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THE RELATIONSHIP BETWEEN URIC ACID LEVELS AND THE OCCURRENCE OF BENIGN PAROXYSMAL POSITIONAL VERTIGO

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Abstract
Background: Benign Paroxysmal Positional Vertigo (BPPV) is associated with a fundamental condition that causes the release of large amounts of otoconia, due to deficits in the structure of the interotoconial filament matrix which implants otoconia in the gelatinous matrix. Increased uric acid levels cause an inflammatory response in the gelatinous matrix so that it can cause BPPV attacks.
Objective: To determine the relationship between uric acid levels with BPPV events
Research Methods: This research uses a case control design. Sampling was conducted at H. Adam Malik General Hospital Medan and RS. University of Sumatera Utara. The research sample consisted of 36 BPPV cases and 36 non BPPV cases. subject on a consecutive basis. Anamnesis and physical examination are performed to diagnose BPPV and examination of uric acid levels for hyperuricemia status. Data analysis using chi-square test
Results: The majority of BPPV patient characteristics were found in women (63,9%), age range 41-50 years (36,1%), high school education level (33,3%), working as a housewife (30,6%), and Batak ethnicity (69,4%). The distribution of uric acid levels in BPPV patients was 6.59 (± 1.30) mg / dl. The distribution of hyperuricemia of BPPV patients was 58.3%. There is a significant relationship between uric acid levels with BPPV events. (p = 0.033; OR = 3.18).
Conclusion: there is a significant relationship between uric acid levels with BPPV.

Introduction

Background
Benign Paroxysmal Positional Idiopathic vertigo is associated with a fundamental condition that causes the release of large amounts of autoconia, due to deficits in the matrix structure of the interotoconial filament that implants otoconia in the supporting gelatinous matrix.[1] Otoconia are interconnected and bound by the gelatinous matrix with surface adhesion and by attaching to a loose interotoconial filament matrix.[2] Increased uric acid levels induce an inflammatory response in this matrix with an activated immunopathological mechanism, which is similar to that which occurs in the gout joints, and then triggers gradual damage proportional to exposure to high uric acid levels throughout adult life.[3]

Gout is the end product of purine metabolism.[4] Uric acid is formed by the catalysis of the xanthine oxidase (XO) enzyme from the xanthine molecule. Women tend to have lower levels than men, because of the urikosurik effects of estrogen.[5] Uric acid levels also vary significantly in humans as a result of factors that increase formation (such as a diet high in purine or protein, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decreased excretion (such as diuretics, especially thiazid).[4] Hyperuricemia is a metabolic disorder characterized by excess uric acid in the blood. Gout is the end product of purine metabolism in humans, serum uric acid concentrations of no more than 7 mg / dL in men and 6 mg / dL in women.[6]

While many prospective studies have mentioned an independent relationship between uric acid levels and future risk of cardiovascular and metabolic morbidity and mortality, only a small number of randomized clinical trials and observational studies have examined the relationship between uric acid levels and BPPV. In a study conducted by Lin et al[7] found a positive relationship between gout and peripheral vertigo in a population-based study. Chemical composition of otoconia as a buildup of purine crystal deposits in the semicircular canal can be responsible for BPPV in patients with gout.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Method

Research sample
The study sample was taken from patients with BPPV who came to H. Adam Malik General Hospital Medan and Sumatra University Hospital using consecutive sampling techniques. Research subjects were 36 BPPV patients and 36 were healthy

Study design
This research is a case-control design. The case came from a BPPV patient whose diagnosis was made through history taking and examination of the dix hallpike (+) while the control came from a healthy population. Furthermore, the two groups of research subjects were examined for uric acid levels and the results were categorized as hyperuricemia and not hyperuricemia.

Statistic analysis
Data from the study were statistically analyzed using the SPSS computer program version 22.0. To determine the relationship between uric acid levels with BPPV events using the chi square test.

Results

Case study subjects consisted of patients diagnosed with BPPV and undergoing treatment at H. Adam Malik General Hospital Medan and Sumatra Utara University Hospital in December 2019 until March 2020, as many as 36 subjects and controls came from 36 healthy subjects who met the research criteria. Age characteristics of all study subjects had a median value of around 50 (21-66) years with the most age range in BPPV subjects at age 41-50 years as many as 13 subjects (36.1%) while in the non BPPV subjects the most in ages 51-60 years 11 subjects (30.6%). BPPV and not BPPV subjects were mostly female, with 23 subjects (63.9%). The highest level of education of BPPV and not BPPV subjects is SMA, with 12 subjects (33.3%) and 15 subjects (44.4%). The occupational status of BPPV and not BPPV subjects were mostly housewives, namely 11 subjects (30.6%) and 13 subjects (36.1%). Most of the BPPV and non BPPV patient tribes were Batak tribes, namely 25 subjects (69.4%) and 26 subjects (72.2%). For complete data on the characteristics of the subjects of this study are presented in table 1 below.

Table 1. Overview of Characteristics of Research Subjects

Characteristics of Research Subjects	Average	BPPV	non BPPV
		n (%)	n(%)
Age (years) • 21 – 30 years • 31 – 40 years • 41 – 50 years • 51 – 60 years • 61 – 70 years	50(21-66)*	50(21-66)* 2(5,6) 5(13,9) 13(36,1) 9(25) 7(19,4)	50(24-66)* 5(13,9) 6(16,7) 9(25) 11(30,6) 5(13,9)
Gender • Male • Female		 13(36,1) 23(63,9)	 13(36,1) 23(63,9)
Education • Elementary School • Junior High School • Senior High School • Diploma • bachelor		 4(11,1) 10(27,8) 12(33,3) 7(19,4) 3(8,3)	 2(5,6) 7(19,4) 15(44,4) 6(16,7) 5(13,9)

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Occupation • Not have a job • Housewife • Entrepreneur • Civil Servants • Private employees • Labor • Retired		6(16,7) 11(30,6) 5(13,9) 3(8,3) 3(8,3) 6(16,7) 2(5,6)	5(13,9) 13(36,1) 7(19,4) 1(2,8) 7(19,4) 2(5,6) 1(2,8)
Etnics • Batak • Java • Aceh		25(69,4) 3(8,3) 8(22,2)	26(72,2) 4(11,1) 6(16,7)

Descriptive analysis of the average distribution of uric acid levels in this study using mean values and standard deviations due to the distribution of data about uric acid levels in normal distribution. The mean uric acid level in BPPV patients was 6.59 (± 1.30) mg / dl, whereas in non-BPPV subjects it was 5.75 (± 1.01) mg / dl, thus the average uric acid level in subjects with BPPV higher than non BPPV subjects. Based on the independent T test, it was obtained that the p value was 0.003 so it was concluded that there were significant differences in the average uric acid level between BPPV and not BPPV subjects. This can be seen in table 2 below.

Table 2 Distribution of Mean Uric Acid Levels

	Average (mg/dl)	***p value***
Uric Acid Levels	6,17 ± 1,23	
• BPPV	6,59 ± 1,30	0,003
• non BPPV	5,75 ± 1,01	

In this study the condition of hyperuricemia has been classified in advance based on the cut-off point between men and women. In men it is said to be hyperuricemia when uric acid levels > 7 mg / dl while women are said to be hyperuricemia when uric acid levels > 6 mg / dl. In BPPV subjects, they had 21 hyperuricemia levels (21.3%) and no hyperuricemia (15.7%), whereas non-BPPV had 11 hyperuricemia levels. 11 subjects (30, 6%) and no hyperuricemia as many as 25 subjects (69.4%), so it can be concluded that the percentage of hyperuricema in BPPV subjects is higher than in subjects without BPPV. Based on the chi-square test the p value is 0.033 and the odds ratio is 3.18 thus it can be concluded that there is a significant relationship between hyperuricemia with the occurrence of BPPV, where the condition of hyperuricemia can increase the risk of BPPV as much as 3.18 times greater. The complete results can be seen in table 3 below.

Table 3 Relationship of Uric Acid Levels with BPPV

Uric Acid Levels	**BPPV incident**		***p value***	***OR***
	BPPV	**Non BPPV**		
hyperuricemia	21 (58,3%)	11 (30,6%)	0,033	3,18
Non hyperuricemia	15 (41,7%)	25 (69,4%)		

Chi-square test

Discussion

In this study the results showed that the age characteristics of all study subjects had a median value of about 50 (21-66) years with the most age range on BPPV subjects at the age of 41-50 years as many as 13 subjects (36.1%). The results of this study are relevant to previous studies conducted by Dewi et al[8] who reported the most common age characteristics of patients with BPPV> 35 - 50 years. A study has shown that the peak incidence of idiopathic BPPV occurs at 45-59 years of age and rarely occurs before the age of 20 years and is increasingly becoming

more common in old age due to otoconia release from otolith organs or due to degeneration of the natural age-related otolith membrane. [9]

The prevalence of large BPPV of sex in this study was assigned to female subjects by 23 subjects (63.9%) while men were 13 (36.1%) so that it can be concluded that the number of female BPPV subjects was higher than men with a ratio of close to 2: 1 The results of this study are relevant to von Brevern[10] which states that the number of BPPV sufferers in women is greater than that of men in a ratio of 2: 1. In addition, Sumadilaga et al [11] also reported the incidence of BPPV in women at 67.31% higher than men at 32.69% and Tambunan and Fithrie[12] also reported that the majority of BPPV sufferers were found in women at 61, 4% In this study female subjects had a higher BPPV percentage than men related to hormonal factors in women. According to Tambunan and Fithrie[12] in their research stated that reproductive hormones especially estrogen not only affect the reproductive system, but also the entire body. The role of estrogen in regulating the increase in uric acid excretion by the kidneys through a mechanism of increasing renal clearance. In addition, in the presence of estrogen, URAT1 (Urate Transporter 1) which is a uric acid transporter becomes lower so that it can reduce uric acid reabsorption by the kidneys. High estrogen levels in women of reproductive age have been shown to contribute to maintaining normal secretion of uric acid through urine by the kidneys. [13] In this study the average age of the study subjects was around 50 (21-66) years with the largest age range in BPPV subjects at the age of 41-50 years as many as 13 subjects (36.1%). Functionality of the reproductive system, female subjects> 41 years have entered the premenopausal and menopausal stages. This is related to the decline in the function of the hormone estrogen so that it can result in uric acid levels which can be an independent risk factor for BPPV attacks. [13,14]

The education level of the most BPPV subjects was SMA, which was 12 subjects (33.3%). The results of this study are relevant to previous studies conducted by Dewi et al[8] who reported the characteristics of the level of education in the most common BPPV subjects were SMA. According to Pulungan and Iqbal[15] also reported the level of education in BPPV patients are mostly high school. The occupational status of BPPV subjects is mostly housewives, namely 11 subjects (30.6%). The results of this study are relevant to previous studies conducted by Pulungan and Iqbal [15] who reported the majority of patients with BPPV undergoing treatment at Adam Malik General Hospital and University Of Sumatera Utara Hospital has a job status as a housewife at 33%. In addition, Tambunan and Fithrie [12] reported the same thing where the employment status of patients experiencing BPPV was mostly housewives at 31.6%. This result is related to the proportion of BPPV sufferers in this study, the majority of whom were women, namely 63.9%. Tambunan and Fithrie[12] also reported in their research results that the employment status of BPPV patients was related to the most frequent distribution of BPPV sufferers to women (61.4%), and the highest proportion of events according to type of work was to housewives. In the opinion of Kesser and Gleason [16], housewives are women who are married and not working, spending part of their time caring for the household and inevitably every day will encounter the same atmosphere and routine tasks. Housewives who feel uncomfortable with housework can be more aggressive and sensitive when doing housework. Individuals with sensitive attitudes tend to experience stress because it is difficult to socialize, and this is one of the risk factors for BPPV.

In this study, the majority of BPPV patient tribes were Batak tribes, namely 25 subjects (69.4%). The results of this study are relevant to previous studies conducted by Tambunan and Fithrie[12] who reported that the ethnic group that suffered the most BPPV came from the Batak tribe as many as 38 patients (66.7%), followed by Javanese as many as 10 patients (17, 5%), 6 patients came from the Acehnese tribe (10.5%), Malay was 1 patient (1.8%), Nias was 1 patient (1.8%), and Sundanese was 1 patient (1 , 8%). In populations originating from the Batak tribe, it is inseparable from traditional events that consume foods such as high fat meat (animal fat), and causes the majority of the population to be hyperlipidemic, which is one of the risk factors for BPPV.

In this study the average distribution of uric acid levels in BPPV patients was 6.59 (± 1.30) mg / dl, whereas in non-BPPV subjects it was 5.75 (± 1.01) mg / dl, thus the average uric acid level in subjects with BPPV higher than subjects who were not BPPV. Based on the independent T test, it was obtained that the p value was 0.003 so it was concluded that there were significant differences in the average uric acid level between BPPV and not BPPV subjects

The results of this study are relevant to previous studies conducted by Ceklikbilek et al[17] who reported an average uric acid level in patients with a higher BPPV of 4.85 mg / dl compared to a control (not BPPV) of 3.6 mg / dl and a significant difference in mean uric acid levels between subjects with BPPV and not BPPV with $p < 0.01$. Although the results of this study are relevant, there are differences in the average levels of uric acid between

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

BPPV subjects in previous studies, this can be influenced by the limitation of body mass index in previous studies which were only measured in people who had a normal body mass index (BMI) 24- 25 mg / kg2 and a relatively younger age at 33 (25-40) years. Besides examinations during and after attacks also affect uric acid levels, where during and during vertigo attacks found an increase in uric acid levels while examinations carried out after vertigo attacks can be found that uric acid levels tend to decrease[17] It is known that the enzyme urikinase which oxidizes uric acid into a tool that is easily disposed of will decrease with age. If the formation of this enzyme is disrupted, blood uric acid levels rise[18]

In this study BPPV subjects had hyperuricemia levels as many as 21 subjects (58.3%) and not hyperuricemia as many as 15 subjects (41.7%), while those without BPPV had hyperuricemia levels of 11 subjects (30.6%) and no hyperuricemia as many as 25 subjects (69.4%), so it can be concluded that the percentage of hyperuricema in BPPV subjects is higher than in subjects without BPPV. The results of this study are relevant to systematic review studies based on BPPV pasiein population studies in China conducted by Yang et al[19] reported that the percentage of hyprurisemia in BPPV patients ranged from 42.2% - 57.8%. Hyperuricemia is said to be an independent risk factor that can lead to BPPV. Increased uric acid levels induce an inflammatory response in this matrix with an activated immunopathological mechanism, which is similar to that which occurs in the gout joints, and then triggers gradual damage proportional to exposure to high uric acid levels throughout adult life. [3]

In this study based on the chi-square test p value of 0.033 and an odds ratio (OR) of 3.18 can be concluded that there is a significant relationship between hyperuricemia with BPPV, where hyperuricemia conditions can increase the risk of BPPV by 3.18 times greater than. The results of this study are relevant to previous studies conducted by Ceklikbilek et al[17] who reported a significant relationship with increased uric acid levels with the occurrence of BPPV with an odds ratio (OR) of 3.35. In addition, Ceklikbilek et al[17] also added that an increase in 1 unit of serum uric acid could increase 3.35-fold in predicting BPPV in multimodel regression (95% CI, p <0.001). In a study conducted by Lin et al[7] found a positive relationship between gout and peripheral vertigo in population-based studies. The chemical composition of otoconia as a buildup of purine crystal deposits in the semicircular canal can be responsible for BPPV in patients with gout.

At present, little is known about the true metabolism of otoconia particles and what causes their release from the uterine macular gelatinous matrix and their precipitations, which are prerequisites for BPPV. Benign paroxysmal positional vertigo (BPPV) is often preceded by head trauma, vestibular neuritis or other inner ear diseases which can cause otoconia release from the utriculus. [20] Benign Paroxysmal Positional Idiopathic vertigo is associated with a fundamental condition that causes the release of large amounts of autoconia, due to deficits in the matrix structure of the interotoconial filament that implants otoconia in the supporting gelatinous matrix. [1] Otoconia are interconnected and bound by the gelatinous matrix with surface adhesion and by attaching to a loose interotoconial filament matrix. [2] According to Wang et al[21] states that gout can promote the release of inflammatory mediators that induce the production of destructive Reactive Oxygen Species (ROS). Through a similar inflammatory mechanism, elevated serum uric acid levels can trigger ROS production which can damage blood vessels, thereby disrupting blood supply to the inner ear. In line with this Sahin et al[22] mentioned that oxidative stress contributes to BPPV through calcium metabolism and the direct toxic effects of free oxygen radicals.

In general, recurrence rates after successful BPPV therapy with medical and maneuverers range from 40% -50% under 5 years of surveillance. Some sufferers relapse individually.[23] According to Yang et al[19] reported that high uric acid levels (hyperuricemia) is one of the independent risk factors for BPPV attacks. Thus efforts to control blood uric acid levels in BPPV patients can be considered in order to prevent recurrence and the onset of BPPV attacks.

Conclusion

There was a significant relationship between uric acid levels with BPPV (p = 0.033; OR = 3.18)

Suggestion

In BPPV patient's periodic examination of uric acid levels with the aim of controlling uric acid levels so as not to increase (hyperuricemia).

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