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Dietary Method for Reducing Fluctuations in Parkinson's Disease

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Motor fluctuations and non-response to carbidopa-levodopa (Sinemet) therapy are major problems in the long-term management of Parkinson's disease. Levodopa manipulation, addition of adjuvants, and drug holidays are often unsuccessful. Others have shown that the clinical state of stabilized Parkinsonians can be reversed with intravenous administration of large neutral amino acids. Reasoning that dietary protein might precipitate motor oscillations and non-response, a low-protein daytime diet (7 g) was offered to fifteen patients. Eighty-six percent of this sample demonstrated immediate sensitivity to Sinemet. While on a low-protein diet, patients' clinical function was predominantly choreatic. Eight patients required a 10–60 percent reduction in their daily levodopa dose in order to minimize this choreatic tendency. Discontinuation of adjuvants did not compromise motor independence. Conversely, while on a high-protein diet (160 g), patients were predominantly immobile with markedly elevated plasma amino acid and levodopa levels.

Consequently, elimination of dietary protein from breakfast and lunch can offer an effective and easily modified method for the ameloriation of motor fluctuations and non-response to Sinemet in Parkinson's disease during working hours.

INTRODUCTION

The development of random, daily motor fluctuations and non-response to carbidopa-levodopa (Sinemet) therapy are major problems in the long-term management of patients with Parkinson's disease. It is reported that up to eighty-four percent of patients treated with Sinemet will experience response fluctuations within ten years of initiating therapy [1]. A variety of approaches for optimizing clinical management, such as readjustment of levodopa, addition of costly adjuvant prescriptions, and/or hospitalization for drug holidays have met with only varying degrees of success. Nutt and others have reported that the clinical state of Parkinsonian patients that have been stabilized by continuous levodopa infusion could be reversed by intravenous administration of certain large neutral amino acids or by having patients consume meals high in protein content [2,3,4]. Reasoning that dietary protein might antagonize the clinical effectiveness of levodopa, a low-protein diet was offered to two groups of Parkinson's patients: those patients with daily motor oscillations and those with apparent non-response to carbidopa-levodopa therapy.

METHODOLOGY

Adults referred to the Yale Parkinson's Clinic with idiopathic Parkinson's disease of more than three years' duration, who were experiencing unpredictable motor fluctua-

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TABLE 1
Clinical Status of Parkinson Patients on Low-Protein Diet

	Fluctuators	Non-Responders
Sex	4 males, 4 females	5 males, 2 females
Mean age (years)	56 (range: 45–68 years)	66 (range: 64–69 years)
Mean duration of Parkinson's	12 years (range: 5–20 years)	8 years (range: 3–12 years)
Mean duration of fluctuations	3 years (range: 2–6 years)	—
Mean L-Dopa requirement for best function		866 mg (range: 450–1,750 mg)
On regular diet	1,497 mg (range: 575–2,000 mg)	
On low-protein diet	959 mg (range: 300–500 mg)	828 mg (range: 400–1,500 mg)
Mean Parkinson disability score		
On regular diet	—	33 (range: 18–50)
On low-protein diet	—	16 (range: 2–34)*

*Six of seven demonstrated increased sensitivity to levodopa-carbidopa.

tions or non-response to carbidopa-levodopa therapy, were invited to participate in this clinical investigation. Some but not all patients were admitted to the Clinical Research Center at Yale–New Haven Hospital for a brief inpatient stay. While hospitalized, patients received differing isocaloric oral diets. On one day of hospitalization, patients received a low-protein diet containing 7 g of protein between 8:00 A.M. and 4:00 P.M. The next day, they received a high-protein diet containing 160 g of protein between 8:00 A.M. and 4:00 P.M. Patients served as their own controls. The dosage and timing of medication administration were held constant. The only variable that was altered was the amount of dietary protein. Each day from 8:00 A.M. to 4:00 P.M. hourly determinations of plasma levodopa and neutral aromatic amino acids (phenylalanine, tyrosine, leucine, isoleucine, valine, tryptophan, and methionine) were obtained. Concomitant clinical assessment using the Northwestern Disability [5] and AIMS [6] Dyskinesia Scale was documented on videotape.

RESULTS

Fifteen patients have followed this low-protein diet. Eight patients suffered with crippling daily motor fluctuations in response to carbidopa-levodopa therapy (Table 1). There were four males and four females, ranging in age from 45–68 years of age, with a mean age of 56. They had Parkinson's disease of 5–20 years' duration, with a mean of 12 years. These patients had experienced fluctuations for two to six years, during which time they had not responded to changes in their dose schedule, adjuvants, or, in two cases, drug holidays. Seven patients (86 percent) derived immediate clinical benefit from a low-protein diet, while one patient (14 percent) did not. Six patients (75 percent) required a 10–60 percent reduction in their total daily levodopa dose in order to avoid chorea. The mean reduction in total daily levodopa dose was 39 percent. No patient required an increase in levodopa, while all adjuvant therapy was successfully discontinued in three patients (38 percent). The mean daily levodopa dosage while on a regular diet was 1,497 mg, whereas the mean daily levodopa requirement while on the low-protein diet was 959 mg (Table 1).

The second subset of this study sample was composed of seven patients who had been categorized as non-responders to carbidopa-levodopa therapy (Table 1). There were five males and two females, ranging in age from 64–69 years, with a mean age of 66. They had Parkinson's disease of 3–12 years' duration, with a mean of eight years. Just

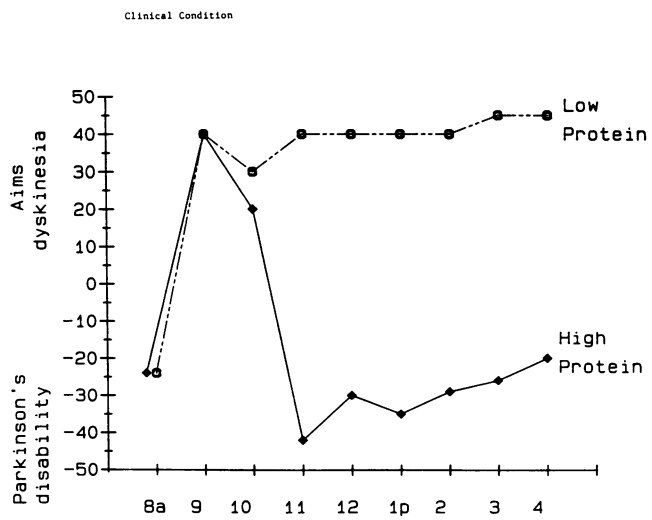

FIG. 1. This represents the hourly clinical condition of one Parkinson patient who had experienced marked fluctuations. On both days of the study the amount of l-dopa-carbidopa was held constant. One 25/100 tablet was administered every two hours, starting at 8:00 A.M. While on a low-protein diet, he consumed 7 g protein diet between 8:00 A.M. and 4:00 P.M. While on the high-protein diet, he consumed 160 g protein diet during the same hours. Dyskinesia was scored using the AIMS Scale. The higher numbers on the y axis represent greater dyskinesia. Parkinsonism was scored using the Northwestern scale. Greater negativity on the y axis represents more severe Parkinsonism. A score of 0 on the y axis represents normal function.

prior to starting the low-protein diet, they were receiving a mean of 866 mg of levodopa per day without significant clinical benefit. While on a low-protein diet, patients required a mean of 828 mg per day (Table 1). Six patients (86 percent) demonstrated immediate sensitivity to Sinemet, while one patient did not. Two patients (29 percent) required a slight reduction in their total levodopa daily requirement by 11 percent and 14 percent, respectively, in order to avoid chorea. Three patients (43 percent) were maintained on their same daily levodopa dose, and two of these patients experienced

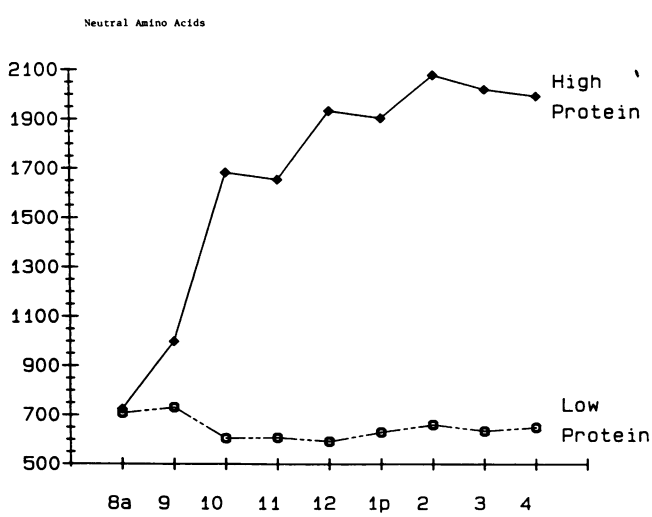

FIG. 2. This displays the sum of the neutral amino acids found in the plasma of the patient whose clinical condition is represented in Fig. 1. The amino acids summed are: phenylalanine, leucine, tyrosine, isoleucine, valine, tryptophan, and methionine.

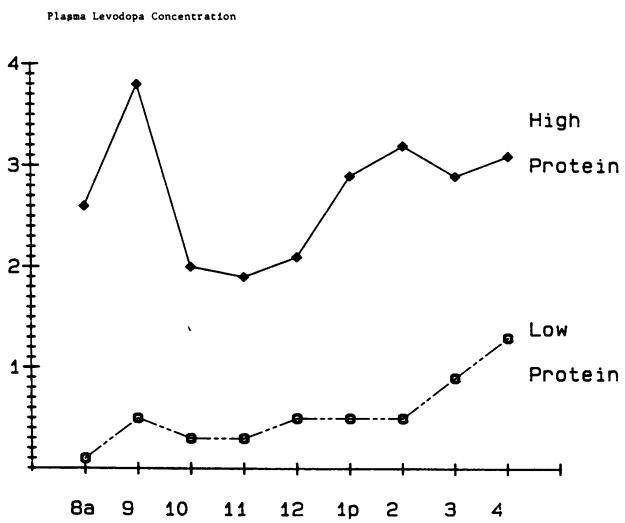

FIG. 3. This demonstrates the hourly plasma l-dopa concentrations of the patient represented in Fig. 1 while on a high- and low-protein diet. The timing and amount of administered l-dopa was the same on both days.

clinical improvement. One patient was improved by restarting carbidopa-levodopa at a dosage that had previously been "ineffective," and only one patient required an increase in the levodopa dose. Discontinuation of levodopa agonists did not compromise motor improvement. Northwestern Disability score before the introduction of a low-protein diet ranged between 18–50, with a mean disability of 33. Northwestern Disability score while on a low-protein diet ranged between 2–34, with a mean of 16 (Table 1). While on a low-protein diet, there was a mean improvement of the disability score of 17 points, and all but one patient were receiving less or the same amount of anti-Parkinson medication.

While on the low-protein diet, both groups (the fluctuators and the non-responders) were predominantly choreatic (Fig. 1). This result correlated with depressed plasma amino acid levels (Fig. 2). Conversely, while on a high-protein diet, patients were predominantly immobile and had markedly elevated plasma amino acid levels. Levodopa levels were higher in the immobile patients when they received the protein-elevated diet (Fig. 3).

DISCUSSION

Fluctuations and non-response to carbidopa-levodopa therapy during daytime hours can be markedly ameliorated by eliminating dietary protein from breakfast and lunch. This method has permitted patients to achieve a smooth response to therapy with markedly improved global function and sensitivity to Sinemet. In the management of motor oscillations, the low-protein daytime diet necessitated a reduction in total levodopa dose and discontinuation of adjuvant therapy in order to avoid dyskinetic toxicity while preserving mobility. The achievement and maintenance of optimal motor function endured until the evening meal, after which most patients became immobile. Non-responders were made responsive to Sinemet merely by eliminating dietary protein until the evening meal. To date, the length of follow-up through the Yale Parkinson's Clinic is one to ten months. All patients have remained healthy. All patients have remained at or above ideal body weight, though some have lost weight on this diet. The effective dose of levodopa in both fluctuators and non-responders was comparable, in that it ranged around 850 and 950 mg per day. In controlled studies, the

levodopa plasma concentrations were higher in the immobile patients who were receiving high-protein meals. This finding may be the result of reduced transport of levodopa into the brain caused by markedly elevated plasma amino acid levels.

Though the explanation for the clinical phenomenon is conjectural and depends upon data compared in single-day consecutive studies, it has become clear that protein antagonizes the clinical effectiveness of Sinemet. A low-protein dietary regimen may offer an important therapeutic device for the control of fluctuations and non-response to Sinemet therapy in Parkinson's disease.

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