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Low Serum Uric Acid Level Increased the Risk of Parkinson's Disease

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Abstract: ***Low Uric acid serum level can affect and deactivate ROS and RNS substantially that will yield in the cells death of substansia nigra pars compacta which is responsible for the occurrence of Parkinson's Disease (PD). The aim of this study was aimed at testing low serum levels of uric acid increased the risk of PD. A case control was performed as the design of this study. Patients with PD enrolled in the case group and patients without PD as control group. Examination of serum uric acid level in the patient's venous blood held after fasting for approximately 8 hours. Uric acid was stated low when the rate is ≤ 4.68mg/dl. In this study, 44 cases and 44 controls who met the eligibility criteria included as a sample and matched according to age and sex. There were 31 males (70.5%) and 13 females (29.5%) PD patients in this study.Factors associated with an increased risk of PD was a lower level of serum uric acid (OR = 3.40; CI 95%: 1.36-8.53, p = 0.008) and a low purine diet (OR = 3.07; CI 95%: 1.29-7.33, p = 0.01). Only a low purine diet became a significant and independent PD risk factor (OR = 2.86; CI 95% :1.02-8.02, p = 0.046) in multivariate analysis. Low serum uric acid level and low purin diet increased the risk of PD. Efforts need to be made based on dietary adjustments, especially food contained sufficient purine to maintain serum uric acid level within normal limit so that PD can be prevented.***

Keywords: serum uric acid level, risk, Parkinson Disease

1. Introduction

Parkinson's Disease (PD) is caused by the decrease in dopamine level in the pars compacta substantial nigra. The clinical manifestation of this disease is tremor, rigidity, bradikinesia/akinesia and postural instability. The prevalence of this disease increases with age. At the age of 65 the prevalence is about 1% and it increases 4 – 5 % at the age of 85 years. PD is also caused by the death of dopamine neuron in the substantial nigra pars compacta due to the depletion of dopamine in the striatum (caudatus nucleus and putamen) with the presences of Lewy bodies. [1] Until now the etiology of PD is unknown (idiopathic) but there were a few risk factors that were identified. A few theory states that old age, hereditary (genetic), surrounding and food consumption patterns including a low purine diet.

Uric acid can influence and inactivate the reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the cell. It also contains metal ion with complex characteristics which can reduce ROS and RNS. When there is a decrease in the uric acid level in the blood, the formed ROS and RNS will react towards the formation of free radical, oxidative stress and exsitotoksisity. This process will cause DNA damage, preoxidative lipid and protein damage, which will end in cell death especially in the pars compacta substansia nigra which is responsible in the cause of Parkinson disease. [2]. This study is to estimate the amount of uric acid in a Parkinson patient and to identity whether the low level of uric acid can increase the risk of Parkinson disease.

2. Material and Methods

Data sampling
The planning of this study was done using the case-control method and was designed as a observational analytic epidemiologic study. Patients suffering from PD were put in the case group and the patients without PD in the control group. The study was carried out from the month of April till June 2014.

The sample was taken using a eligibility criteria. The eligibility criteria includes: A. Inclusion criteria: 1) People suffering from Parkinson Disease, 2) Still undergoing therapy in Sanglah General Hospital, Denpasar and Wangaya Hospital, 3) Coperative and able to read and write, 4) Willingness to participate in the study. Exclusion criteria of the case and control were: 1) patients with drug addiction, 2) Patient with history of neurological disturbance such as stroke, head trauma, intracranial infection, intracranial tumor. A matching age and gender was performed.

Data collection
In data collection the technique used was the consecutive sampling. Each and every patient suffering from PD who underwent treatment in Sanglah General Hospital Denpasar, until it finally reached the amount of sample needed. If the amount of sample did not reach the estimated target, patients from Wangaya Hospital were added in.

The uric acid level was evaluated using blood from the vein of Parkinson patients who were told to fast for at least 8 hours by using the dry chemistry system and Vitros 250 in clinical pathology laboratory of Wangaya Hospital Denpasar. They were differentiated into 2 groups, which were low uric acid group and high/normal uric acid group. Uric acid is stated low when the rate is ≤ 4.68mg/dl and > 4.68mg/dl when its normal/ high.[3] This study has been approved by Ethic Committee, Sanglah Hospital-Udayana University Denpasar Bali.

Data Analysis
Data analysis were done in two stages, descriptive statistic to identify the subject principal characteristic of this study and

analytic statistic study to calculate odds ratio (OR) with confidence interval (CI) about 95% bigger. The hypothesis test was done for bivariate analysis with independent variable and dependent variable with a nominal scale using the Chi-Square method, is said to be significant if p<0,05. A multivariate analysis was also done with a logistic regression to identify the independent risk factor. The process of data analysis were done using a statistical analysis in a computer program (SPSS verse 16).

3. Results

In this study it is seen that male patients were more compared to female patients. Whereby, the male patients were 31 (70,5%) and female 13 (29,5%). Almost most of the Parkinson patients were married 42 (95,5%) and in the control group about the same 40 (90,9%). In the case group 12 (27,3%) patients have been to university whereas, in the control group about 17(38,6%) have been to elementary school. Most of the patients in the case group were already in their pension era 18(40,9%), whereas in the control group most of them were private sector workers 14(31,8%). 1(2,3%) worked as a farmer in the case group and 12(27,3%) in the control group. Estimated rate of uric acid in the case group was lower compared to the control group. Estimated rate of uric acid in Parkinson patients from this study is 4,98±1,88 mg/dl meanwhile, in the control group the estimated rate is about 7,21±3.53 mg/dl (table 1).

Table 1: Subjects Characteristics

Variabel	Cases n=44	Controls n=44
Age (years) mean±SD	61,86±8,03	61,48±8,17
40-59 years	18(40,9%)	18(40,9%)
≥ 60 years	26(59,1%)	26(59,1%)
Gender		
Male	31 (70,5%)	31 (70,5%)
Female	13(29,5%)	13(29,5%)
Marital status		
Married	42(95,5%)	40(90,9%)
Single	2(4,5%)	4(9,1%)
Highest education		
<Elementary school	5(11,4%)	13(29,5%)
Elementary school	10(22,7%)	17(38,6%)
Junior high school	0(0%)	8(18,2%)
Senior high school	11(25%)	4(9,1%)
Diploma	6(13,6%)	1(2,3%)
University	12(27,3%)	1(2,3%)
Occupation		
Civil worker	9(20,5%)	1(2,3%)
Private sector	6(13,6%)	14(31,8%)
Independent contractor	0(0%)	8(18,2%)
Laborer	0(0%)	1(2,3%)
Farmer	1(2,3%)	12(27,3%)
Pension	18(40.9%)	2(4,5%)
Others	10(22,7%)	6(13,6%)
Uric acid serum level (mg/dl) ±SD	4,98±1,88	7,21±3.53

In table 2 the relationship between numerous factors and the risk of PD can be seen. Factors which are related to the increase risk of PD are high uric acid level OR=3,40; 95%CI: 1,36-8,53, p=0,008 and low purine diet habit OR=3,07; 95%CI: 1,29-7,33, p=0,01. meanwhile, occupation, family history, pesticide exposure, smoking habits and coffee addiction is not related to the increase of risk in PD (P≥ 0,05).

Table 2: Bivariate Analysis of PD Risk Factors

Variable		Cases n (%)	Controls n (%)	OR 95%CI	p
Uric acid serum level	Low	22(50%)	10(22,7%)	3,40 (1,36-8,53)	0,008*
	Normal/high	22(50%)	34(77,3%)		
Occupation	Formal	33(75%)	25(56,8%)	2,28 (0,92-5,64)	0,07
	Informal	11(25%)	19(43,2%)		
Family history	Yes	7(15,9%)	5(11,4%)	1,48 (0,43-5,06)	0,53
	No	37(84,1%)	39(88,6%)		
Pesticide exposure	Yes	4(9,1%)	10(22,7%)	0,34 (0,10-1,18)	0,08
	No	40(90,9%)	34(77,3%)		
Purine diet	Low	27(61,4%)	15(34,1%)	3,07 (1,29-7,33)	0,01*
	Normal/High	17(38,6%)	29(65,9%)		
Smoking	Yes	10(22,7%)	13(29,5%)	0,70 (0,27-1,83)	0,47
	No	34(77,3%)	31(70,5%)		
Coffee	Routine	11(25%)	15(34,1%)	0,64 (0,26-1,62)	0,35
	Rarely/No	33(75%)	29(65,9%)		

*p<0,05

Table 3: Multivariate Analysis

Variable	Coefficient	OR	(95%CI)	p
Occupation	0,43	1,54	0,52-4,53	0,44
Family history	0,66	1,94	0,43-8,81	0,39
Pesticide exposure	-0,98	0,38	0,09-1,64	0,19
Low Purine Diet	1,05	2,86	1,02-8,02	0,046*
Smoking	0,20	1,23	0,35-4,26	0,75
Coffee consumption	-0,335	0,72	0,23-2,19	0,56
Uric acid serum level	1,12	3,07	0,98-9,58	0,054

*p<0,05

In table 3 the multivariate analysis can be seen that the low purine diet intake factor which is significant as an independent risk factor of PD whereby subjects that have the habit of consuming low purine diet have risk of 2,86 times more higher than to others who eat purine at a normal rate or higher.

4. Discussion

The age of patients with PD in this study is 61,86±8,03 years. The results from this study is very appropriate with a few other studies which has got the same average age of above 60 years of age. [4,5]

This disease is a type of neurodegenerative disease which ia most experienced at old age and rarely below 30 years of age. It normally occurs at the age of 40 – 70 and reaches the peak in the patients 6th decade. Old age is a risk factor which cant be neglected as the cause of PD.[6] This happens because with the increase of age, environment influences or exposure to toxic or infection or other secondary factors with a increase in longer duration due to the increase in age.[7]

Age is correlated towards the progressivity of brain cell damage, this may be because with the increase of age, the defense mechanism or brain cell protection begins to reduce especially at the basal ganglia area which is related to the dopaminergic pathway which is proved by the PET scan in the study.[8]

This study results with a similar outcome with other study, whereby male patients with Parkinson are more susceptible than women.[9] The confirm reason on why PD is more consistent in male is still unknown. This can be due to the presences of estrogen in female, which acts as a neuro-protector. The experimental prove indicates that's estrogen effects using a few mechanism, which is by inhibiting transporter chain and preventing neurotoxic agents from entering the dopaminergic terminal nerve which causes the decrease in nigrostriatal degeneration.[10] In additon to neuro-protection, estrogen is also said to contain a few other important function such as, enriches blood flow to the brain and suppression of ApoE which acts as a degenerative process cofactor.[11]

This may also be related to the type of occupation or male mobility which are related to toxic exposures from work surrounding, especially toxins that acts on the degenerative process and rate of physical activities which are higher than in female are said to be risk factors of neuro degenerative disease.[12] In this study, it is seen that the average rate of uric acid in Parkinson patients are lower than in the control group (4,98±1,88 mg/dl *vs* 7,21±3.53 md/dl). The results are similar to other studies.[4] Subjects with a lower uric acid level have 3,4 times more risk than in Parkinson patients with a normal/ higher uric acid level.

It is concluded that the low rate of uric acid level in Parkinson patients shows a low concentration of intracellular uric acid in the brain tissue. This finding shows that uric acid has the ability of neuro protection, which acts as an antioxidant and iron chelator. Pathological evaluation shows a decreases level of uric acid in the autopsy of Parkinson patients, although the number of cases for examination are still low.[5]

As a prevention of PD it is not recommended to increase the rate of uric acid because a number of disease have been related to high level of uric acid (hyperuremia). Increased level of uric acid contributes to gout artritis (uric acid cyrstal deposits and causes inflammation in the joint) and kidney stone. Moreover, hypertension, myocardial infacrtion, congestive heart failure, stroke and kidney failure can all be correlated with high level of uric acid. Due to this, it is suggested that uric acid level should be control within normal range.[13]

This study shows that occupation does not have any relationship in increasing the risk of PD (p=0,07). Other research results obtained some work was not associated with an increased risk of Parkinsonism. Employment history in business and finance, law, construction and extraction or transport and transportation of materials associated with postural instability and difficulty walking, which is one subtype of parkinsonism.[5] The cause is not meaningless results of this study may be caused by the presence of bias due to the distribution of types of work are quite different between case and control groups, which in the case group was dominated by formal employment whereas in the control group was dominated by work on the informal sector.

Parkinson patients have a family history variables in this study to get 15.9% of cases have family suffered from Parkinsonism. This variable does not have a significant association with an increased risk of PD (p> 0.05). Similar results were also obtained in other studies that show no found association between family histories with PD.[14] A person suffering from PD likely to have a family who suffered PD. But this does not mean that the disease has been genetically inherited but due to environmental influences, or exposure to the elements such as toxins or infections or other secondary disorders larger with a longer duration with age.[15]

History of pesticide exposure in this study was not associated with an increased risk of PD. These results are consistent with other epidemiological studies that show there is no relationship between the work as farmers and pesticide exposure and the risk of PD.[16,17] Whereas in another study actually showed the opposite of the relationship between agricultural work and pesticide exposure with an increased risk of PD.[5,18]

Low-purine diet habits significantly associated with an increased risk of PD. Subjects who have a habit of low-purine diet such as rice, yams, cassava, bread, milk, and eggs have a 3.07 times higher risk of developing PD compared to normal subjects or high-purine diet. These results are consistent with a 16-year prospective study conducted by Gao et al. (2007) concluded that a low purine diet is associated with increased risk of PD. In humans, levels of urate in the blood depend on the purine diet, uric biosynthesis and excretion of urate. Low purine diet habits will also affect

uric acid levels in plasma, thereby increasing the risk of PD. [13,19]

Smoking habits in this study appears to have a protective function is evident from the figure OR <1, although the effect is not significant with an increased risk of PD (p = 0.47). A variety of biological mechanisms have been proposed to explain the protective effect of smoking. In animal studies, nicotine appears to provide protection against damage induced by pesticides on dopaminergic neurons in the nigrostriatal region of the brain involved in PD.[20] Smoking habit although it seems to have a protective function on PD, not recommended for smoking individuals as prevention of PD because only nicotine has a protective effect, while other substances contained in cigarettes has no protective function.

Coffee drinking habits similar to smoking appears to have a protective function is evident from the figure OR <1, although the effect is not significantly associated with an increased risk of PD (p = 0.35). Caffeine consumption has also been linked in some studies with reduced incidence of PD.[21,22] The proposed mechanism involves the capacity of caffeine and related chemicals to block the activity of the neuromodulator adenosine in the brain that is. In clinical trials, administration of caffeine reduce severe muscle stiffness in people with PD and improve the response to other therapies.[23]

Obtained results of this study shows only a low purine diet habit factors are statistically significant as a independent risk factor of PD in which subjects have a habit of consuming foods low in purine will have a 2.86 times greater risk of suffering from PD than subjects who have a habit of consuming foods with high levels of purine are normal or high. While the risk factors for low serum uric acid levels and other factors did not reach statistical significance as an independent risk factor ($p \geq 0.05$). Diet is an important determinant of uricemia, partly because it is a purine metabolic precursor of the vein, and partly through indirect effects on the metabolism of uric acid purine. The rate of uric acid is greatly influenced by the high intake of foods containing purines.[19]

Lower serum uric acid levels is not an independent risk factor due to the levels of uric acid in the blood is strongly influenced by long-term purine diet and biosynthesis of urate and urate excretion.[13] Although obtained serum uric acid levels low during the examination, this level cannot reflect the consumption pattern of the previous patient. Lower serum uric acid can not stand alone to increase the risk of PD so there must be more than one factor may increase the risk for PD.

5. Conclusion and Recommendation

Based on the results, the conclusion that lower serum uric acid levels can increase the risk of PD, so efforts need to be made dietary adjustments, especially the consumption of foods that contain purines are balanced enough to maintain serum uric acid levels in the normal range so that PD can be prevented.

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