Original research article

The relation between plasma $\alpha$-synuclein level and clinical symptoms or signs of Parkinson's disease

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ABSTRACT

Introduction: Parkinson disease (PD) is the common neurodegenerative disease. $\alpha$-Synuclein (ASN), main aggregating protein in neural cells of CNS in PD, was found in peripheral fluids. Testing ASN in plasma is potential test for diagnose PD, but previous studies are controversial. The aim of this study was to investigate if plasma ASN level may be a valuable biomarker, is the level of plasma ASN concentration different in various motor subtypes of diseases, is there a relation between the level of plasma ASN and the severity of motor symptoms.

Methods: Patients with PD hospitalized in Neurology Department, Medical College were performed sequencing the 8th and 9th exon of GBA gene. Next plasma ASN level was tested in 58 patients with sequenced GBA gene and in 38 healthy volunteers (HV), matched by the age (respectively 68.43 vs. 64.57 years of age) and sex (female %, respectively: 43.10 vs.44.74). Patients were assessed with the scales: UPDRS (II, III, IV), Hoehn–Yahr (HY) and qualified to PIGD or TD subtype. For homogeneity of the group patients with GBA mutation were excluded from the analysis.

Results: The ASN level did not differ between patients and HV (respectively: 4.53 vs. 3.73 ng/ml) and between patients with different subtypes. There was inverse correlation between ASN and HY in PIGD subtype.

Conclusions: Plasma ASN level is not valuable marker of the disease. It does not differ in subtypes of the disease. There is relation between plasma ASN level and the severity of the disease in PIGD subtype.

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1. Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease characterized by a wide range of clinical features. Because of heterogeneous motor manifestations of early PD, some authors suggest three subtypes of the disease: postural instability and gait difficulty (PIGD), tremor dominant (TD) and with mixed symptoms (MPD) [1]. PIGD is associated with worse prognosis, poorer response to treatment, greater risk of dementia and higher prevalence of autonomic disturbances [2]. PD patients differ also in presence and intensity of non-motor symptoms. The most common of them are depression and cognitive impairment. Parkinson’s disease dementia (PDD) is the next clinical entity of PD spectrum diseases [3].

The pathogenesis of PD is associated with aggregation of pathologically conformed proteins. The main aggregating protein in PD is α-synuclein (ASN) [4]. ASN has many physiological functions in central nervous system (CNS). In vivo and in vitro experiments have demonstrated that ASN is released from the cells to the peripheral fluids [5,6]. This was the trigger to search ASN as the biomarker of PD. Finding the objective marker for PD is very important because making an accurate diagnosis of PD is difficult, especially in early stages of the disease. Even 15–25% of patients with parkinsonian symptoms and signs do not have correct diagnosis [7].

The level of ASN in PD patients was investigated in blood [6,8–21] and cerebrospinal fluid (CSF) [22,23], but the results of these studies are controversial. The total plasma ASN in PD patients was found to be higher [9,15], lower [13,16], or similar to the control group [8,11,12,17,24]. Other forms of ASN, such as oligomers [10] or phosphorylated ASN [11–13] were measured also, but the result were also inconclusive. The reasons for that could be associated with different origin of ASN in plasma. Some amount of ASN can originate from erythrocytes and platelets [20]. Min Shi et al. measured the only exosomal ASN, and found that this form of ASN, originated from CNS, is significantly higher in PD patients than in healthy controls [19]. In other study analyzing the ratio of ASN oligomers to total erythrocytes’ proteins, they explored that it is higher in PD patients than in healthy controls [14].

However there are only a few studies analysing the relation between ASN level in plasma and motor subtypes of PD (PIGD, TD, MPD), cognitive impairment and the presence of other non-motor symptoms [8].

Heterozygous carrier status of glucocerebrosidase (GBA) mutation is thought nowadays to be the most important genetic risk factor for idiopathic PD [25]. The relation between ASN and GBA on the cellular and molecular level has been proven [26]. It is connected with more intensive neurodegenerative process by forming toxic forms of ASN, which influences clinical picture of PD [27]. There are no publications concerning the relation between the plasma ASN concentration and GBA mutation in PD. However the level of plasma ASN oligomers is higher in patients with GD and some other lysosomal diseases than in healthy volunteers. Interestingly is the fact that there was no difference of plasma ASN oligomers level between healthy volunteers and patients with GD who were treated with enzyme replacement therapy (ERT) unlike GD patients without ERT. Moreover the authors mentioned that carriers of GBA mutation with PD had higher level of plasma ASN oligomers than healthy volunteers, but the data were not yet published [18]. In other publication they showed that the relation of dimers/monomers originated from erythrocytes in patients with GD is higher than in healthy volunteers. Dimerisation is restrictive stage of ASN oligomerisation [28]. And finally in the last study they proved reverse correlation between the level of plasma ASN oligomers and the activity of GBA in leukocytes of GD patients [29].

The aim of the study was to evaluate plasma ASN level as a valuable biomarker of PD, and to answer the questions of whether the level of plasma ASN concentration is different in various motor subtypes of diseases (PIGD, TD, MPD) and is there a relation between the level of plasma ASN and if there is a relation between the level of plasma ASN and cognitive impairment or depressive symptoms. Additional aim was to analyze the relation of plasma ASN level between GBA mutation carriers and non-carriers with PD.

2. Material and methods

The investigations were carried out on patients diagnosed with PD, hospitalized at the Subdivision of Movement Disorders in Clinical Department of Neurology, University Hospital, etc. in years 2007–2014.

All patients were physically examined by a neurologist and underwent head MR to exclude vascular disease which could cause the Parkinsonism. The actual severity of motor symptoms and the stage of the disease in PD patients group were assessed with UPDRS part II, III and IV as well as Hoehn–Yahr (HY) Scale. Jankovic method was used to classify patient to different motor subtypes of disease (PIGD, TD, MPD) based on UPDRS, part II and III [1]. The Hamilton Depression Rating Scale (HDRS) and Miniminal State Examination (MMSE) were used to make the screening for depressive symptoms and cognitive impairment respectively. The blood samples were taken from all of the patients for sequencing the 8th and 9th GBA gene exon with the method preventing amplification of GBA pseudogene, which was the subject of previous publication [30].

Healthy volunteers were invited to the study as the control group (CG). They were selected on the basis of gender and age to match the plasma ASN evaluation group. The subjects of CG group were unrelated members of the patients’ families, their minders as well as persons accompanying the patients. They were examined physically by neurologist, than they were assessed with screening tests for cognitive impairment and depressive symptoms. In the CG, there were persons without neurological disease and severe systemic illness. 5 ml of blood was collected from all participants to test the level of plasma ASN by ELISA. All subjects gave their written informed consent. The study was approved by Bioethics Committee of Medical College, etc. (KBET/106/B/2013, date 28.11.2013).

Inclusion criteria for PD patients:

- Parkinson’s disease diagnosed according to Q3BB criteria;
- age above 40 years;
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