeping in mind this limitation our data justify the necessity of further research on the impact of the psychological factors on the occurrence of PDPH and consequently on the opportunity of new treatment options. Finding new treatment options or prevention opportunities by limiting the risk factors would be of benefit for the patients subjected to LP.

Figure 1: Median values and 95% confidence interval of the mean for HADS-A and HADS-D sub-scores in both groups.

- significant difference between both groups, Mann-Whitney U test, p < 0.05
- - significant difference between HADS-A and HADS-D score within the groups, Wilcoxon signed ranks test, p < 0.05.

Discussion

Thirty - eight percents of the patients in the present study reported PDPH. This result is close to previous reports, suggesting frequency of PDPH between 13% to 50% [1,9,23]. The indications for LP in the current study were mainly demyelinating diseases and polynuropathy that also corresponds to the indications for nonurgent LP in a neurological department [24].

The well-known significant increase in risk of PDPH with younger age [3] is confirmed in the current study. Our results are consistent with the notion that female sex may be risk factors for the development of PDPH [3]. In our study, 73,3% of the patients with PDPH were women, but this difference was not statistically significant compared to subjects without a headache (group 2). No correlation between PDPH and BMI was found in our study, which is in agreement with some studies [9,11], but not with others [3,8]. In terms of the LP method, it has been shown that needle type, needle size, operator experience, and procedure technique might all be major factors in the development of PDPH. In the recent study all these factors were well controlled – all needles were Quince type, an experienced neurologist made the LP, so these factors could not be analyzed as risk factors.

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Conclusion

In conclusion, in the recent study we have found that younger female patients with anxiety have a higher rate of PDPH. These findings contribute to the small database linking anxiety disorders with medical conditions and provide further evidence that clinicians may improve patients’ cares by screening and treating anxiety in different medical populations.

Authors’ Statements

Competing Interests

The authors declare no conflict of interest.

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