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Headache attributed to acute pyelonephritis

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Abstract

Objective: This study identified the incidence and risk factors for headache attributed to acute pyelonephritis. *Methods:* The inclusion criteria were patients who were admitted with acute pyelonephritis at our hospital and ≥ 18 years of age. The following exclusion criteria were used: 1) patients who could not express their headache because of mental deterioration, 2) the presence of meningitis or meningoencephalitis, or 3) structural lesions on brain computed tomography or magnetic resonance images that could cause headache. The primary outcome was headache attributed to acute pyelonephritis as a dependent variable. The differences were analyzed using demographic and laboratory profiles as independent variables. Additionally, correlation analysis was performedbetweenseverity of headache using VAS score and demographic and laboratory profiles including age, WBC, and CRP. *Results:* A total of 479 patients met the inclusion criteria for this study, and 97 patients developed headache attributed to acute pyelonephritis. Patients with headache were younger and more likely to be female, and had a lower incidence of diabetes than those without headache. However, laboratory profiles that reflected the severity of acute pyelonephritis were not predictive factors for headache. Multiple logistic regression analysis demonstrated that young age and non-diabetes were independently significant variables for the prediction of headache attributed to acute pyelonephritis. In addition, the VAS score was found to be negative correlated with age, whereas it was not correlated with WBC and CRP. *Conclusions:* We determined that headache attributed to acute pyelonephritis was relatively common, and it was related to demographic characteristics but not acute pyelonephritis severity.

INTRODUCTION

Urinary tract infection (UTI) is one of the most frequent bacterial infections in all age groups.[1] Acute pyelonephritis (APN) is a severe form of upper UTI, and it often requires hospitalization.[1] The typical symptoms of APN include high-grade fever, flank pain, urinary frequency, and dysuria, and the mortality rate of APN ranges from 10 to 20%.[2,3] However, unusual presentations of APN are common, and some patients may lack the typical APN symptoms. The absence of typical APN symptoms can be present in patients with complicating features, such as a history of recurrent UTI, diabetes mellitus, pregnancy, male gender, and immunosuppression.[4] Moreover, clinicians sometimes conduct lumbar puncture for suspected meningitis in patients with APN because of the ambiguity of symptoms, such as headache, fever, and vomiting, which suggest meningeal or intracranial pathology.[4,5] Lumbar puncture is the most valuable procedure to establish the diagnosis, and it is performed whenever the disease is suspected. However, lumbar puncture has some complications, such as post-dural puncture headache, bleeding, and infection.[6] Therefore, knowledge of the incidence and risk factors for headache attributed to APN is required to avoid unnecessary lumbar puncture in patients without meningitis. We also commonly encounter patients with APN who complain of headache during hospitalization. To our knowledge, there have been no previous studies describing headache attributed to APN. This study identified the incidence and risk factors for headache attributed to APN.

METHODS

This study was conducted with the approval of the Institutional Review Board at our institution, in a single tertiary hospital. The inclusion criteria were patients who were admitted with APN at our hospital and ≥ 18 years of age. The exclusion criteria were: 1) patients who could not express their headache because of mental deterioration, 2) the presence of meningitis or meningoencephalitis,

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or 3) structural lesions on brain computed tomography or magnetic resonance imaging that could cause headache.

The presence of the following criteria were used for the diagnosis of APN: 1) fever, which was defined as an axillary temperature of 38°C or greater; 2) costovertebral angle tenderness; 3) pyuria, which was defined as the presence of 10 or more leukocytes per high-power field in a centrifuged specimen; and 4) positive urine culture ($>10^5$ colony-forming units/mL).[2] All patients had community-acquired APN. We divided the patients into two groups, patients with and without headache attributed to APN. The primary endpoint for this study was headache attributed to APN as a dependent variable. Headache attributed to APN was diagnosed after the patients were discharged to observe the time course of headache during admission in accordance to the International Classification of Headache Disorders 2 (ICHD-II) criteria:[7] 1) Presence of at least one of the following factors: a) diffuse pain, or b) associated with fever, general malaise or other symptoms of systemic infection; 2) Headache develops during APN; and 3) Headache resolves within 72 hours after effective treatment of the APN. All patients with APN were asked about the presence of their headache attributed to APN when they were admitted to our hospital. We also evaluated the severity of headache attributed to APN using visual analog scale (VAS) scores and the presence of nausea or vomiting. Differences between the two groups were analyzed using demographic and laboratory profiles as independent variables. We collected patient demographic profiles, including age, sex, and diabetes mellitus, and laboratory profiles including white blood cells (WBC), platelets (PLT), C-reactive protein (CRP), aspartate aminotransferase (AST), and alkaline aminotransferase (ALT) in blood, pathogens in urine culture, positive blood culture, nitrites in urine, and fever duration. We defined positive blood culture when the same pathogens were isolated in blood and urine cultures. Fever duration was calculated as the time from the day of admission to the first day with no fever higher than 38°C. We analyzed the first laboratory profiles after hospitalization if multiple laboratory profiles were collected. Additionally, correlation analysis was performed between the severity of headache using the VAS score and demographic and laboratory profiles including age, WBC, and CRP.

We analyzed variables using the Chi-square testfor categorical variables, and Student's t-test or Mann-Whitney U-test for numerical variables. We performed multiple logistic regression analyses using dependent variables and expressed the odds ratio with 95% confidence interval of having headache attributed to APN. For multivariate analyses, age was dichotomized as > or≤ 54 years. This cutoff value was calculated using areas under receiver operating characteristics curves. All statistical tests were performed using MedCalc®(MedCalc Software version 13, Ostend, Belgium). Categorical variables are presented as the frequency and percentage. Numerical variables with normal distributions are presented as means ± standard deviation, and numerical variables without normal distributions are described as medians with the 95% confidence interval and range. A *p*-value less than 0.05 was considered statistically significant for all calculations.

In addition, we calculated the power of this study using Power and Sample Size Program (http://ps-power-and-sample-sizecalculation.software.informer.com/download/). It revealed that the statistical power of this study was more than 90%, which was enough to exclude type 1 error.

RESULTS

A total of 479 patients met the inclusion criteria for this study. Fifty-five patients were men, and 424 patients were women. The median age was 63 years (95% CI 60-66 years, range 18-93 years). A total of 137 patients had diabetes mellitus. Serological studies revealed the following median values: WBC count of 12,050*10^6/L (95% CI 11,440-12,678 *10^6/L, range 530-344,440 *10^6/L), PLT count of 181,000 *10^6/L(95% CI 176,000-192,000 *10^6/L, range 23,000-1,874,000 *10^6/L), CRP of 11.4 mg/dL (95% CI 10.1-12.9 mg/dL, range 0.0-40.0 mg/dL), AST of 25.0 IU/L (95% CI 23.0-26.0IU/L, range 2.0-4,977.0IU/L), and ALT of 20.0 IU/L (95% CI 18.0-22.0IU/L, range 2.0-999.0IU/L). A total of 411 (85.8%) patients had *E. coli* as pathogens for APN according to urine culture results, and 68 (14.2%) patients had non-*E.coli* pathogens (19 patients with *Klebsiella* species, 12 patients with *Enterococcus* species, 9 patients with *Enterobacter* species, 8 patients with *Pseudomonas* species, 8 patients with *Proteus* species, and 12 patients with other species). A total of 175 (36.5%) patients had positive blood cultures, and 304 (64.5%) patients had negative blood cultures. A total of 236 (49.2%) patients had nitrites in urine. The median fever duration was 3 days (95% CI 3-3days, range 1-14days).

Table1: Comparison of demographic and laboratory profiles between patients with and without headache attributed to acute pyelonephritis

Parameter	With Headache (n = 97)	Without Headache (n = 382)	*p*-value
Men, n (%)	5 (5.2)	50 (13.1)	0.0436
Age, years (range)	53 (19-84)	66 (18-93)	<0.0001
Diabetes mellitus, n (%)	12 (12.4)	124 (32.5)	0.0001
WBC, $*10^6$/L (range)	10,290 (530-101,160)	12,460 (1,637-344,440)	0.0702
PLT, $*10^6$/L (range)	177,500 (24,000-410,000)	183,000 (23,000-1,874,000)	0.1593
CRP, mg/dL (range)	11.3 (0.1-40.0)	11.9 (0.0-40.0)	0.5257
AST, IU/L (range)	24 (9-335)	25 (2-4977)	0.4744
ALT, IU/L (range)	20 (7-313)	19 (2-999)	0.9004
E. coli in urine culture, n (%)	82 (84.5)	315 (82.5)	0.2078
Positive blood culture, n (%)	27 (27.8)	148 (38.7)	0.0571
Nitrites in urine, n (%)	47 (48.4)	189 (49.5)	0.8927
Duration of fever, days (range)	3 (1-6)	13 (1-14)	0.1437

WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alkaline aminotransferase

A total of 127 (26.5%) patients had nausea or vomiting at the time of admission.

Ninety-seven (20.2%) of the 479 patients developed headache attributed to APN. Table 1 shows a comparison of demographic and laboratory profiles between patients with and without headache attributed to APN. Age(53 vs. 66 years, $p<0.0001$ by Mann-Whitney test), male gender (5/97 vs. 50/381, $p=0.0436$ by Chi-square test), and diabetes mellitus (12/97 vs. 124/381, $p=0.0001$ by Chi-square test) were significantly different between the two groups. Patients with headache attributed to APN were younger and more likely to be female, and had less diabetes mellitus. However, laboratory profiles were not predictive factors for headache attributed to APN.

Multiple logistic regression analysis showed that a young age (≤ 54 years, OR=2.1, 95% CI 1.28-3.38) and the absence of diabetes mellitus (OR=2.5, 95% CI 1.29-4.98) were independently significant variables for the prediction of headache attributed to APN (Table 2). Patients with headache attributed to APN also had more nausea or vomiting than patients without headache attributed to APN (41/97 vs. 86/382, $p=0.0001$ by Chi-square test), and the median VAS score was 3 (95% CI 3-3, range 1-10). In addition, the VAS score was found to be negative correlated with age, whereas it was not correlated with WBC and CRP (age, r = -0.1554, p = 0.0008; WBC, r = -0.0440, p = 0.3449; CRP, r = -0.0259, p = 0.5840, by Pearson's correlation test) (Figure 1).

Table 2: Results of multivariate analysis of variables in patients with and without headache attributed to acute pyelonephritis

Independent variable	Adjusted odds ratio	95% confidence interval	*p*-value
Female	2.3	0.88-6.05	0.0894
Young age (≤ 54 years)	2.1	1.28-3.38	0.0030
Non-diabetes mellitus	2.5	1.29-4.98	0.0069

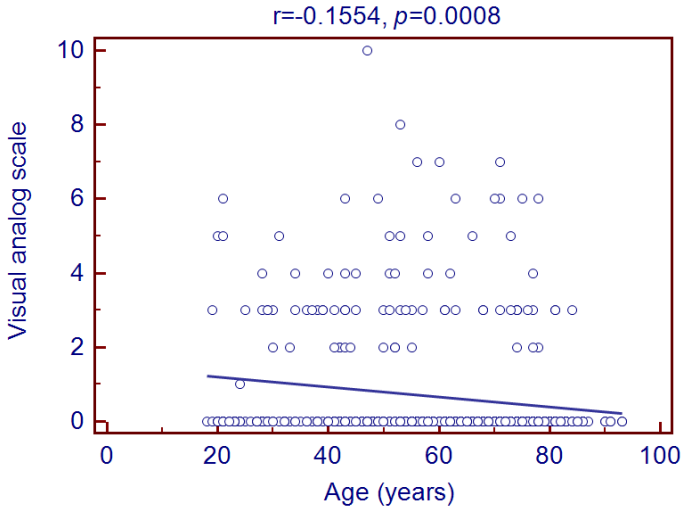

Figure 1. A negative correlation between the age and the visual analog scale.

DISCUSSION

This report was the first study of headache attributed to APN. We found that young age and the absence of diabetes mellitus were independently significant variables for the prediction of headache attributed to APN, but laboratory profiles that reflect the severity of APN were not predictive factors for headache attributed to APN. In addition, the VAS score was found to be negative correlated with age, whereas it was not correlated with WBC and CRP. We also found that the median VAS score in headache attributed to APN was only 3, which reflects a mild to moderate degree of pain.

The strengths of our study were that we only included patients with APN to increase homogeneity, and we used the ICHD criteria for the diagnosis of headache attributed to APN. Only one previous study investigated the incidence of headache in UTI, and this study found that patients with *E.coli* UTI had more headache than patients with non-*E.coli* UTI.[8] The authors of the study explained this result as the high virulent effect of *E.coli*, which causes a strong inflammatory host response that results in headache.[8] There was some tendency to increase the frequency of headache attributed to APN in patients with *E.coli* UTI in our study, but this increase was not statistically significant, which contrasts the previous study. One plausible explanation for these different results was the different criteria used to identify the samples. The previous study included all patients with UTI, including upper and lower UTI, and it did not use ICHD criteria.

The reason why young patients with APN more frequently experienced headache attributed to APN compared to older patients is not certain. One plausible explanation was age-related changes that are associated with neuroinflammation. Glial cells, such as microglia, play a role in neuroinflammation via the release of a variety of inflammatory modulating chemicals.[9] There was some evidence that dystrophic microglia are present in the human brain with increased age, and these changes included a slight enlargement of the cell, distinct loss of fine branches, formation of cytoplasmic spheroids, gnarling, beading, and fragmentation of the cytoplasm.[10] We suggest that dystrophic microglia underlie the decreased neuroinflammation, which led to decreased headache attributed to APN with increased age. A similar phenomenon is observed in migraine.[9] Decreased neuroinflammation may contribute to the decline in the prevalence of migraine with age. We also found that patients with headache attributed to APN had more nausea or vomiting than patients without headache attributed to APN. Notably, we found that patients with nausea or vomiting were also younger than patients without nausea or vomiting (60 vs. 65 years, $p<0.0001$ by Mann-Whitney test). Therefore, our study revealed that extra-urinary symptoms, such as headache, nausea, or vomiting, were much more common in young patients than old patients with APN. These findings suggest that the symptoms of APN mimic meningitis, especially in young patients with APN. Therefore, clinicians should be cautious when conducting lumbar punctures under a suspicion of meningitis in this patient population.

Diabetes mellitus increases the risk of APN, and it substantially contributes to increased hospitalization rates in patients with APN.[11,12] Severe complications of APN, such as emphysematous pyelonephritis, renal abscess, and bacteremia, also occur more frequently in patients with diabetes mellitus.[12-14] Our study demonstrated that diabetes mellitus was a factor that decreased the incidence of headache attributed to APN. The exact mechanism for the decrease in the incidence of headache attributed to APN in patients with diabetes mellitus is not known. However, this finding may be explained by an assumption that originated from neuropathy in patients with diabetes mellitus. We did not investigate the presence of neuropathy in our patients with diabetes mellitus, but diabetic neuropathy is a common complication, and the prevalence is generally estimated as 30% to 50% in patients with diabetes mellitus.[15,16] The prevalence of diabetic neuropathy is likely higher than expected because of the existence of subclinical or asymptomatic diabetic neuropathy.[17,18] Diabetic neuropathy is nerve damage that is associated with microvascular injuries and reduced nerve blood flow, which results in chronic nerve ischemia in patients with diabetes mellitus.[18] Diabetic neuropathy decrease pain sensations, such as headache, which may contribute to the decrease in the incidence of headache attributed to APN in patients with diabetes mellitus.

In contrast to demographic characteristics, laboratory profiles reflecting the severity of APN were not predictive factors for headache attributed to APN. Neither the inflammatory markers in serological tests, such as WBC and CRP, nor bacteremia were related with presence of headache attributed to APN. We infer from these findings that neuroinflammation may be more important than systemic inflammation in determining the presence of headache attributed to APN. Systemic inflammation is associated with neuroinflammation, but neuroinflammation may be modified by host status, such as age and the presence of diabetes mellitus. Additionally, neuroinflammation may be different from systemic inflammation because the blood-brain barrier, which is structural and functional barrier that regulates the passage of blood-borne substance and cells into the brain, maintains the homeostasis of the neural microenvironment.[19]

There were several limitations in this study. First, we did not investigate the characteristics of headache, such as duration, location, and nature, but we studied the presence and severity of headache. Second, the presence of diabetes mellitus was only determined using historical diagnosis. The characteristics of diabetes mellitus, such as age of diagnosis, current treatment, fasting glucose level, and HbA1c, were not analyzed. Third, this study was conducted in a single tertiary hospital. Therefore, selection bias may also affect the results of this study. Large multicenter trials may be needed to confirm our study.

In conclusion, our novel results demonstrated that headache attributed to APN was relatively common, and this type of headache was related to demographic characteristics but not APN severity.

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DISCLOSURE

Conflict of interest: None

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