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Original article

Amino acid supplementation in L-dopa treated Parkinson's disease patients

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SUMMARY

Background: The correlation between Parkinson disease and malnutrition is well established, however a protein-restricted diet is usually prescribed because of potentially negative interactions between dietary amino acids and L-dopa pharmacokinetics. This strategy could increase the risk of further nutritional deficits.

Methods: A monocentric, prospective, randomized, double-blind pilot study was performed on two groups of Parkinson-affected, protein-restricted, patients: Intervention (n = 7; amino acid supplementation twice daily) and Placebo (n = 7; placebo supplementation twice daily). At enrolment, after 3- and 6-month supplementation, neurological evaluations (UPDRS III, Hoenh–Yahr scale, L-dopa equivalent dose assessment) were performed and blood sample was collected to define insulin sensitivity (QUICKI index) and oxidative stress (oxidized and reduced glutathione). Repeated measure ANCOVA was applied to define time effect and time × treatment interaction.

Results: Participants were comparable at baseline for all assessed parameters. Neurological outcomes and L-dopa requirement were comparable in both group after 6-month of supplementation, without time × treatment interaction. The decrease in insulin sensitivity, as assessed by QUICKI index, observed after 6 months in both groups, was greater in Placebo than in Intervention (time effect $p < 0.001$; time × treatment interaction $p = 0.01$). Moreover, despite no changes in total erythrocyte glutathione concentrations, oxidized glutathione levels decreased by 28 ± 17% in the Intervention while increased by 55 ± 38% in Placebo (time effect $p = 0.05$; time × treatment interaction $p = 0.05$), after 6-month supplementation.

Conclusions: Amino acid supplementation, assumed with shrewd temporal distribution, did not show detrimental effects on neurological and pharmacological control in protein-restricted Parkinson-affected patients, chronically treated with L-dopa. Furthermore, daily amino acid supplementation partially counteracted insulin resistance development and the loss in antioxidant availability.

1. Introduction

Malnutrition has relevant consequences on some metabolic parameters closely related to Parkinson's disease (PD) pathogenesis, among which chronic systemic inflammation [1], oxidative stress [2], plasma homocysteine levels [3], and, especially, insulin resistance [4]. An increasing number of evidence suggests a close relationship between insulin resistance and dopaminergic degeneration [4]. Also, it should be considered that some drugs used to treat PD, like L-dopa itself, can induce both hyperglycemia and hyperinsulinemia [5]. Growing experimental evidence points to a pathogenic link between insulin resistance and loss of mitochondrial function [6]. Inflammatory background with impaired redox homoeostasis and mitochondrial dysfunction are well recognized factors which contribute to the onset of the dopaminergic damage in PD and its amplification [1,7]. It has been largely demonstrated that amino acids (AAs) represent a useful nutritional approach to

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guarantee a correct functioning of the main endogenous antioxidant systems [8] – such as the reduced glutathione one [9,10]. Furthermore, nutritional supplementation with essential AAs has positive effects on insulin resistance [11,12]. Nevertheless, such nutritional intervention is not commonly performed in PD patients because of negative interactions between dietary AAs and L-dopa pharmacokinetics [13,14]. In accordance with these observations, dietary regimens that shift protein intake to the evening and restrict daily protein intake have been proposed to increase the efficacy of L-dopa which is normally taken 30–60 min before meals. Indeed, protein intake reduction during the first part of the day along with a strict control of the total protein amount to the recommended daily allowance is associated to a reduction in both postprandial and total off time in fluctuating PD patients [15]. On the other hand, a long lasting low-protein regimen rises the question of potential detrimental effects on protein energy balance in a population with an intrinsic tendency toward chronic protein malnutrition [16]. It is believed that long-lasting PD affected patients display a higher risk of developing malnutrition and sarcopenia [17]. The estimated overall prevalence within the Parkinson's population ranges from 0% to 24% [18]. The risk of developing malnutrition increases with the disease progression [17]. Causes of malnutrition in PD are various: motor disability, with mastication and deglutition difficulties, especially in the advanced stage, together with some non-motor symptoms like anxiety, depression and apathy can lead to a reduction in caloric intake [19]. Some motor symptoms such as increased muscular tone, tremor and dyskinesias may increase the energy expenditure [20].

Furthermore, reduced gastro-intestinal motility causes a delayed gastric emptying with a risk of early satiety, nausea and vomiting [21]. These symptoms can also be enhanced by the dopaminergic therapy [22]. Indeed, patients with a long-lasting disease often show a significant loss in body size and changes in their micronutrient composition [17–20]. A high-protein diet may be proficiently administered in hypercatabolic states, such as chronic inflammations, sepsis, cachexia and senile sarcopenia, as it could be helpful in both counteracting anabolic resistance and preventing further muscle loss [23,24]. Thus, the aim of the study was to evaluate whether AA supplementation has not only positive effects on some systemic parameters involved in PD's progression but also to verify the impact of AA supplementation on the patients' nutritional status and motor performances, as well as on the pharmacological control of the disease. Therefore, in this pilot study, we investigated the effect of 6 months of AA supplementation in PD-affected patients chronically treated with L-dopa showing fluctuations in their therapeutic response.

2. Methods

2.1. Study design

This is a monocentric, prospective, randomized, double-blind study carried out in 2010–2013 on two groups of PD-affected patients. The diagnosis of PD was made by a Neurologist specialized in movement disorders according to the UK PD Brain Bank criteria. We enrolled patients (aged from 50 to 90 years, with a body mass index lower than 30 kg/m^2) on L-dopa therapy for at least two years with a suggested protein redistribution diet. All patients showed fluctuations in their therapeutic response (Table 1). Meanwhile the following exclusion criteria were established: diabetes, kidney failure (glomerular filtration rate lower than 30 mL/min), heart failure (NYHA III or more), liver cirrhosis or any other relevant systemic comorbidity (e.g. infectious, neoplastic or immune-mediated diseases). The active treatment group (Intervention group) received AA supplementation with *Aminotrofic*® (Errekappa Euroterapici, SPA) for 6 months. Each bag contained 4 g of free essential, water-soluble AAs (pharmaceutical composition reported in supplemental materials). Patients took 2 bags of essential AA mixture 60 min after lunch and 60 min after dinner, for a total daily dose of 16 g, each time at least 60 min before the following L-dopa administration. Every administration of amino acid mixture corresponds to 28 g of proteins, since leucine concentration in muscle protein, as previously reported [25] is estimated to be around 9%. The control group (Placebo group) received placebo according to the same procedure. The two groups consisted of patients followed by the Centre for Parkinson's disease and Movement Disorders at the Cattinara University-Hospital, Trieste, Italy.

Table 1
Participants general characteristics at baseline.

	Intervention	Placebo	p
Number	7	7	
Sex (F/M)	3/4	4/3	
Age (y)	74 ± 1	74 ± 4	0.97
BMI (kg/m^2)	25 ± 1	26 ± 1	0.30
Waist circumference (cm)	95 ± 3	100 ± 2	0.28
Disease duration (y)	5.6 ± 1.5	6.0 ± 1.4	0.84

Data expressed as mean ± SEM. Statistical analysis performed using Student t test. BMI, body mass index.

Patients who agreed to participate signed a written informed consent. The study complies with the Declaration of Helsinki and its amendments and was approved by the Institution's Ethics committee. Patients were randomly allocated on a consecutive basis, according to their enrolment order and their gender.

2.2. Study population

A total of 22 patients were enrolled in this study (10 females and 12 males, see also the flow-chart in supplemental materials). Five patients included into the Intervention group dropped-out. Two of them showed side-effects potentially related to AA supplementation such as early satiety, pyrosis and nausea. Two patients were dropped-out because of low adherence to the study. One dropped-out because of concurrent morbidity (bronchial pneumonia). Among the Placebo group, three patients dropped out: one showed low adherence to the study, whereas the other two were due to concurrent medical problems (major surgery, neoplastic pathology). The overall most frequent cause of dropping-out was low or no adherence to the protocol. In all cases, patients explained the lack of compliance with their difficulty in taking the product twice daily, since an already complex polytherapy consisting of various medications was taken at different times per day. Fourteen patients completed the study correctly. General characteristics of this sample are detailed in Table 1.

2.3. Assessments

Patients underwent a baseline anamnestic and neurological assessment together with an analysis of clinical and metabolic parameters of interest (T0). After three (T3) and six (T6) months of treatment, patients were re-assessed, according to the same methods. Patients were assessed in the “on” state, 1 h after taking the morning dose of L-dopa. After each evaluation, 12 mL of overnight fasting blood were collected in EDTA tubes, immediately centrifuged and stocked at −80 °C, until analyses. Blood analyses were performed at the laboratory of the Department of Medical, Surgical and Health Sciences of the University of Trieste. During each week before the three scheduled visits, patients were asked to complete a specific diary where the “on” and “off” periods had to be reported each day.