·综述·

血清尿酸与神经变性病研究进展

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【摘要】 血清尿酸作为人体内天然抗氧化剂，近年发现其与多种神经变性病的发生与发展相关，包括帕金森病、多系统萎缩、阿尔茨海默病和肌萎缩侧索硬化症等。血清尿酸水平升高可以减少帕金森病和肌萎缩侧索硬化症的发病风险，但与多系统萎缩和阿尔茨海默病等神经变性病的关系尚不明确。体外研究和动物实验证实血清尿酸水平升高可以增强神经元抗氧化应激能力，从而延缓神经元变性和凋亡。本文拟对近年来血清尿酸与神经变性病的研究进展进行综述，以为探寻神经变性病新的预防与治疗策略提供信息。

【关键词】 尿酸；　帕金森病；　阿尔茨海默病；　肌萎缩侧索硬化；　多系统萎缩；　综述

Progress of the relationship between serum uric acid and neurodegenerative diseases

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【Abstract】 Serum uric acid (sUA), a natural antioxidant in human body, has been found to be related to the occurrence and development of various neurodegenerative diseases in recent years, including Parkinson´s disease (PD), multiple system atrophy (MSA), Alzheimer´s disease (AD) and amyotrophic lateral sclerosis (ALS). Increasing of sUA level has been found to reduce the incidence of PD and ALS, but the relationship between sUA and AD, MSA remains largely unknown. The *in vitro* studies and animal experiments revealed that sUA can enhance the antioxidant capacity of neurons and delay neurodegeneration and apoptosis. This paper mainly reviews the progress in epidemiological and basic studies of the relationship between sUA and neurodegenerative diseases in recent years, and aims to provide a reference for future novel prevention and treatment strategies for neurodegenerative diseases.

【Key words】 Uric acid;　Parkinson disease;　Alzheimer disease;　Amyotrophic lateral sclerosis;　Multiple system atrophy;　Review

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血清尿酸(sUA)是人体内表达丰富的天然抗氧化剂，不仅与高血压、冠心病和肾脏病的发病息息相关[1]，而且与神经变性病具有一定相关性。多项流行病学调查显示，高水平血清尿酸与帕金森病(PD)的发病密切相关[2-3]。此后，越来越多的研究逐渐聚焦于血清尿酸在神经变性病中的作用，发现血清尿酸与多系统萎缩(MSA)、阿尔茨海默病(AD)、肌萎缩侧索硬化症(ALS)和亨廷顿病(HD)等神经变性病的发病风险、疾病进展和预后均有一定相关性。亦有体外研究和动物实验揭示血清尿酸对神经变性病的保护机制，认为血清尿酸可能通过增强神经元对氧化应激的抵抗性，对神经元变性和死亡发挥一定的保护作用，从而延缓疾病进展。本文拟对近年来血清尿酸与帕金森病、多系统萎缩、阿尔茨海默病和肌萎缩侧索硬化症等神经变性病的关系研究进展进行综述，以为探寻神经变性病新的预防与治疗策略提供信息。

一、血清尿酸与神经变性病相关临床研究

1. 血清尿酸与帕金森病　(1)血清尿酸与帕金

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表1 血清尿酸与帕金森病发病风险相关性的流行病学研究

Table 1. Epidemiological studies on the association between sUA and the risk of PD

Reference	Study design	Study objective	Study population	Main conclusions
de Lau, et al [2]	Prospective cohort study	Whether sUA was related to future risk of PD	4695 persons aged 55 years or older in a district of Rotterdam, the Netherlands (free of parkinsonism and dementia at baseline), on average 9.40 years of follow-up	Higher sUA levels seemed associated with a lower risk of PD in the age- and sex-adjusted analyses, adjusted *HR* value for highest (>374 μmol/L) compared with lowest quartile (<267.80 μmol/L) was 0.420 (95%CI: 0.180–0.960), no significant difference for men and women
Davis, et al [4]	Prospective cohort study	Whether sUA was related to future risk of PD	7968 male Japanese residents in Hawaii, followed up for 30 years (the Honolulu Heart Program)	Men with sUA concentrations above the median at enrollment had a 40% reduction in PD incidence. Reduced PD incidence rates persisted in analyses restricted to nonsmokers and cases younger than 75 years
Weisskopf, et al [5]	Nested case-control study	Whether sUA was related to future risk of PD	18 018 participants in Health Professionals Follow-up Study cohort, with an average age of 67.20 years, on average 8 years follow-up	The *RR* value of PD for the highest quartile (>411 μmol/L) of uricemia compared to the lowest (<309 μmol/L) was 0.430 (95%CI: 0.180–1.020). This association was stronger in analyses excluding cases diagnosed within 4 years (median) from blood collection
Chen, et al [6]	Prospective cohort study	Whether sUA was related to future risk of PD	14 941 cases of 45–64 years American residents (3891 African Americans and 11 050 Caucasians), followed up once every 3 years, for 20 years of follow-up	Plasma urate concentration was inversely associated with PD occurrence. The *OR* value between extreme quartiles of plasma urate were 0.400 (95%CI: 0.200–0.800) in the overall analysis, but the association was not statistically significant among women and African Americans
O´Reilly, et al [7]	Nested case-control study	Whether sUA was related to future risk of PD	32 826 women in Nurses´ Health Study, followed up for 14 years (105 confirmed cases matched with 518 controls)	The adjusted *RR* value of PD comparing the highest (≥345.10 μmol/L) with the lowest (<238 μmol/L) quartile of urate was 1.330 (95%CI: 0.690–2.570). Plasma urate levels were not significantly associated with PD risk
Jain, et al [8]	Prospective cohort study	Whether sUA was related to future risk of PD	5749 American adults aged 65 years and older in whom data was prospectively collected for 14 years	With the middle range as reference, the risk of developing PD was significantly increased for urate <300 μmol/L (*OR* = 1.690, 95%CI: 1.030–2.780) but not for urate >500 μmol/L (*OR* = 1.550, 95%CI: 0.720–3.320) in men. In women no associations between urate and PD risk were observed
Gao, et al [9]	Nested case-control study	Whether sUA was related to future risk of PD	90 214 participants of 3 ongoing US cohorts (388 new PD cases matched with 1267 controls)	The multivariate-adjusted *RR* value of PD comparing extreme quartiles of urate were 0.630 (95%CI: 0.350–1.100, *P* = 0.049) in men and 1.040 (95%CI: 0.610–1.780, *P* = 0.440) in women

sUA, serum uric acid, 血清尿酸; PD, Parkinson´s disease, 帕金森病

森病发病风险：近年来，多项流行病学调查显示，血清尿酸水平与帕金森病发病密切相关，但前瞻性研究并不多见，迄今仅不足10项前瞻性临床研究探讨人群血清尿酸水平与帕金森病发病的关系[2,4-9]，且主要源自高加索人群或欧洲人群[2,5-9]，仅1项临床研究源自日裔夏威夷人群[4]，而缺少黑种人和除日裔外亚洲人群的大规模前瞻性临床研究，结果显示，总体血清尿酸水平与帕金森病发病率呈负相关，血清尿酸升高可以降低帕金森病发病风险，尤其是男性患者更加显著[6-9]（表1）。大量横断面研究（包括医院和社区）亦证实此观点[10-13]。高尿酸血症临床多表现为痛风，既往研究显示，痛风患者帕金森病发病风险明显降低[3,14]，但2015年的一项Meta分析却显示痛风与帕金森病发病风险无明显关联性，可能与痛风患者高氧化应激反应或服用排尿酸药有关[15]。因此尚待更多关于痛风患者血清尿酸水平与帕金森病发病风险关系的研究，尤其是亚洲人群的前瞻性临床研究。（2）血清尿酸与帕金森病运动症状、疾病进展和预后的关系：血清尿酸水平除与帕金森病发病风险相关外，亦有多项临床研究显示，血清尿酸水平与帕金森病严重程度或疾病进展相关，与早期帕金森病患者相比，统一帕金森病评价量表第三部分（UPDRS Ⅲ）评分较高、Hoehn-Yahr分期较高的晚期帕金森病患者血清尿酸水平较低[10-13,16-17]（表2）；少数研究不支持上述结论[18-19]；亦有研究显示，血清尿酸水平与帕金森病不同运动症状相关，低血清尿酸水平与症状波动[20]、冻结步态（FOG）[21]、姿势不稳和步态障碍[22-23]等非震颤的运动症状相关，而上述运动症状又与帕金森病病程、UPDRS评分和Hoehn-Yahr分期相关，提示血清尿酸水平可能与帕金森病严重程度相关；此外，^{123}I-FP-CIT SPECT显像研究证实低血清尿酸水平与壳核、尾状核和纹状体低多巴胺转运体（DAT）密度相关[23-24]。因此，无论是临床症状还是影像学表现，大多数研究均支持血清尿酸水平与帕金森病疾病进展呈负相关，且这种关联性在男性患者中尤为突出。（3）血清尿酸与帕金森病认知功能障碍及其他非运动症状（NMS）的关系：血清尿酸水平不仅与帕金森病运动症状相关，而且与非运动症状亦密切相关，尤以帕金森病认知功能障碍的相关研究较多[16,25-33]（表3）。2008年的一项芬兰研究显示，低血清尿酸的帕金森病患者认知功能较高血清尿酸患者明显降低，尤以执行功能下降更加明显[25]。此后，中国[26-27]及其他国家[28-32]也相继采用不同神经

表2 血清尿酸与帕金森病运动症状和疾病进展的相关临床研究

Table 2. Clinical studies on the relationship between sUA and motor symptoms and disease progression of PD

Reference	Study design	Study objective	Study population	Main conclusions
Ikeda, et al [10]	Cross-sectional study	To elucidate whether serological data are correlated with disease progression	119 PD patients with an average course of 6.90 years and average age of 73.20 years in Japan and 120 matched healthy controls	The level of sUA was negatively related to the severity of disease progression (Hoehn-Yahr stage) and course of disease, and there was no significant gender difference
Sun, et al [11]	Cross-sectional study	To evaluate whether sUA levels are associated with Chinese PD patients	411 PD patients with an average course of 5.73 years and average age of 63.10 years in China and 396 matched healthy controls	There was a significantly inverse correlation of sUA levels with Hoehn-Yahr stage and disease duration in PD patients of both females and males
Zhang, et al [12]	Cross-sectional study	To seek the evidence in favor of using sUA as a PD biomarker	534 PD patients with an average course of 4.13 years and average age of 63.90 years in China and 614 matched healthy controls	The sUA levels in PD patients were correlated with PD progression and duration in Chinese population. The associations were stronger among men compared to women and older people compared to younger people
Jesus, et al [13]	Cross-sectional study	To investigate whether or not sUA is related to PD clinical parameters and disease severity	161 patients with PD and 178 controls from Southern Spain	The sUA concentration was lower in patients with PD in severe stages than in those in moderate stage, and no significant association was found between sUA concentration and age at disease onset or disease duration
Pan, et al [16]	Cross-sectional study	To assess whether sUA levels in PD is associated with poor motor function and levodopa (L-dopa) dosage	80 PD patients with an average course of 4.10 years and average age of 60.25 years in China	Low sUA levels may be more prone to developing PD and the inverse relationship between sUA and severity of PD was robust for men, but weak for women
Vieru, et al [17]	Cross-sectional study	To investigate the association of sUA levels with disease progression and L-dopa treatment in PD patients	80 cases of PD patients with an average age of 67.99 years in Turkey and 80 controls	PD patients at Hoehn-Yahr stage 3 and over had significantly lower sUA levels than PD patients at earlier stages
Sakuta, et al [18]	Cross-sectional study	To investigate the associations among sUA levels and background clinical factors in PD	100 PD patients with an average duration of 5.30 years and average age of 68.50 years in Japan and 100 healthy controls	No significant correlations of sUA levels with those parameters (disease duration, UPDRSⅢ and Hoehn-Yahr stage) were observed in PD patients
Wang, et al [19]	Cross-sectional study	To investigate the correlation between PD and levels of sUA and albumin	96 PD patients with an average duration of 3.78 years and average age of 67.54 years in China and 108 matched healthy controls	The sUA levels was no statistical difference in Hoehn-Yahr stage
Fukae, et al [20]	Cross-sectional study	To estimate the association between sUA concentration and the prevalence of wearing-off fluctuation	123 PD patients with an average duration of 11.20 years and 69.20 years of average age in Japan	The sUA concentration was inversely correlated with development of wearing-off fluctuation. This inverse association was significant in men but not in women
Ou, et al [21]	Cross-sectional study	To explore the association between FOG and sUA levels in Chinese PD patients	321 PD patients with an average duration of 4.96 years and average age of 62.40 years in China	Low sUA levels are associated with the occurrence of FOG in PD
Lolekha, et al [22]	Cross-sectional study	To evaluate sUA level in patient with tremor dominant PD compared to non-tremor dominant PD and healthy controls	100 PD patients with an average duration of 4.40 years and 68.14 years of average age in Thailand and 100 matched healthy controls	There was statistically significantly lower sUA levels in non-tremor dominant PD compared to tremor dominant PD, and no statistically significant difference in sUA levels between patients with tremor dominant PD and healthy controls
Huertas, et al [23]	Cross-sectional study	To investigate whether tremor and non-tremor dominant PD differ in sUA levels and degree of dopaminergic degeneration	75 PD patients [disease duration after symptom onset: (12 ± 6) years] in Spain	Non-tremor dominant PD patients had lower levels of sUA and striatal DAT availability than PD patients with a predominance of tremor
Moccia, et al [24]	Cross-sectional study	To investigate the relationship between sUA levels and DAT availability in newly diagnosed, drug-naive PD patients	52 early PD patients in Italy, with an average age of 58.90 years	The sUA levels were significantly correlated with the severity of dopaminergic impairment in caudate, putamen, and striatum. No significant relationships were found between sUA levels and disease duration, UPDRSⅢ and Hoehn-Yahr stage

PD, Parkinson´s disease, 帕金森病; sUA, serum uric acid, 血清尿酸; UPDRS, Unified Parkinson´s Disease Rating Scale, 统一帕金森病评价量表; FOG, freezing of gait, 冻结步态; DAT, dopamine transporter, 多巴胺转运体

心理学测验量表[包括蒙特利尔认知评价量表(MoCA)、简易智能状态检查量表(MMSE)、非运动症状量表(NMSS)、额叶功能评价量表(FAB)]评价帕金森病患者认知功能,结果显示,低血清尿酸的帕金森病患者认知功能较高血清尿酸患者下降得更加明显,主要表现为视空间能力和执行功能[25,27]、记忆力[27,30,32]等认知域。尽管个别研究显示,血清尿酸水平与痴呆无明显关联性[29],但更多的前瞻性和横断面临床研究均支持上述研究结果。同时亦有研究显示,血清尿酸水平下降与早期帕金森病患者抑郁和焦虑症状[30,32]、情感淡漠[33]等均相关,尚待更多研究的证实。

2. 血清尿酸与多系统萎缩 研究显示,多系统萎缩患者血清尿酸水平明显低于正常对照者,尤其是男性患者更加显著[34-35](表4)。Fukae等[36]的回顾性研究显示,高血清尿酸的多系统萎缩患者疾病

表3 血清尿酸与帕金森病非运动症状的相关临床研究

Table 3. Clinical studies on the relationship between sUA and NMS of PD

Reference	Study design	Study objective	Study population	Main conclusions
Pan, et al [16]	Cross-sectional study	To identify any associations between NMSS domains and sUA levels	80 PD patients with an average disease duration of 4.10 years and average age of 60.25 years in China	A significant correlation between sUA and MMSE (r_s = 0.405, P = 0.009) in male PD patients but not in female patients. Significant correlations were also found between sUA and NMS burden of sleep/fatigue, and sUA and NMS burden of mood in men and women
Annanmaki, et al [25]	Cross-sectional study	To examine the associations of sUA levels and cognitive changes	40 PD patients in Finland, mean age 60.80 years, disease duration not more than 10 years	Low sUA level predicted worse performance both in the picture completion and similarities subtest of the WAIS-R, which were considered sensitive to subcortical and frontal regions damage
Wang, et al [26]	Cross-sectional study	To explore the relation of cognition and sUA in PD	104 Chinese PD patients, mean age 65 years, disease duration 1–22 years	The sUA level in the group with cognitive impairment was lower than that without cognitive impairment, the cognitive scores correlated with sUA levels, education, age, Hoehn-Yahr stage and depression levels, but didn't with gender, disease duration, smoking and BMI
Chen, et al [27]	Cross-sectional study	To explore the incidence of cognitive dysfunction and associated factors in Chinese PD patients	61 Chinese PD patients and 60 normal controls, mean age 65 years, mean disease duration 4.70 years	Statistical differences existed in visual space/execution, naming and delay memory between PD and controls. In PD patients, cognitive scores were correlated with levels of sUA, education, UPDRS Ⅲ and depression levels, but didn't with gender, disease duration
Annanmaki, et al [28]	Prospective cohort study	To examine the association of sUA levels with cognitive changes in PD patient cohort over 3 years follow-up	40 PD patients in Finland, mean age 60.30 years, disease duration not more than 10 years, followed up for 3 years	The baseline sUA levels of patients showed no correlations with follow-up neuropsychological parameters
Gonzalez-Aramburu, et al [29]	Cross-sectional study	To study whether low sUA levels is associated with the presence of dementia in a cohort of patients with PD	343 Spanish PD patients, mean age 63.40 years, mean disease duration 8.50 years	The sUA levels were not different between PD patients with or without dementia (MMSE < 26 or not)
Moccia, et al [30]	Cross-sectional study	To investigate the relationship between sUA and occurrence of NMS in de novo PD patients	80 de novo drug-naive PD patients, mean age 59.30 years, disease duration not more than 2 years	The sUA levels showed a significant negative correlation with NMSQuest, especially in attention/memory, cardiovascular and sleep domains of NMSQuest
Pellecchia, et al [31]	Prospective cohort study	To assess whether baseline sUA levels may be related to later development of MCI in a cohort of early drug-naive PD patients	40 de novo drug-naive PD patients from Italy, mean age 59.30 years, disease duration not more than 2 years, followed up for 4 years	Both sUA levels (OR = 0.540, 95%CI: 0.300–0.980; P = 0.044) and age (OR = 1.160, 95%CI: 1.030–1.300; P = 0.009) were significant predictors of occurrence of MCI at 4 years follow-up
Moccia, et al [32]	Prospective cohort study	To evaluate the usefulness of baseline sUA as a marker of NMS progression in newly diagnosed PD patients	69 de novo drug-naive PD patients from Italy, mean age 59.50 years, disease duration not more than 2 years, followed up for 2 years	Patients with NMS absence presented significantly higher sUA values than patients with NMS presence with regard to attention/memory, depression/anxiety and cardiovascular domains
Picillo, et al [33]	Prospective cohort study	To explore the relationship between sUA levels and pure apathy in early, drug-naive PD patients	49 de novo drug-naive PD patients from Italy, mean age 59 years, mean disease duration 13 months, followed up for 2 years	Lower sUA levels were associated with greater apathy (as assessed with both clinical rating scales and diagnostic criteria), irrespective of age, gender, attention/executive functions and LEDD

NMSS, Non-Motor Symptoms Scale, 非运动症状量表; sUA, serum uric acid, 血清尿酸; PD, Parkinson's disease, 帕金森病; MMSE, Mini-Mental State Examination, 简易智能状态检查量表; NMS, non-motor symptoms, 非运动症状; WAIS-R, Wechsler Adult Intelligence Scale-Revised, 韦氏成人智力量表修订版; BMI, body mass index, 体重指数; UPDRS, Unified Parkinson's Disease Rating Scale, 统一帕金森病评价量表; NMSQuest, Non-Motor Symptoms Questionnaire, 非运动症状问卷; MCI, mild cognitive impairment, 轻度认知损害; LEDD, levodopa equivalent daily dose, 左旋多巴日等效剂量

进展速度较慢;他们进一步采用总体衰退量表(GDS)/病程比值评价疾病进展速度,结果显示,随着血清尿酸水平的升高,疾病进展速度减慢,且这种关系在男性患者(r_s = - 0.419, P = 0.037)和疾病早期(r_s = - 0.527, P = 0.002)更加明显,与Chen等[35]和Lee等[37]的研究结果相一致。Cao等[38]纳入89例早期多系统萎缩患者[平均病程(2.6 ± 1.5)年],发现存在认知损害的患者血清尿酸水平较低;但是他们进一步对107例多系统萎缩患者的随访研究显示,血清尿酸水平与疾病进展[统一多系统萎缩评价量表(UMSARS)评分年变化率]并无关联性[34]。另一项随访研究比较不同血清尿酸水平的多系统萎缩患者生存期,结果显示无明显差异[39]。因此,血清尿酸水平与多系统萎缩疾病进展的相关性尚待进一步研究。

3. 血清尿酸与阿尔茨海默病 多项临床研究显示,血清尿酸水平与阿尔茨海默病发病率和疾病进展相关[40-47](表5),例如,Lu等[40]对英国健康促进网络(THIN)数据库中298 029名老年人进行回顾性研究发现,经校正性别、年龄、体重指数(BMI)等因素

表4 血清尿酸与多系统萎缩的相关临床研究

Table 4. Clinical studies on the relationship between sUA and MSA

Reference	Study design	Study objective	Study population	Main conclusions
Cao, et al [34]	Prospective cohort study	To verify the relationship between sUA and MSA	234 Chinese MSA patients (mean age was 58.90 years, mean disease duration was 2.60 years) and 240 age- and gender-matched subjects	The sUA levels in MSA patients was significantly lower than that of healthy controls, especially in males. No correlation was found between the mean rate of annualized changes of UMSARS and levels of sUA
Chen, et al [35]	Cross-sectional study	To compare serum levels of CRP/Hcy/UA between MSA patients and normal healthy subjects	47 Chinese MSA patients and 50 healthy age-matched controls	The sUA levels in male MSA patients was significantly lower than that in healthy subjects, but sUA had no significant correlation with severity of both motor and non-motor dysfunctions in MSA patients
Fukae, et al [36]	Retrospective cohort study	To examine whether sUA concentration was linked to disease progression in MSA patients	53 Japanese MSA patients, mean age was 65.50 years, mean disease duration was 3.77 years	MSA patients with a higher sUA concentration had lower disease progression rates, especially in male patients
Lee, et al [37]	Prospective cohort study	To evaluate whether the concentration of sUA influenced MSA disease progression	53 Korean MSA patients, mean age was 57.80 years, mean disease duration was 2.72 years	The sUA levels had a significant negative correlation with the annualized UMSARS changes (r = - 0.400, P = 0.004)

sUA，serum uric acid，血清尿酸；MSA，multiple system atrophy，多系统萎缩；UMSARS，Unified Multiple System Atrophy Rating Scale，统一多系统萎缩评价量表；CRP，C-reactive protien，C-反应蛋白；Hcy，homocysteine，同型半胱氨酸

表5 血清尿酸与阿尔茨海默病的相关临床研究

Table 5. Clinical studies on the relationship between sUA and AD

Reference	Study design	Study objective	Study population	Main conclusions
Lu, et al [40]	Retrospective cohort study	To examine the relationship between gout and the risk of AD	59 224 patients with gout and 238 805 matched non-gout individuals in UK (mean age at baseline was 65 years, mean follow-up time more than 5 years)	Gout was inversely associated with the risk of developing AD, compared with individuals without gout, the multivariate *HR* value was 0.760 (95%CI: 0.660–0.870)
Euser, et al [41]	Prospective cohort study	To assess the relation between sUA levels and the risk of subsequent dementia in a prospective population-based cohort study	4618 inhabitants aged 55 years and over of a district of Rotterdam, the Netherlands, followed up for more than 10 years	After correcting for several cardiovascular risk factors, higher sUA levels were associated with a decreased risk of dementia [*HR* value for the highest versus the lowest quartile of sUA was 0.730 (95%CI: 0.550–0.970)]
Al-khateeb, et al [42]	Case-control study	To assess whether sUA levels would be altered in AD Jordanian patients compared to those of healthy controls	41 AD patients and 40 healthy controls from the senior homes and Jordan University Hospital	AD group showed lower sUA level than control subjects, but there was no correlation between level of sUA and progress of cognitive impairment
Rinaldi, et al [43]	Cross-sectional study	To assess peripheral levels and activities of a broad spectrum of non-enzymatic and enzymatic antioxidants in elderly subjects with MCI and AD	25 subjects with MCI, 63 free-living subjects with AD, and 56 healthy elderly community-dwellers in Italy (mean age 75.80 years)	AD and MCI patients showed lower levels of sUA, vitamin C, vitamin E, and red blood cell superoxide dismutase as compared to controls
Kim, et al [44]	Cross-sectional study	To assess whether plasma levels of albumin, bilirubin and UA would be altered in AD patients compared to those of healthy controls	101 Korean AD patients and 101 healthy controls	A significant reduction in albumin, bilirubin and sUA levels in AD group was found compared to those of control group
Irizarry, et al [45]	Prospective cohort study	To test the hypotheses that high plasma urate at baseline is associated with: 1) a reduced rate of conversion from MCI to AD and 2) a lower rate of cognitive decline in MCI	747 participants from the USA and Canada in a 3-year, randomized, double-blind, placebo-controlled study of donepezil, vitamin E or placebo for delaying the progression of MCI to AD	While sUA levels did not predict the progression of MCI to AD, high urate may be associated with a reduced rate of cognitive decline in MCI patients not treated with donepezil or vitamin E
Cervellati, et al [46]	Cross-sectional study	To evaluate a panel of distinct indicators of systemic oxidative stress in large sample of older patients affected by AD or MCI	101 patients with AD, 134 MCI patients, and 99 normal older individuals (controls) from Italy	Compared with controls, high levels (over median value) of serum hydroperoxides were independently associated with an increase in the likehood of having MCI or AD
Latourte, et al [47]	Prospective cohort study	To investigate the risk of incident dementia and brain MRI features by sUA level in a large cohort of older adults	1578 French people (mean age 72.40 years), followed up for more than 12 years	After multiple adjustments, higher sUA levels were associated with a increased risk of dementia, the multivariate *HR* value with the highest vs. lowest sUA level was 1.790 (95%CI: 1.170–2.730, P = 0.007). The *HR* value of AD with the highest vs. lowest sUA level was 2.310 (95%CI: 1.050–5.080, P = 0.037)

AD，Alzheimer's disease，阿尔茨海默病；sUA，serum uric acid，血清尿酸；MCI，mild cognitive impairment，轻度认知损害

后，痛风组阿尔茨海默病患病率较非痛风组降低24%。另一项纳入国内外24项血清尿酸与阿尔茨海默病关系临床研究的Meta分析显示，与正常对照者相比，阿尔茨海默病患者血清尿酸水平更低（*WMD* = - 0.770，95%CI：- 2.280 ~ - 0.360；P = 0.000）；与低血清尿酸人群相比，高血清尿酸人群罹患阿尔茨海默病的风险更低（*RR* = 0.660，95%CI：0.520 ~ 0.850；P = 0.001）[48]。多项流行病学调查和病例对照研究均显示，高血清尿酸水平可能是阿尔茨海默病的保护因素[41-44]。亦有研究显示，血清尿酸水平与轻度认知损害（MCI）和阿尔茨海默病认知功能障碍进展速度有一定相关性，低血清尿酸的患者认知

表6 血清尿酸与肌萎缩侧索硬化症的相关临床研究

Table 6. Clinical studies on the relationship between sUA and ALS

Reference	Study design	Study objective	Study population	Main conclusions
Zoccolella, et al [51]	Cross-sectional study	To determine whether sUA levels were lower in subjects with ALS compared to healthy controls	132 ALS patients and 337 age- and sex-matched controls	In univariate analysis, high sUA levels were less likely to be associated with ALS (*OR* = 0.530, 95%CI: 0.290–0.970; *P* = 0.040), but after adjusting for age, sex and kidney function, the association was not statistically significant
Zheng, et al [52]	Cross-sectional study	To clarify the relationship between level of sUA and occurrence, progression and survival of ALS	512 Chinese ALS patients and 501 age- and sex-matched healthy controls	Low level of sUA may be associated with increased occurrence of ALS in Chinese population, and sUA level may not contribute to the survival or progression of ALS
Oh, et al [53]	Cross-sectional study	To determine levels of sUA in Korean patients with ALS and to search for a correlation between sUA levels and disease progression	136 Korean ALS patients and 136 age- and sex-matched healthy controls	ALS patients had lower sUA levels than that of healthy individuals. The sUA levels in ALS were negatively correlated with the rate of disease progression and positively associated with survival
O'Reilly, et al [54]*	Prospective cohort Study	To determine whether sUA predicts ALS progression	942 ALS participants of a phase Ⅲ clinical trial, followed up for 12 months	In males, outcomes improved with increasing sUA (comparing highest to lowest sUA quartile: *HR* value for death was 0.600 with *P* value for trend was 0.070), but there was not a significant relation between sUA and outcomes in females
Mandrioli, et al [55]	Retrospective cohort study	To evaluate the association between changes in several laboratory tests and tracheostomy-free survival in the cohort of ALS patients	275 ALS patients diagnosed between 2000 and 2013 in Modena Italy	An increase of sUA was directly associated with the odds of death or tracheostomy
Paganoni, et al [56]	Retrospective cohort study	To investigate whether sUA levels would predict disease progression and survival in a large cohort of ALS clinical trial participants	251 subjects from 2 clinical databases: trial of celecoxib in ALS and trial of arimoclomol in ALS	There was a 39% reduction in risk of death during the study for men with each 1 mg/dl increase in sUA levels, this association was seen not in women

sUA, serum uric acid, 血清尿酸; ALS, amyotrophic lateral sclerosis, 肌萎缩侧索硬化症

功能下降更加明显[45]。亦有研究显示，血清尿酸水平与阿尔茨海默病无关联性[49-50]，甚至轻度认知损害和阿尔茨海默病患者血清尿酸水平高于正常对照者[46-47]。法国一项针对1578名社区老年人的为期12年余的随访研究显示，经校正性别、年龄、受教育程度、相关病史和药物应用史等多项混杂因素后，高血清尿酸人群罹患痴呆的风险是低血清尿酸人群的1.79倍；进一步排除应用非甾体抗炎药（NSAID）人群后，高血清尿酸人群罹患阿尔茨海默病的风险是低血清尿酸人群的2.31倍[47]。目前，血清尿酸水平与阿尔茨海默病患病风险的关系尚存争议，虽然多数病例对照研究显示阿尔茨海默病患者血清尿酸水平低于正常对照者，但仍有大规模前瞻性临床研究[47]和Meta分析[49]不支持这一结论，尚待更多大样本的前瞻性临床研究和作用机制研究以明确二者之间的关系。

4. 血清尿酸与肌萎缩侧索硬化症　多项临床研究显示，肌萎缩侧索硬化症患者血清尿酸水平低于正常对照者[51-53]，但是由于肌萎缩侧索硬化症较低的发病率和较短的自然病程，目前尚缺乏大规模队列研究支持血清尿酸与肌萎缩侧索硬化症发病风险相关（表6）。更多的临床研究显示，血清尿酸可能与肌萎缩侧索硬化症疾病进展和生存率有一定相关性[51,54-55,57]，例如，Atassi等[57]对20年间的11项肌萎缩侧索硬化症相关Ⅱ和Ⅲ期临床试验数据进行统计分析，结果显示，基线血清尿酸水平较高的肌萎缩侧索硬化症患者较基线血清尿酸水平较低患者疾病进展速度更缓慢、生存期更长。另一项回顾性研究也显示，经校正多项疾病严重程度相关指标[年龄、体重指数、发病时间、用力肺活量（FVC）、改良肌萎缩侧索硬化症功能评价量表（ALSFRS-R）评分、利鲁唑应用史]后，基线血清尿酸水平较高的患者生存率更高，但这种关系仅在男性患者中有统计学意义[56]。然而亦有研究不支持这一结论[52]。

二、血清尿酸在神经变性病中作用机制研究

上述流行病学调查和临床研究证实，血清尿酸水平对帕金森病、多系统萎缩、阿尔茨海默病和肌萎缩侧索硬化症等神经变性病的发生与发展是保护因素。尽管目前尚不清楚血清尿酸在这些疾病中的保护机制，但体外研究和动物实验显示，尿酸对神经元变性、氧化应激诱导的细胞死亡具有一定保护作用。Cipriani等[58]的体外研究显示，尿酸可以增强小鼠多巴胺能神经元对1-甲基-4-苯基吡啶离子（MPP^+）的抗凋亡能力，可能是受星形胶质细胞内尿酸水平所调控。Chen等[59]发现，与尿酸氧化酶基因过表达（*Uox* Tg）小鼠相比，尿酸氧化酶基因敲除（*Uox* KO）小鼠血清尿酸水平更高；早期予两组小鼠单侧纹状体内注射相同剂量多巴胺能神经元毒

性物质6-羟基多巴胺(6-OHDA),与正常对照者相比,*Uox* KO小鼠出现黑质多巴胺能神经元数目减少、纹状体多巴胺水平降低、旋转行为下降。此外,Du等[60]的体外研究显示,尿酸通过上调星形胶质细胞胞膜兴奋性氨基酸转运体(EAAT)水平以清除谷氨酸对神经元的毒性作用。此后,亦有研究显示,星形胶质细胞是通过核因子E2相关因子2(Nrf2)信号转导通路以增加谷胱甘肽(GSH)的合成与释放,从而介导血清尿酸对帕金森病细胞模型的神经保护作用[61]。体外研究[62]和动物实验[63]还显示,除星形胶质细胞的辅助作用外,血清尿酸还可以降低多巴胺能神经元内氧化应激产物[丙二醛(MDA)、8-羟基脱氧鸟苷(8-OHdG)]水平,增加抗氧化物质(谷胱甘肽)水平和超氧化物歧化酶(SOD)活性,从而减少6-OHDA诱导的神经毒性作用。Gong等[63]发现,可能与血清尿酸对糖原合成酶激酶-3β(GSK-3β)/丝氨酸/苏氨酸激酶(AKT)信号转导通路的调节相关,血清尿酸可以增强GSK-3β Ser9、AKT Ser473位点磷酸化以降低GSK-3β活性、增强AKT活性,进而发挥神经保护作用。Sheng等[64]还发现,尿酸可能通过抑制哺乳动物雷帕霉素靶蛋白(mTOR)/哺乳动物基因编码酵母自噬基因Atg1同源物(ULK1)信号转导通路以增强多巴胺能神经元自噬/溶酶体途径活性,减少*SNCA* A53T转基因小鼠脑组织α-突触核蛋白(α-Syn)聚集,延缓帕金森病进展。

三、小结

血清尿酸对帕金森病和肌萎缩侧索硬化症的发生、发展和预后均有一定的保护作用,但与多系统萎缩和阿尔茨海默病等神经变性病的关系尚未达成共识。普遍认为,帕金森病、多系统萎缩、阿尔茨海默病和肌萎缩侧索硬化症等神经变性病患者血清尿酸水平显著低于正常对照者,且这种相关性在男性患者中更加显著,但是关于血清尿酸水平与疾病进展的相关性尚无定论。尽管体外研究和动物实验已证实尿酸可以增强神经元抗氧化应激能力、自噬/溶酶体途径活性,但尚待更多作用机制研究和临床试验验证血清尿酸是否可以有效预防帕金森病及其他神经变性病的发生与发展。此外,对于高血清尿酸导致的痛风和心脑血管病高发生率,如何取得平衡也是尚待进一步探讨的问题。

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·小词典·

中英文对照名词词汇（五）

神经原纤维缠结 neurofibrillary tangles（NFTs）
神经源性肺水肿 neurogenic pulmonary edema（NPE）
剩余碱 base excess（BE）
事件相关电位 event-related potential（ERP）
视觉诱发电位 visual-evoked potential（VEP）
视野 field of view（FOV）
手足口病 hand-foot-month disease（HFMD）
数字减影血管造影术 digital subtraction angiography（DSA）
睡眠剥夺 sleep deprivation（SD）
丝裂原激活蛋白激酶 mitogen-activated protein kinase（MAPK）
随机对照试验 randomized controlled trial（RCT）
髓样细胞触发性受体2 triggering receptor expressed on myeloid cells 2（TREM2）
糖化血红蛋白 glycosylated hemoglobin（HbA1c）
糖原合成酶激酶-3β glycogen synthase kinase-3β（GSK-3β）
梯度回波序列 gradient echo sequence（GRE）
体重指数 body mass index（BMI）
天冬氨酸转氨酶 aspartate aminotransferase（AST）
同型半胱氨酸 homocysteine（Hcy）
统计参数图 statistical parametric mapping（SPM）
统一多系统萎缩评价量表 Unified Multiple System Atrophy Rating Scale（UMSARS）
统一帕金森病评价量表 Unified Parkinson's Disease Rating Scale（UPDRS）
^{18}F-脱氧葡萄糖 ^{18}F-fluoro-2-deoxy-D-glucose（^{18}F-FDG）
晚发性阿尔茨海默病 late-onset Alzheimer's disease（LOAD）
微管相关蛋白 microtubule-associated protein（MAP）
微小RNA microRNA（miRNA）
吸气峰压 peak inspiratory pressure（PIP）
吸入氧浓度 fraction of inspired oxygen（FiO_2）
小儿危重病例评分 Pediatric Critical Illness Score（PCIS）
信噪比 signal-to-noise ratio（SNR）