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Short communication

Is serum uric acid related to non-motor symptoms in de-novo Parkinson's disease patients?

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ABSTRACT

Background: Low serum uric acid (UA) has been consistently shown to be associated with increased risk of Parkinson's disease (PD), and to predict faster motor and cognitive decline in established PD. The aim of the present study is to evaluate the relationship between serum UA and non-motor symptoms (NMS) in de novo PD.
Methods: Serum UA was measured in consecutively recruited, early drug-naïve PD patients. Exclusion criteria were: treatment with UA modifying drugs; current smoking status; metabolic or cardiac morbidity. All patients completed the NMS Questionnaire (NMSQuest). The relationship between UA levels and NMSQuest domains was explored by logistic regression, subsequently adjusted for age, gender, disease duration (months since reported motor onset) UPDRS part III, H&Y scale, and MMSE. Regression analysis studied the overall relationship between UA levels and total NMS score, and was subsequently adjusted for age, gender, disease duration UPDRS part III, H&Y scale and MMSE.
Results: Eighty PD patients were recruited. At logistic regression, higher UA levels were related to lower involvement of Attention/Memory ($p = 0.004$), Cardiovascular (0.009) and Sleep ($p = 0.028$) domains of NMSQuest. UA levels showed a significant negative correlation with total NMSQuest score at regression analysis ($p = 0.001$; Adjusted R-squared $= 0.319$).
Discussion: The present study investigated, for the first time, the relationship between NMSQuest and UA in de novo PD. Lower UA was related to higher NMSQuest total score and in particular to Attention/Memory, Cardiovascular and Sleep domains. Thus, UA seems to be a major candidate to be a valuable biomarker of such early features of PD as NMS.

1. Introduction

Non-motor symptoms (NMS) of Parkinson's disease (PD) are widely diverse, and significantly affect quality of life [1,2]. It is known that some NMS may predate the diagnosis of PD by several years. In particular olfactory, gastrointestinal, sleep and mood disorders have been strongly related to the premotor phase of PD. Furthermore, there is increasing evidence that other NMS, such as autonomic, visual and cognitive dysfunctions, may be possible premotor markers [3]. Early involvement of brainstem nuclei and myenteric plexus could explain NMS onset in a premotor phase of PD, while motor symptoms would be determined by a caudorostral progression of pathological process [4,5]. Thus, early recognition of NMS may be useful to identify premotor phase of PD and the development of simple screening tools has notably improved NMS detection [1].

Besides clinical markers, also biological markers of PD have gained relevance in the recent years. With regard to this, low plasma uric acid (UA) has consistently been shown to be associated with increased risk of PD, and to predict faster motor and cognitive decline in established PD [6–9]. As it has been suggested that both

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oxidative damage and accumulation of un-sequestered iron play a role in the pathogenesis of PD, UA antioxidant and iron scavenger features could provide natural neuroprotection against PD [9,10]. Thus, UA seems to be a major candidate to be a valuable biomarker in the early stages of PD.

Although a relationship between uric acid levels and cognitive decline in PD has been demonstrated [7–9], up to date a possible link with the broader spectrum of NMS has not been explored. The aim of the present cross-sectional study is to investigate the relationship between serum UA and occurrence of NMS in de novo PD patients, in order to evaluate if UA levels could be useful as markers of early non-motor involvement in PD.

2. Methods

We enrolled de novo, drug-naive, patients with Parkinsonism consecutively referred to the Department of Neurosciences at the University "Federico II" of Naples, Italy between January 1, 2008 and June 30, 2009. The local ethical committee approved the study and all patients provided written informed consent.

Inclusion criteria were: presence of a parkinsonian syndrome according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (UKPDSBBDC) (bradykinesia plus one other sign, i.e., rigidity, resting tremor or postural instability); onset less than 2 years; no previous or current treatment with dopaminergic drugs [11]. Additional criteria for inclusion were lack of significant cerebral lesions on MRI or CT. Exclusion criteria were: diagnosis of secondary (such as vascular and drug-induced) or familial parkinsonism, diagnosis of atypical parkinsonism, namely, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBS), and dementia with Lewy bodies (LBD), according to current diagnostic criteria. Parkinsonism was diagnosed by movement-disorder specialists experienced in parkinsonian disorders. Patients were clinically re-evaluated 1 year later to assess the diagnosis of PD according to both exclusion and supportive criteria of the UKPDSBBDC for PD [11,12].

At baseline evaluation all patients completed the NMSQuest, a validated tool for detection of NMS. The NMSQuest consists of 30 questions with dichotomous (yes/no) answers and a total score, which ranges between 0 and 30, can be determined, with higher scores reflecting more NMS. Moreover, NMSQuest is currently divided into nine domains, each of which include 2–7 specific questions, and subsequently nine domain scores can be assessed [1]. Furthermore, expert physicians evaluated patients by means of Unified Parkinson's Disease Rating Scale (UPDRS) part III, Hoehn and Yahr scale (H&Y), and Mini Mental State Examination (MMSE), corrected for age and education.

At baseline, UA was determined in serum obtained from fasting blood by UA2 enzymatic method using ACN700 reagent kit and COBAS® c501 analyzer (Roche Diagnostic). Moreover, we recorded factors possibly modifying UA activity, such as comorbidities, drugs, smoking status (classified as current, former, or never smoking), alcohol intake (mg/day), or height and weight by calculation of body mass index (BMI). Exclusion criteria were: treatment with diuretics, non-steroidal anti-inflammatory drugs or other UA modifying agents; current smoking status; metabolic or cardiac morbidity (i.e. gout or increased blood pressure); to be over (BMI $>$ 25) or under-weight (BMI $<$ 19) [8].

The relationship between UA levels and domain involvement of NMSQuest was explored by means of logistic regression, using the measured UA value as explanatory variable. NMSQuest domains in the logistic regression model were treated as binary endpoints (0: domain values = 0; 1: domain values $\geq$ 1). Subsequently, an adjusted model was run including age, gender, disease duration (months since reported motor onset), UPDRS part III, H&Y scale, and MMSE. Moreover, regression analysis was carried out to study the overall relationship between UA levels and the total NMS score. Subsequently, an adjusted model was run including age, gender, disease duration (months since reported motor onset), UPDRS part III, H&Y scale, and MMSE. All the analyses were performed using STATA 12.0. Results were considered statistically significant if $p < 0.05$.

3. Results

One hundred and thirty-six de novo patients were considered to participate in the study. Fifty-six patients were excluded because of concomitant therapies or morbidities (15/56, 8 use of antihypertensive drugs, 6 use of non-steroidal anti-inflammatory, 1 gout), atypical parkinsonism (11/56, 5 PSP, 3 LBD, 2 MSA and 1 CBD at one-year follow-up visit), significant cerebral lesions on MRI (1/56), overweight (7/56) and smoking status (22/56). Demographics of 80 recruited patients are shown in Table 1. Among recruited patients, no present concomitant treatments or morbidities were reported.

At basal assessment by means of logistic regression, higher UA levels were related to lower impairment of Attention/Memory ($p = 0.001$; OR = 0.45), Depression/Anxiety ($p = 0.027$; OR = 0.59) and Cardiovascular ($p = 0.001$; OR = 0.29) domains of NMSQuest (Table 1). When the latter model was adjusted for age, gender, disease duration, UPDRS part III, H&Y scale, and MMSE, Attention/Memory ($p = 0.004$; OR = 0.23) and Cardiovascular ($p = 0.009$; OR = 0.11) domains were confirmed to be related to UA levels, and influenced by age ($p = 0.043$ with OR = 1.14, and $p = 0.032$ with OR = 0.83, respectively). On the other hand, Depression/Anxiety domain was not confirmed to be related to UA levels, while Sleep domain resulted associated with UA levels ($p = 0.028$; OR = 0.48). No significant relation was found with Digestive, Urinary, Hallucinations/Delusions, Sexual, and Miscellany domain scores at basal models, and after adjusted analysis.

UA levels showed a significant negative correlation with total NMSQuest score both at basal regression analysis ($p = 0.001$; R-squared = 0.148; Fig. 1), and with the adjusted model (age, gender,

Table 1
Demographics, UA values, clinical features and NMSQuest of the population.

Men/woman					51/29
Age years ± SD (range)					59.3 ± 7.9 (42–74)
UA levels, mg/dL ± SD (range)					4.9 ± 1.1 (2.9–7.0)
Onset, months ± SD (range)					13.2 ± 5.7 (6–24)
UPDRS part III ± SD (range)					15.25 ± 7.7 (3–40)
H&Y (range)					2 (1.0–2.5)
MMSEc ± SD (range)					27.3 ± 1.6 (24–30)
NMSQuest domains:	Domain prevalence (%)	*p* Value	Adj. *p* value	Adj. O.R.	95% Conf. Int.
1 Digestive	38 (47.5)	0.937	0.198	0.667	0.360–1.235
2 Urinary	23 (28.7)	0.353	0.269	1.616	0.690–3.781
3 Attention and memory	40 (50.0)	0.001*	0.004*	0.227	0.082–0.631
4 Hallucinations/delusions	1 (1.3)	0.815	0.913	1.230	0.216–6.990
5 Depression/anxiety	55 (68.8)	0.027*	0.077	0.474	0.207–1.084
6 Sexual	9 (11.3)	0.195	0.641	0.448	0.015–13.090
7 Cardiovascular	15 (18.8)	0.001*	0.009*	0.093	0.015–0.550
8 Sleep	44 (55.0)	0.131	0.028*	0.478	0.248–0.924
9 Miscellany	25 (31.3)	0.170	0.509	0.769	0.352–1.677
NMSQuest total score ± SD (range)	4 ± 3 (0–12)	0.001*	<0.001*		

p Values from logistic regression and regression analysis are shown (basal analysis and adjusted for age, gender, disease duration, UPDRS part III, H&Y and MMSEc).
UA: uric acid; NMSQuest: non-motor symptoms questionnaire; UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr scale; MMSEc: Mini Mental Status Examination corrected for age and education; NMS: non motor symptoms; Adj. O.R.: adjusted odds ratio; Conf. Int.: confidence interval; SD: standard deviation; *statistically significant relationships with UA levels.