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Original Article

A study of the correlation between vitamin D uric acid levels and senile acute cerebral infarction

Ling Hao[1*], Yingting Zhou[1*], Hanrong Xu[2]

[1]*Department of Basic Medicine, Jiangsu Vocational College of Medicine, Yancheng City, Jiangsu Province, China;* [2]*Department of Neurology, Yancheng City No. 1 People's Hospital, Yancheng City, Jiangsu Province, China.* [*]*Equal contributors.*

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Abstract: Vitamin D and serum uric acid may participate in cerebral infarction. This study investigated serum Vitamin D and uric acid levels in aged, acute cerebral infarction patients along with their clinical conditions. A total of 209 aged, acute cerebral infarction patients were recruited, in parallel with 209 healthy individuals as the control group. Logistic regression was performed on the clinical information of both groups. The cerebral infarction patients were further divided into two groups based on their 25-hydroxyl Vitamin D (25(OH)D) levels (20 ng/mL as border line). The patients were also divided into normal and HUA groups based on their serum uric acid levels (416 μmol/L in males and 357 μmol/L in females). The patients' clinical information, stenosis of carotids, cerebral infarction conditions, infarction areas, prognoses, and cognitive functions were compared. The disease group had significantly higher systolic/diabolic pressure, FPG, TC, hs-CRP, [25(OH)D] and UA levels ($P<0.05$ compared to the control group). Logistic regression indicated systolic pressure, FPG, TC, 25(OH)D, and UA as independent risk factors for cerebral infarction. Those patients with 25(OH)D<20 had more severe carotid stenosis, cerebral infarctions, worse prognoses, and more cognitive dysfunction ($P<0.05$ compared to those with higher 25(OH)D levels). The HUA patients also had more severe carotid stenosis, larger infarction areas, and worse prognoses ($P<0.05$ compared to the normal group). A Person correlation analysis found a negative correlation between 25(OH)D and UA. Vitamin D and uric acid may affect the onset, progression and prognosis of cerebral infarction and may serve as a predicting indicator for monitoring cerebral infarction disease conditions in clinics.

Keywords: Vitamin D, serum uric acid, aged acute cerebral infarction, risk factors

Introduction

Cerebral infarction is caused by a blockade of cerebral blood flow, leading to hypoxia, focal cerebral ischemia necrosis or softening, and accompanied by clinical symptoms and body signs such as paralysis or aphasia [1]. Cerebral infarction has a relatively high morbidity and mortality, as more than 40% of surviving patients have an irreversible disability that severely affects the patient's survival period and quality of life [2]. Therefore, the identification of test parameters that can manage the incidence of the disease, predict its prognosis, and that are easy to use will make its clinical management more efficient.

A previous study showed insufficient levels of vitamin D across all age groups, especially among the aged [3]. Besides regulating calcium/phosphorous metabolism and facilitating bone growth, vitamin D also has a wide range of biological roles. Recent studies showed the direct or indirect participation of vitamin D in cerebral infarction onset [4, 5]. Vitamin D can inhibit the proliferation of vascular smooth cells under the induction of endothelin by suppressing the activation of cell cycle protein dependent enzymes, thus antagonizing atherosclerosis [6]. Shaban et al. suggested certain roles of vitamin D in regulating blood glucose by modulating insulin sensitivity [7], possibly exerting indirect effects on the onset of cerebral infarction. Shea et al. indicated that vitamin D could suppress the inflammatory response and impede the progression of atherosclerosis [8], thus protecting vascular functions. Another study demonstrated a negative correlation between vitamin D levels and blood pressure. The replenishment of vitamin D could decrease

blood pressure and decrease the formation of plaque or rupture occurrence [9]. Uric acid is the final product of purine metabolism and is one water soluble anti-oxidant that can clear oxygen free radicals. An *in vitro* study showed the protective roles of uric acid on hypoxic brain tissues [10]. However, the relationship between uric acid and cerebral infarction in clinics is still unclear. Some studies found that hyperuricemia could increase the risk of cerebral infarction, affecting the prognosis of patients [11].

It is likely that both vitamin D and uric acid probably participate in the onset and progression of cerebral infarction. This study measured serum vitamin D and uric acid levels in acute, aged cerebral infarction patients in Jiangsu City, and investigated their inter-correlations, thus providing a strategy and counter-measures for preventing cerebral infarction and improving prognosis.

Information and methods

Research subjects

A total of 209 acute cerebral infarction patients who were admitted within 48 hours of onset to the Jiangsu Vocational College of Medicine (Jiangsu, China) between October 2016 and October 2017 were recruited. Diagnoses of all patients were made in accordance with the diagnostic criteria stipulated by the fourth Committee of Cerebral Vascular Disease [12], followed by confirmation made through a head CT or MRI. There were 107 males and 102 females in the patient groups, with ages ranging between 60 and 82 years (average = 68.74±7.05 years). Another cohort of 209 healthy people over 60 years old were recruited as a control group, which included 110 males and 99 females, with ages ranging between 60 and 79 years (average age = 67.98±6.83 years). Those patients having complications such as malignant tumors, kidney/renal dysfunction, or acute/chronic infection, or those taking blood lipid management drugs within 4 weeks or vitamin D/analogues within 3 months were excluded from this study. All the patients signed informed consents for this study, which was approved by the ethical committee.

General information

A questionnaire was created to survey the patients or their families, to collect each patient's gender, age, medical history, medication history, and disease conditions.

Biochemical assay

Static blood pressure was measured three times in a supine position after admission (2 min intervals). Blood samples were collected from the patients' elbow veins the next morning. An enzymatic assay was performed to quantify serum total cholesterol (TC), low density lipoprotein (LDL), blood glucose (FPG) and uric acid (UA). An immune turbid assay was adopted to test hs-CRP. An enzyme linked immunosorbent assay (ELISA) was used to test 25-hydroxyl vitamin D (25(OD)D) using a test kit provided by Rongzhi Haida Biotech (China).

Grouping based on 25(OH)D and serum UA

Patients were diagnosed as vitamin D deficient with 25(OH)D<20 ng/mL. This study thus subdivided the patients into two groups based on 20 ng/mL. The normal range of serum UA is 149~416 μmol/L in males and 89~357 μmol/L in females. Patients with higher than 416 μmol/L (males) or 357 μmol/L (females) were thus classified into the HUA group, while the others were classified into the normal group.

Carotid stenosis

The condition of carotid stenosis was examined by Doppler ultrasound based on echo strength. Those with smooth endomembrane and no plaque were considered normal, and those with less than 50% stenosis rate were considered to have mild stenosis. Those with a rate between 50% and 70% were considered to have moderate stenosis, and those with a rate >70% were considered to have severe stenosis.

Condition of cerebral infarction

The aged acute cerebral infarction condition was evaluated based on the NIH Stroke Scale (NIHSS) when admitted. Mild, moderate, and severe cases were identified with scores between 0~6, 7~14, and ≥15.

Cerebral infarction area

The diameter at the maximal layer of infarction lesions on a head CT or MRI was measured. Cavity cleft infarction was identified when the diameter was <1.5 cm. Those lesions with diameters between 1.5 cm and 5.0 cm, and larger than 5 cm were classified as having small or major cerebral infarctions, respectively.

Table 1. The clinical information of the two groups

	Control	Patient	t/χ^2	*P*
Sex (M/F)	107/102	110/99	0.086	0.769
Age (years)	68.74±7.05	67.98±6.83	1.119	0.132
Systolic BP (mmHg)	122.34±6.82	133.92±8.17	15.730	<0.001
Diabolic BP (mmHg)	81.57±4.26	87.41±5.68	11.891	<0.001
FPG (mmol/L)	5.34±0.95	6.47±1.62	8.699	<0.001
TC (mmol/L)	4.63±1.02	5.49±1.15	8.088	<0.001
LDL (mmol/L)	3.14±0.11	3.32±0.13	1.239	0.108
hs-CRP (mg/L)	3.15±1.34	5.28±3.87	7.519	<0.001
[25(OH)D] (ng/mL)	21.84±3.06	15.29±2.73	23.091	<0.001
UA (μmol/L)	304.52±51.65	418.37±63.24	20.158	<0.001

Patient prognosis

All patients received 3-month follow-ups after discharge. Each patient's prognosis was evaluated based on pre-designed criteria [12]. Specifically, a cure was defined when the NIHSS score was decreased by 91% to 100%, with grade 0 morbidity. Major recovery was identified when the NIHSS score was decreased by 46% to 90%, with grade 1 to grade 3 morbidity. Recovery was defined when the NIHSS score was decreased by 18% to 45%. No major change was defined when the NIHSS score was decreased by less than 17%. Aggravation was identified when the NINSS score was unchanged or increased by more than 18%, or when the patient died. Total effective number = number of cure + number of major recovery + recovery.

Cognitive functions

MMSE was performed on the third day after admission to recognize cognitive dysfunction, with a total possible score of 30 points. The test result was related to education level: normal was defined between 27 and 30 points. Patients with less than 27 points (college above), 24 points (middle school), 20 points (junior school) or 17 points (no education) were identified as having cognitive dysfunctions.

Statistical analysis

SPSS 18.0 was used to collect and analyze all the data. The measurement data were presented as the mean ± standard deviation (SD). Student's *t*-test was used to compare the means between the groups. The enumeration data were presented as N (number) or percentage and were analyzed using the chi-square method. A correlation analysis was performed by logistic regression. Statistical significance was defined as P<0.05.

Results

Clinical information of the patients

As shown in **Table 1**, the patients had significantly higher systolic/diabolic blood pressure, FPG, TC, hs-CRP, 25(OH)D, and UA levels (P<0.05 compared to control group). However, no significant differences were observed regarding sex, age, or LDL between the two groups (P>0.05).

Logistic regression analysis for risk factors of cerebral infarction

Mute parameters were set for cerebral infarction (infarction = 0, no infarction = 1) and gender (male = 0, female = 1). A multivariate logistic regression analysis showed that systolic BP, FPG, TC, 25(OH)D, and UA were all independent risk factors for cerebral infarction (**Table 2**).

The patients were divided into two groups using 25(OH)D=20 ng/mL as the dividing line. In addition, the patients were also divided into normal UA and HUA groups using 416 μmol/L (males) or 357 μmol/L (females) of UA as the dividing line. Patients with a lower than 20 25(OH)D level had significantly higher systolic pressure, FPG, hs-CPG, and UA compared to those with a higher than 20 25(OH)D level (P<0.05) (**Table 3**). The HUA patients also had significantly higher FPG, TC, and hs-CRP levels, but had lower 25(OH)D levels compared to the normal group (P<0.05).

Effects of 25(OH)D and serum UA levels on carotid stenosis

Compared to the patients with 25(OH)D ≥20, those with a less than 20 25(OH)D level had more severe carotid stenosis. The HUA patients also had more severe carotid stenosis (P<0.05, **Table 4**).

The effects of 25(OH)D and serum UA levels on cerebral infarction

Compared to those having higher than 20 25(OH)D levels, those with less than 20 25(OH)D levels had more severe cerebral infarction (P<0.05) (**Table 5**), worse prognosis (P<0.05)

Table 2. Logistic regression analysis for the risk factors of cerebral infarction

	B value	S.E.	χ^2 value	*P* value	OR value	95% CI
Sex	-0.158	0.114	0.819	0.817	0.346	0.175~1.436
Age	0.283	0.217	0.452	1.013	1.342	0.872~1.614
Systolic BP	1.036	0.483	8. 407	<0.001	5.548	4.438~6.746
Diabolic BP	2.347	1.083	0.547	0.925	1.824	0.917~2.308
FPG	1.674	0.625	10.453	<0.001	4.673	3.056~5.812
TC	2.376	0.812	2.053	0.003	3.814	2.472~4.924
LDL	-1.472	0.843	1.035	0.104	0.779	0.613~1.348
hs-CRP	-0.285	0.142	1.217	0.083	0.628	0.542~1.107
[25(OH)D]	0.961	0.247	4.378	<0.001	2.967	1.273~4.032
UA	1.083	0.315	9.217	<0.001	1.548	1.162~2.794

Table 3. The clinical information of the cerebral infarction patients with different levels of 25(OH)D and UA

	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	Normal	HUA
N	114	95	101	108
Sex (M/F)	61/53	49/46	54/47	56/52
Age (years)	66.81±6.83	67.98±7.25	67.08±7.14	67.35±6.92
SBP (mmHg)	126.25±6.04	137.13±7.12*	129.85±6.73	134.52±7.06
DBP (mmHg)	86.92±4.37	87.21±5.58	86.45±4.66	88.04±4.73
FPG (mmol/L)	6.08±0.95	7.12±1.48*	6.28±1.06	6.97±1.39*
TC (mmol/L)	5.38±1.08	5.52±1.13	5.31±1.12	5.58±1.17*
LDL (mmol/L)	3.14±0.11	3.32±0.13	3.14±0.11	3.32±0.13
hs-CRP (mg/L)	4.65±1.45	6.03±1.96*	4.72±1.38	5.84±1.72*
[25(OH)D] (nmol/L)	-	-	16.88±3.24	14.86±2.79*
UA (μmol/L)	403.57±65.48	447.52±64.71	-	-

Note: *, P<0.05 compared to 25(OH)D ≥20 or normal UA groups.

Table 4. The effects of 25(OH)D and UA levels on carotid stenosis (N, %)

Carotid stenosis	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	Normal	HUA
Normal	32 (28.07%)	16 (16.84%)	32 (31.68%)	16 (14.81%)
Mild	31 (27.19%)	29 (30.53%)	31 (30.69%)	29 (26.85%)
Moderate	28 (24.56%)	41 (43.16%)	28 (27.72%)	41 (37.96%)
Severe	10 (8.77%)	22 (23.16%)	10 (9.90%)	22 (20.37%)
χ^2	8.865		12.128	
P	0.034		0.007	

Correlation between 25(OH)D and serum UA levels

A Pearson analysis showed a significantly negative correlation between 25(OH)D and blood UA levels (r = -0.635, P = 0.013).

Discussion

Cerebral infarction is a common cerebrovascular disease, with an increasing incidence and mortality rate by years as a result of the aging population, thus causing a major threat to public health [13]. Over many years, people have become concerned about the risk factors for cerebral infarction including age, sex, racial groups, family heredity, hypertension, cardiac issues, diabetes, and high blood lipid levels.

(**Table 6**) and a higher percentage of cognitive dysfunction (P<0.05) (**Table 7**) without any significant difference in the cerebral infarction area (P>0.05) (**Table 8**). The HUA patients had more severe cerebral infarctions (P<0.05, **Table 5**), a larger infarction area (**Table 8**), a worse prognosis (P<0.05, **Table 6**) but had no difference in the percentage of cognitive dysfunction compared to the control group (**Table 7**).

Table 5. Effects of 25(OH)D and UA levels on condition of cerebral infarction (N, %)

Disease severity	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	normal	HUA
Mild	60 (52.63%)	43 (45.26%)	62 (61.39%)	41 (37.96%)
Moderate	42 (36.84%)	27 (28.42%)	30 (29.70%)	39 (36.11%)
Severe	12 (10.53%)	25 (26.32%)	9 (8.91%)	28 (25.93%)
χ^2	8.981		14.995	
P	0.011		0.001	

Table 6. Effects of 25(OH)D and UA levels on cerebral infarction prognosis (N, %)

Prognosis	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	Normal	HUA
Improvement	86 (75.44%)	60 (63.16%)	79 (78.22%)	66 (61.11%)
No change	18 (15.79%)	14 (14.74%)	14 (13.86%)	19 (17.59%)
Aggravation	10 (8.77%)	21 (22.11%)	8 (7.92%)	23 (21.30%)
χ^2	7.367		8.957	
P	0.025		0.011	

Table 7. Effects of 25(OH)D and UA on cognitive functions (N, %)

Cognitive functions	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	Normal	HUA
Normal	95 (83.33%)	68 (71.58%)	81 (80.20%)	87 (80.55%)
Dysfunction	19 (16.67%)	27 (28.42%)	20 (19.80%)	21 (19.45%)
χ^2	4.171		0.0042	
P	0.041		0.948	

Table 8. Effects of 25(OH)D and UA levels on cerebral infarction area (N, %)

Infarction area	[25(OH)D] (ng/mL)		UA (μmol/L)	
	≥20	<20	Normal	HUA
Massive	28 (24.56%)	22 (23.16%)	14 (13.86%)	36 (33.33%)
Small	33 (28.95%)	30 (31.58%)	35 (34.65%)	28 (25.93%)
Cavity	53 (46.49%)	43 (45.26%)	52 (51.49%)	44 (40.74%)
χ^2	0.179		10.902	
P	0.915		0.004	

However, still there are some cerebral infarction patients without those risk factors, an indication of other possible pathogenic factors [14]. The exploration and investigation of risk factors for cerebral infarction is thus a critical step in the disease's prevention and treatment, and with major clinical implications.

Vitamin D and cerebral infarction

Vitamin D deficiency is a risk factor for osteoporosis and bone fracture. Recent studies have found a close correlation between vitamin D and cardiovascular disease, metabolic disorders, and the human immune system [15]. Low levels of vitamin D can increase mortality and bring an unfavorable prognosis for cardiovascular disease. Chowdhurry et al. showed a significantly positive correlation between decreased serum vitamin D levels and the occurrence of cerebral infarction [16], suggesting that vitamin D may become another risk factor for cerebral infarction.

In this study, serum levels of 25(OH)D level were significantly lower in cerebral infarction patients compared to healthy people, indicating a possible correlation between low serum vitamin D levels and cerebral infarction occurrence. A logistic regression analysis found vitamin D to be an independent risk factor for cerebral infarction. Brondum-Jacobsen et al. performed a prospective study [17] and demonstrated that lower vitamin D levels could lead to a higher incidence and mortality rates from cerebral infarction. Kienreich et al. found that vitamin D was an independent risk factor for cerebral infarction [18], which is consistent with our study. A further analysis showed that people with lower than 20 ng/mL of 25(OH)D had a significantly higher SBP, FPG, and hs-CRP compared to those patients having higher than 20 ng/mL of 25(OH)D, indicating that 25(OH)D may exert its functions by affecting blood pressure, blood glucose levels, and the inflammatory response. In this study, we did not find sex or age to be high risk factors for cerebral infarction, probably due to the selection of the study cohorts. This study only covered people over 60

years old, with an incomplete coverage of gender and age factors, causing some inconsistency with previous studies [12].

This study revealed the correlation between the serum 25(OH)D level and the risk of cerebral infarction, as those patients with lower vitamin D levels had a more severe disease condition, a worse prognosis, and a higher rate of cognitive dysfunction. Moreover, vitamin D levels are correlated with carotid stenosis. This study found significant differences in carotid stenosis conditions among patients with various vitamin D levels, as lower vitamin D levels indicated severe stenosis. Therefore, vitamin D is probably one risk factor for predicting acute cerebral infarction and may work as an objective index for disease evaluation and prognosis prediction. Turetsky et al. found a negative correlation between serum vitamin D levels and the volume or prognosis of cerebral infarction lesions, as patients having lower vitamin D levels showed larger lesions and a higher risk in the early stages of an unfavorable prognosis [19], as this study also found. Vacek et al. demonstrated that the replenishment of Vitamin D significantly improved the prognosis of cerebral infarction patients, decreased the total morality rate, and elongated the survival span [20], further supporting our study results.

Uric acid and cerebral infarction

Our study found that elevated uric acid levels are closely correlated with the occurrence of atherosclerosis, which is the pathological basis for cerebral infarction. Recent studies showed that an increase in blood UA might be a risk factor for cerebral infarction [21]. Strasak et al. demonstrated that serum UA is one independent predictive factor for the prognosis of cerebrovascular disease, as elevated serum UA levels frequently cause the occurrence of cerebral infarction and are related to an unfavorable prognosis [22]. Other studies showed a close correlation between high serum UA and type 2 diabetes [23]. This study performed a logistic regression analysis and found UA to be an independent risk factor for cerebral infarction, and further study showed remarkably higher FPG, TC, and hs-CRP levels in the HUA group of patients compared to those with a normal UA, suggesting that UA may affect cerebral infarction pathogenesis by blood glucose, lipids, or the inflammatory response. Li et al. performed a meta-analysis and showed a significant correlation between high blood UA and cerebral infarction occurrence [24], further supporting our results.

This study found that high blood UA could affect the cerebral infarction area, disease conditions, and patient prognosis. Moreover, high uric acid can also affect carotid stenosis conditions, but it has only minor effects on cognitive functions. Kashyap et al. showed that the above-normal levels of serum UA could form UA crystals [25], which precipitated on the endothelial layers of vessels, causing damage, thus facilitating the occurrence of atherosclerosis. Moreover, elevated UA can also enhance the absorption potency of plasma proteins on red blood cells, thus elevating viscosity and facilitating atherosclerosis, thus supporting our results describing its mechanisms. In summary, these results indicate that high serum UA affects the occurrence, progression, and prognosis of cerebral infarction, thus working as a major predictive index for the disease conditions of cerebral infarction.

In this study, serum 25(OH)D and serum UA levels may work as a predictive index for acute, aged cerebral infarction, providing values for decreasing infarction incidence and improving patient prognosis, thus having a major promise for clinical promotion. Although this study showed the correlation between vitamin D, UA levels, and aged cerebral infarction, its detailed mechanisms, and whether the replenishment of vitamin D or intervention on the UA level after cerebral infarction can improve a patient's prognosis, atherosclerosis condition, or cognitive functions, still require detailed studies but has a promising outlook.

Conclusion

Both Vitamin D and serum UA can affect the occurrence, progression, and prognosis of cerebral infarction and can work as a predictive index for the clinical monitoring of infarction disease conditions.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ling Hao, Department of Basic Medicine, Jiangsu Vocational College of Medicine, No. 283 Jiefang South Road, Yancheng City, Jiangsu Province, China. Tel: +86-05-15-88159060; Fax: +86-0515-88159060; E-mail: nmwg4e6@sina.com

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