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ORIGINAL COMMUNICATION

Clinical determinants of primary and secondary fatigue in patients with Parkinson's disease

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Abstract Clinical and psychosocial factors associated separately with primary and secondary fatigue in Parkinson's disease (PD) patients have not been thoroughly studied before. The aim of our study was to assess factors associated with different fatigue domains in groups with primary and secondary fatigue in PD separately. We divided 165 non-demented PD patients according to the absence/presence of depression, anxiety and excessive somnolence into groups with primary fatigue ($N = 63$) and with secondary fatigue ($N = 102$). Fatigue domains examined using the multidimensional fatigue inventory were associated through multiple linear regression analyses for each group separately with sociodemographic data, disease duration, functional status as assessed by the Unified Parkinson's Disease Rating Scale, treatment, depression, anxiety, excessive somnolence and sleep quality. Out of the assessed non-motor symptoms, fatigue was the most frequent (77.6 %). The prevalence of fatigue in the secondary fatigue group was significantly higher than in the primary fatigue group. Both fatigue groups differed significantly in factors associated with different fatigue domains. Functional status or other disease-related factors were not associated with primary fatigue. In the secondary fatigue group, we found associations between some fatigue domains and functional status, older age, male gender and higher anxiety scores. To our knowledge, this is the first study to separately describe clinical determinants and psychosocial factors associated with different fatigue domains in primary and secondary fatigue in PD, underlining the importance of distinguishing primary and secondary fatigue in future PD studies and clinical practice.

Keywords Parkinson's disease · Primary fatigue · Secondary fatigue · Depression · Anxiety · Excessive daytime somnolence

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Introduction

Fatigue is one of the most common non-motor symptoms associated with Parkinson's disease (PD), with a prevalence of up to 70 % among PD patients [1]. Fatigue was found to be the most frequent of all non-motor symptoms assessed in 1,072 consecutive patients examined in the PRIAMO study [2]. Fatigue also has a significant impact on quality of life [3, 4]. In one of the first studies on fatigue in PD, 15–33 % of patients rated it as their most disabling symptom, and more than half rated fatigue among their three worst symptoms [5]. In a recent study of veterans with PD, patients rated fatigue and pain as having the greatest impact on their daily activities [6]. In a study

which examined treatment expectations of PD patients, fatigue was found to be the third most relevant problem [7]. The first articles highlighting the importance of fatigue in PD were published only in 1993 [5, 8]; however, fatigue has received more recognition only in the last decade. Despite its high prevalence and importance, fatigue in PD remains an under-recognized problem in routine clinical practice [9].

There is currently no universally accepted definition of fatigue. PD patients complaining about fatigue describe it as being different from the fatigue they experienced before developing PD [10]. Fatigue in PD can be divided into "peripheral fatigue", which refers to an objectively measurable process in which a muscle loses strength after repeated contractions, and "central fatigue", which refers to a feeling-state, a perception or experience that is yet not objectively measurable [1]. Central fatigue, which is the main focus of this article, can be further divided into physical and mental fatigue.

While more is known about the epidemiology and importance of fatigue in PD, little is known about its etiology, pathogenesis and possible management. One reason is the probable heterogeneity of biological, clinical and psychosocial factors leading to the presence of fatigue. In previous studies, disease severity, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), was associated with fatigue only in some studies [11, 12], while others found no such association [13, 14]. A significant association between disease duration and fatigue has not yet been proven. Indeed, fatigue is present in all PD stages and was previously found in one-third of newly diagnosed untreated, non-demented and non-depressed PD patients [15]. Most previously published articles found a strong link between fatigue and the presence of mood disorders, especially depression [11, 13, 14] and excessive daytime sleepiness (EDS) [16, 17]. Here is some overlap, since fatigue is one of the DSM-IV diagnostic criteria for depression and anxiety, making interpretation of fatigue in the presence of such problems a major challenge. A concept of primary and secondary fatigue has been proposed, in which fatigue in the presence of mood disorders or EDS is qualified as 'secondary fatigue' and fatigue present in the absence of mood disorders and EDS is addressed as 'primary fatigue' [18]. This concept was later adopted in some other studies on fatigue in PD [19, 20]. To the best of our knowledge, studies on fatigue published so far have been either epidemiological or have studied clinical determinants associated with fatigue in non-separated PD populations. Thus, the aim of our study was to identify some clinical and psychosocial factors associated with different fatigue domains separately in primary and secondary fatigue in patients with Parkinson's disease.

Methods

Patients

Patients were recruited from 25 neurology outpatient clinics in Eastern Slovakia between June 2011 and August 2012. All patients were diagnosed according to the United Kingdom PD Society Brain Bank Clinical Criteria [21], and their mental abilities were assessed with the Mini–Mental State Examination (MMSE) [22]. A total of 205 patients initially agreed to participate in the study. Patients with MMSE scores lower than 24 ($N = 18$), forms of Parkinsonism other than idiopathic Parkinson's disease, ($N = 8$) and those who initially agreed to participate and filled in the questionnaire but did not come for the oral interview ($N = 14$) were excluded. A total of 165 non-demented patients (80.5 %) remained for analysis.

Data collection

An invitation letter, written informed consent, and questionnaires comprising questions on sociodemographic background, medical history, current medication and self-report questionnaires (described below) were sent one week before the interview by postal mail to patients diagnosed with PD. All self-report questionnaires used in our study have good internal consistency, with Cronbach's alpha coefficients over 0.8. They have been previously used in PD populations, and recommendations for their use in PD have been published by the Movement Disorder Society [23–26]. After one week, all patients were interviewed by a trained interviewer on relevant issues that were not part of the questionnaire, and their cognitive functioning was assessed using the MMSE [22]. After this structured interview, a single neurologist specialized in Movement Disorders assessed each patient's disease severity using the UPDRS [27], including Hoehn and Yahr staging [28]. Information on PD subtype (tremor dominant versus akinetic-rigid) and the presence of postural instability (>2 steps on pull test) were recorded. Patients unable to fill in the questionnaires themselves due to motor impairment answered the questions during the oral interview. The study was approved by the Local Ethics Committee. All patients participated voluntarily and provided written informed consent prior to the interview.

Measures

Sociodemographic data, disease duration and medication

Demographic data including age, gender and education were obtained from the structured interview. Education level was classified as: low (apprenticeship or primary

school only), middle (finished secondary school) or high (university). Information on disease duration, antiparkinsonian medication, and other treatment was also obtained during the interview. The levodopa equivalent daily dosage (LEDD) was counted using the formula published by Tomlinson et al. [29].

Disease severity

Motor symptoms were rated in ON state by the UPDRS part III. The UPDRS is a four-subscale combined scale (mental state, activities of daily living, motor examination, and complications) [27]. Scores were obtained via a semi-structured interview and physical examination. The disease stage was assessed using the Hoehn and Yahr scale (HY), which is applied to gauge the course of the disease over time [28].

Anxiety and depression

The Beck depression inventory-II (BDI-II) is a self-administered, 21-item scale assessing depression [30]. Each answer was scored as 0–3. Cutoff values used are 0–13: normal range; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression [30]. Higher total scores indicate more severe depressive symptoms.

The Hospital Anxiety and Depression Scale (HADS) is a self-administered scale with two subscales capable of evaluating anxiety (HADS-A) and depression (HADS-D) [31]. This 14-item scale consists of seven items assessing anxiety and seven items assessing depression, with scoring from 0 (no problem) to 3 (extreme problem). Cut-off values applied are: $\leq$7 on each subscale is considered unimpaired; 8–10 on each subscale: possibly impaired; and $\geq$11 on each subscale: probably impaired [31].

Sleep measures

Excessive daytime somnolence (EDS) was evaluated with the Epworth Sleepiness Scale (ESS) [32]. ESS measures dozing behavior in eight different situations. This self-assessment questionnaire asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3. The total ESS score is the sum of all the responses and ranges from 0 to 24; higher scores reflect greater sleep propensity. Consistent with a number of previous investigations, a score of 10 as the cut-off point was used for normal, while scores above this imply pathological sleepiness [26].

The Pittsburgh Sleep Quality Index (PSQI) [33] was used to assess nighttime sleeping problems. The PSQI assesses global sleep quality and disturbances in sleep patterns during the previous month in seven components. After recoding, each component has possible scores of 0–3, where 3 indicates the negative extreme. The global PSQI score is the sum of all component scores (range 0–21); a score of $\geq$5 indicates a poor sleeper.

Fatigue

Fatigue was assessed with the 20-item self-report multidimensional fatigue inventory (MFI) [34], which measures five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each subscale contains four items, which are scored on a five-point Likert-scale. The negative formulated items must be recoded before totaling the scores. Scores range from 4 (absence of fatigue) to 20 (maximum fatigue) for each subscale. Its reliability and structural validity in patients with idiopathic PD has been recently published [35]. We used a uniform cutoff score of $\geq$13 in each MFI domain to define the presence of fatigue. This was in accordance with a previously published MFI general fatigue domain cutoff score of $\geq$13 for defining severe fatigue in chronic fatigue syndrome [36].

Statistical analysis

Statistical analyses were performed using the PASW SPSS version 18.0 statistical software for Windows (SPSS Inc, Chicago, IL, USA). Patients were divided into two groups. The group with "primary fatigue" was characterized by the absence of depression (BDI-II $\leq$ 13), anxiety (HADS-A $<$ 11) and EDS (ESS $\leq$ 10). The group with "secondary fatigue" was characterized by the presence of depression (BDI $>$ 13), anxiety (HADS-A $\geq$ 11) or EDS (ESS $>$ 10). First, we described the demographic and clinical characteristics of our studied groups. Significant differences between the group characteristics were counted by independent sample *t* tests and chi-square tests. Then, the relationships between age, gender, education level, disease duration, functional status, LEDD, depression, anxiety, EDS and sleep quality were analyzed with multiple linear regression analysis, using all separate fatigue domains as dependent variables in both groups of patients separately.

Results

The average age of the total PD sample was 69.7 $\pm$ 8.5 years; average disease duration was 6.9 $\pm$ 4.8 (range 0–30 years), and the average Hoehn and Yahr stage was 2.4 $\pm$ 0.9. A total of 128 patients (77.6 % of the whole sample) were fatigued in at least one MFI domain. After dividing the sample, 102 patients remained in the group with a mood disorder or EDS present ("secondary fatigue"

group) and 63 remained in the group with no mood disorder and EDS ("primary fatigue" group). The two fatigue groups did not differ significantly in age, gender distribution, education level, PD subtype or treatment. The secondary fatigue group had longer disease duration (7.5 vs. 6 years), a higher HY stage (2.6 vs. 2.1), higher scores in all UPDRS subscales, higher fatigue scores, and a higher prevalence of fatigue in all MFI domains. Fatigue associated with physical aspects was more frequent than fatigue associated with mental aspects in both groups. Baseline characteristics of the study groups can be found in Table 1.

Determinants of fatigue in the secondary fatigue group

Older age was strongly associated with higher reduced motivation and mental fatigue scores. Male gender was related to higher reduced activity and mental fatigue. UPDRS-III was significantly associated with more fatigue in all domains except mental fatigue, and anxiety was associated with reduced motivation. Depression and sleep problems were not associated with any MFI domain in this group.

Determinants of fatigue in the primary fatigue group

The only variable significantly associated with MFI reduced activity and mental fatigue domains was BDI-II, even though in the normality range. A similar relation was also found between HADS-D and fatigue in the normality range when the sample was divided according to HADS-D ($\leq$10 pts) instead of BDI (results not shown). UPDRS-III was not associated with any of the MFI domains in this group. There were no determinants related to general fatigue, physical fatigue and reduced motivation in the primary fatigue group Table 2.

Discussion

To the best of our knowledge, this is the first study to separately describe clinical determinants and psychosocial factors associated with different fatigue domains in primary and secondary fatigue in Parkinson's disease. Out of the measured non-motor symptoms, fatigue present in at least one of the MFI domains was the most frequent non-motor symptom, found in 77.6 % of our study population. We found the prevalence of fatigue to be higher than is described in previous studies [15–17], which mostly used uni-dimensional fatigue rating scales. MFI scores and the prevalence of fatigue are significantly higher in the physical domains of fatigue in both groups than in the mental domains, which could be explained by the stronger impact of core motor features of PD on the physical abilities of patients [11]. Both primary and secondary fatigue differed significantly in baseline characteristics and factors associated with different fatigue domains.

Older age was found to be significantly associated with reduced motivation and mental fatigue in the secondary fatigue group, but not in the primary. Fatigue is a common problem in older adults and has been suggested as being a part of the normal aging process [37]. The higher prevalence of fatigue in PD, however, cannot be explained only by older age. In contrast with our finding, most previous studies found no association between older age and fatigue in PD [11, 17]. A recent study on fatigue in early PD found a significant correlation between higher fatigue scores and older age, but when linear regression analysis was applied, only depression and UPDRS activities of daily living subscale remained significant in their population [38]. In contrast with some previous studies, where higher prevalence of fatigue was found in women [39], we found a significant association of MFI domains mental fatigue and reduced motivation with male gender, but only in the secondary fatigue group.

In line with previous findings, disease duration was not related to any of the fatigue domains [11, 17]. There were no differences in antiparkinsonian medication between the primary and secondary fatigue groups. Although some previous studies have suggested a potential effect of dopaminergic treatment on at least some aspects of fatigue [15, 40–42], we did not find any association between LEDD and any of the fatigue domains in either primary or secondary fatigue.

Functional status, measured by UPDRS-III, was significantly worse in the secondary fatigue group compared with the primary. It was also significantly associated with all fatigue domains except mental fatigue in the secondary fatigue group, but not in the primary fatigue group. Previous studies have found conflicting results regarding the association of functional status with fatigue in PD [11–14]. One reason for this incongruity may lie in the selection of different patient samples.

Depressive symptoms and excessive somnolence are significantly associated with more fatigue in PD [1, 11, 14], and the prevalence of fatigue is significantly higher in this population of patients, as found in our study. One important finding is that with patients in the secondary fatigue group, the severity of depression or sleepiness did not play a further role in explaining any of the fatigue domains in that group. Higher anxiety scores contributed to the explanation of reduced motivation in the secondary fatigue group.

Of interest is the fact that BDI-II, even though in the normal range, is the only factor associated with reduced activity and mental fatigue in the primary fatigue group. When we divided the study sample according to HADS-D,

Table 1 Baseline characteristics of the study population ($N = 165$)

	Secondary fatigue group	Primary fatigue group	Significant difference between primary and secondary fatigue groups
Number of patients	102	63	
Gender (male/female)	51/51	35/28	p = ns
Age	70.2 ± 8.4	68.6 ± 8.8	p = ns
Disease duration	7.5 ± 5.3	6.0 ± 3.7	**$p = 0.04$**
Education level			
Low	40 (39 %)	29 (46 %)	p = ns
Middle	42 (41 %)	23 (37 %)	
High	20 (20 %)	11 (17 %)	
Hoehn and Yahr stage	2.6 ± 0.9	2.1 ± 0.8	**$p = 0.002$**
H&Y ≤ 2	44 (43 %)	46 (73 %)	
H&Y > 2	58 (57 %)	17 (27 %)	
UPDRS_I	2.0 ± 2.1	0.6 ± 1.1	**$p < 0.001$**
UPDRS_II	14.9 ± 7.7	8.1 ± 5.5	**$p < 0.001$**
UPDRS_III	33.2 ± 13.7	25.1 ± 12.0	**$p < 0.001$**
Motor fluctuations	58 (57 %)	26 (41 %)	**$p < 0.05$**
PD subtype			
Tremor dominant	21 (20 %)	17 (27 %)	p = ns
Akinetic-rigid	82 (80 %)	46 (73 %)	
Postural instability (>2 steps on pull test)	65 (63 %)	21 (33 %)	**$p < 0.001$**
BDI	21.2 ± 9.0	8.4 ± 3.5	**$p < 0.001$**
>13 pts	94 (91 %)	0	
HADS depression	8.0 ± 3.4	3.9 ± 2.5	**$p < 0.001$**
≥11 pts	26 (26 %)	0	
HADS anxiety	8.2 ± 4.0	4.1 ± 2.9	**$p < 0.001$**
≥11 pts	28 (28 %)	0	
ESS	8.4 ± 4.7	5.1 ± 2.6	**$p < 0.001$**
>10 pts	38 (37 %)	0	
PSQI	8.9 ± 4.1	6.0 ± 3.4	**$p < 0.001$**
≥5 pts	86 (84 %)	40 (64 %)	
MFI general fatigue	15.2 ± 3.0	11.4 ± 3.6	
≥13 pts	83 (81 %)	20 (32 %)	**$p < 0.001$**
MFI physical fatigue	15.0 ± 3.4	11.6 ± 3.6	
≥13 pts	77 (75 %)	25 (40 %)	**$p < 0.001$**
MFI reduced activity	13.4 ± 3.5	10.6 ± 4.1	
≥13	57 (55 %)	18 (29 %)	**$p < 0.001$**
MFI reduced motivation	10.7 ± 3.4	8.3 ± 3.1	
≥13	30 (29 %)	7 (11 %)	**$p < 0.001$**
MFI mental fatigue	11.7 ± 3.6	8.6 ± 3.0	
≥13	37 (36 %)	4 (7 %)	**$p < 0.001$**
LEDD (mg/day)	569 (0–2972)	468 (0–1,525)	p = ns
L-Dopa	71 (69 %)	40 (63 %)	p = ns
L-Dopa + COMT inhibitor	41 (40 %)	19 (30 %)	p = ns
Dopamine agonist	65 (63 %)	45 (71 %)	p = ns
L-Dopa + dopamine agonist	43 (42 %)	27 (43 %)	p = ns
No dopaminergic treatment	10 (10 %)	6 (9 %)	p = ns
Rasagiline	37 (36 %)	21 (33 %)	p = ns
Amantadine	23 (22 %)	11 (18 %)	p = ns

UDPRS unified Parkinson's disease rating scale, *BDI-II* Beck depression inventory-II, *HADS* hospital anxiety and depression scale, *ESS* Epsworth sleepiness scale, *PSQI* Pittsburgh sleep quality index, *MFI* multidimensional fatigue inventory, *LEDD* total levodopa equivalent daily dosage, *ns* non-significant

Bold values indicate the significance $p < 0.05$

Table 2 Determinants associated with the MFI fatigue domains in the divided PD sample

	MFI									
	Secondary fatigue group					Primary fatigue group				
	GenF	PhyF	RedA	RedM	MentF	GenF	PhyF	RedA	RedM	MentF
Age	0.14	0.15	0.16	0.34***	0.29**	−0.25	−0.18	−0.03	0.11	−0.01
Male gender	0.00	0.00	0.25*	0.09	0.22*	−0.05	−0.21	−0.02	0.08	−0.01
Higher education level	−0.04	−0.09	−0.11	−0.13	−0.16	0.02	−0.01	0.02	−0.18	−0.10
Disease duration	−0.20	0.05	0.08	−0.05	0.04	−0.00	0.10	0.15	0.00	−0.03
UPDRS III	0.28*	0.25*	0.28**	0.19*	0.05	0.20	0.13	0.12	0.03	−0.03
LEDD (mg/day)	0.04	0.06	0.09	−0.17	−0.10	−0.20	−0.03	−0.07	−0.02	−0.13
ESS	0.12	0.04	0.09	0.03	0.07	0.22	0.11	−0.23	−0.18	−0.05
PSQI	0.20	0.08	0.08	0.15	0.10	0.13	0.14	0.10	0.12	0.22
BDI	0.04	−0.01	0.08	0.13	0.19	0.07	0.09	0.32*	0.12	0.39*
HADS-A	0.00	0.04	−0.00	0.22*	0.20	0.23	−0.00	0.03	−0.06	−0.07
R square	0.21	0.13	0.24	0.39	0.29	0.29	0.17	0.20	0.09	0.25
Adj. *R* square	0.12	0.03	0.15	0.32	0.21	0.15	0.02	0.05	−0.09	0.10

MFI multidimensional fatigue inventory, *GenF* general fatigue, *PhyF* physical fatigue, *RedA* reduced activity, *RedM* reduced motivation, *MentF* mental fatigue, *UDPRS III* unified Parkinson's disease rating scale, *LEDD* total L-dopa equivalent daily dosage, *ESS* Epsworth sleepiness scale, *PSQI* Pittsburgh sleep quality index, *BDI-II* Beck depression inventory-II, *HADS-A* hospital anxiety and depression scale-anxiety subscale

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

a correlation of fatigue with increased scores of HADS-D in the normal range were also found. A study of fatigue in levodopa-naïve PD patients published by Schiffito et al. [15] found a similar correlation of fatigue with Hamilton Depression Scale scores in the normal range. Primary fatigue in our study was unrelated to functional status, LEDD or other disease-related factors, pointing to a potentially different mechanism underlying fatigue in this group of patients. This is supported by the results of a previously published ELLDOPA trial, where the [123I]-β-CIT SPECT striatal dopamine transporter density was not related to fatigue [15]. On the other hand, a PET study in primary fatigue published by Pavese et al. [20] found an association between fatigue and a relative serotonergic denervation in the basal ganglia and associated limbic circuits and F-dopa uptake reduction in the insular region, but not in basal ganglia, thus suggesting a serotonin-related basis for fatigue in PD. Although selective serotonin reuptake inhibitors (SSRI) are commonly used in the treatment of chronic fatigue, clinical experience reveals that they are not very useful in treating fatigue in PD [1]. Pavese et al. [20] further discuss that due to an effective loss of SERT protein found in their study, SSRI are less likely to be efficacious in PD patients with primary fatigue. A previous observational study by Martinez-Martin et al. [43] found a lower prevalence of fatigue in patients treated with amantadine, which is often used to treat fatigue in multiple sclerosis as well. In our study we did not find an association between amantadine intake and any of the fatigue domains in either the primary or secondary fatigue groups. The only report of successful treatment of fatigue in PD thus far is a double-blind randomized placebo-controlled trial of 36 non-depressed PD patients with methylphenidate 10 mg t.i.d. [44]. This study is also noted in the report of Quality Standards Subcommittee of the American Academy of Neurology on the treatment of non-motor symptoms of PD as the only publication showing improvement of fatigue in PD (evidence level C) [45]. However, due to the stimulant effects of methylphenidate, its use, especially in elderly PD patients with cardiovascular problems, is relatively contraindicated.

Strengths and limitations

To the best of our knowledge, this is the first study which evaluated clinical determinants of primary and secondary fatigue domains in PD patients separately. Using a multidimensional fatigue scale with good psychometric qualities in PD patients enabled us to better explore associations of studied variables with different aspects of fatigue in PD. There were some limitations in this study, however. The concept of primary and secondary fatigue in PD needs further validation. Another limitation of our study is that anxiety, depression and excessive somnolence were evaluated by means of self-report questionnaires only. Our study sample consisted of more motivated patients who agreed to participate in the study and who were able to

attend the examination. Also, the cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables.

Implications for future studies and clinical practice

As found in our study, primary and secondary fatigue consist of distinct samples of PD patients and are determined by different clinical and psychosocial factors. Future studies investigating fatigue should therefore be conducted separately in primary and secondary fatigue groups. Primary fatigue in our study sample did not correlate with disease severity or other disease-related factors in any of the domains, indicating a possibly different underlying mechanism.

In clinical practice, fatigue is one of the most common non-motor symptoms of PD leading to a decreased quality of life. In the secondary fatigue group, efforts should be taken to optimally treat motor symptoms of the disease and to identify and properly manage depression, anxiety and EDS associated with PD, since at least some patients with secondary fatigue might benefit from these measures. So far little is known about the pathophysiology underlying primary fatigue in PD, and although some evidence exists for using methylphenidate in the treatment of primary fatigue in PD, due to its stimulant effects it is useful only in PD patients without cardiovascular problems. Further research on the etiology and pathophysiology of primary fatigue in PD should be encouraged to reveal its underlying mechanism and enable management of this condition.

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Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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