Research article

Spontaneous neurocognitive retrieval of patients with sub-acute ischemic stroke is associated with dietary protein intake

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Objective: To document the relationship between neurocognitive recovery and macronutrient intake of patients suffering from ischemic strokes.
Design: Thirty day prospective study of 17 patients suffering from sub-acute stroke (> 14 days from the index event; 10 males, 7 females; mean age 75 ± 8 years) admitted to our rehabilitation unit.
Results: At admission (ADM), mean energy intake was inadequate (< 24 kcal/kg) for bodily needs, whereas protein (> 0.8 g/kg) and lipid (> 0.7 g/kg) intake was appropriate. Patients were moderately deficient for neurological (NIHSS 10.3 ± 3.5) and cognitive tests (MMSE 22.5 ± 3.3). NIHSS correlated negatively with proteins ($r = -0.47$, $P = 0.05$ at ADM; $r = -0.52$, $P = 0.03$ at 30 days) and positively with carbohydrate/protein ratio (CHO/protein; $r = +0.45$, $P = 0.06$ at ADM; $r = +0.48$, $P = 0.05$ at 30 days). However, MMSE correlated positively with proteins ($r = +0.77$, $P = 0.0003$ at ADM; $r = +0.55$, $P = 0.02$ at 30 days) and negatively with (CHO/Prot; $r = -0.57$, $P = 0.02$ at ADM; not significant at 30 days). The relationship remained significant even when the data at ADM and at 30 days where pooled.
Conclusions: In sub-acute strokes, patient neurological and cognitive retrieval could positively be associated with protein intake.

Keywords: sub-acute stroke, protein intake, neurocognitive retrieval, rehabilitation

Introduction

Many patients surviving strokes (30–60%) remain dependent in certain aspects of daily life activities (DLA).[1] In Italy, 67.6% of patients at the first month[2] and 38.9% at 12 months[3] after stroke are still impeded in their DLA.

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Stroke recovery begins early,[4] is fastest in the first month[5] and is almost complete after one month.[4] So, motor recovery achieved by the first month can predict 86% of recovery variance at 6 months.[4] There is, therefore, clear evidence that, for best recovery, the first month of stroke may be of paramount importance for the future independence of patients. Consequently, every tool that can enhance neurological recovery within the first weeks after the stroke should be used.

We believe that nutrition may constitute added value for stroke patient recovery. Several studies have supported this hypothesis. First, 6 months after stroke, residual neurological deficit and disability can be linked with inadequate protein energy intake.[6] Second, protein supplementation may enhance the retrieval of neurocognitive deficits of patients over 2–5 weeks after an acute stroke.[7,8] In these studies, we had formulated the hypothesis that protein supplementation could favor brain protein synthesis and, therefore, explain these results.

We have documented the possible correlations between the time course of patient nutritional intake (proteins, carbohydrates, lipids) and the spontaneous retrieval of neurocognitive function in order to understand the role played by macronutrients for brain recovery after ischemic stroke. The knowledge of the nutrient(s) best associated with neurocognitive recovery could be of practical importance for patient rehabilitation given that diet might be manipulated to aid the recovery of neurocognition as much as possible.

Patients and methods

Patients

Seventeen patients (10 males) with ischemic stroke for cerebrovascular accident were investigated after ≥ 14 days from index event (sub-acute stroke).[9] To be included, the patients had to be able to eat independently. The patients had been transferred to our rehabilitation unit from other stroke units (70.6%) or neurological departments (29.4%).

Table 1 shows the patients' demographic, clinical and functional data as well as the location of cerebral lesions (determined by computed tomography scanning or nuclear magnetic resonance imaging).

Methods

The following variables were measured for all patients both at admission and after 30 days:

1. Neurological alterations by National Institute of Health Stroke Scale (NIHSS).[10]
2. Cognitive dysfunction by Mini-Mental State Examination (MMSE).[11]
3. Body weight, measured in kilograms using a mechanical weight lifter (Pabish, Pero, Milan, Italy), and height (in cm), calculated from knee height.[12] The body mass index (BMI) was calculated from the body weight and height, according to the formula: BMI = body weight (in kg)/height (in metres)^2.
4. Daily calorie and macronutrient intake (3-day diary). Three-day alimentary diary was collected by nurses who had been previously trained *ad hoc*. The type and weight of cooked and uncooked food, before and after meals were all recorded. When necessary, these data were converted into raw equivalents, using an appropriate table.[7] Nutrient analysis was done by a computerized system set up by our group. Average daily calorie intake (kcal-I) was expressed in absolute values (kcal-I/day and kcal-I/kg per day). Average protein, carbohydrate (CHO) and lipid intakes were considered in g/day, in grams per body weight (g/kg). In addition, the ratio of CHO (in g/day) to protein (also in g/day), CHO/protein , was calculated for all patients. The CHO/protein ratio was considered by referring to an experimental study that documented cerebral metabolic dysfunction in rats[13] following diets rich in carbohydrates but low in proteins. Daily energy ≥ 24 kcal/kg and proteins > 1 g/kg were considered adequate for both nutritional balance[14] and neurocognitive recovery.[7,8]
5. Serum albumin and pre-albumin levels were determined in order to detect body protein metabolism.

Patients or their relatives gave their informed, written consent to enter this study that was approved by the local technical, ethical committee.

Statistical analysis

Differences in nutritional and neurocognitive variables between baseline and 30 days were assessed using a paired *t*-test. Simple linear regression analysis documented the relation between macronutrient intakes and CHO/protein ratio on one hand and NIHSS and MMSE on the other hand. Data are given as mean ± SD. Statistical significance was set at $P < 0.05$.

Results

In Table 1, demographic, clinical, functional characteristics as well as locations of cerebral lesions of stroke patients are shown. Table 2 shows macronutrient intakes, neurocognitive performance, serum albumin and pre-

Table 1 Patients' demographic, clinical and functional data and location of cerebral lesions (determined by computed tomography scanning or nuclear magnetic resonance imaging)

Age (years)	75 ± 8
Gender (M:F)	10:7
Co-morbidities (number of patients)	
Arterial hypertension	11/17 (64.7%)
Atrial fibrillation	5/17 (29.4%)
Chronic coronary artery disease	1/17 (5.88%)
Drugs being taken (number of patients)	
Angiotensin-converting enzyme inhibitors	7/17 (41.1%)
Aspirin	6/17 (35.3%)
Calcium channel blockers	2/17 (11.7%)
Lipid-lowering agents	2/17 (11.7%)
Total functional independence measure (FIM)	50.6 ± 9.3 (normal 118)
Stroke artery zone (number of patients)	
Frontal	7/17 (41.1%)
Parietal	5/17 (29.4%)
Temporoparietal	4/17 (23.5%)
Frontoparietal	1/17 (5.9%)

albumin levels of patients at admission (ADM) to our rehabilitation unit and 30 days from the start of the protocol (30 d). At admission, mean energy intake was inadequate (< 24 kcal/kg) for bodily nutritional needs[7] whereas ingested proteins (> 0.8 g/kg) and lipids (> 0.7 g/kg) were appropriate for body requirements. Body protein metabolism was mildly reduced, as suggested by serum albumin and pre-albumin levels. The patients had a moderate deficit both for neurological and cognitive tests.

Thirty days after the protocol started, nutritional intake remained virtually unchanged compared to the baseline values, even though a trend towards further impairment was noted. Body weight tended to decrease (not significant) compared with baseline values. Albumin and pre-albumin concentrations were virtually unchanged. Despite unchanged nutritional intake, the neurocognitive tests significantly improved: NIHSS by –3.2 ± 2.7 points ($P < 0.001$) and MMSE by 1.27 ± 1.25 points ($P < 0.001$).

Relationship between macronutrient variables and neurocognitive tests

Figures 1 and 2 show the correlations between protein intake, dietary CHO/protein ratio on one hand and neurocognitive tests on the other. Neurological alteration (NIHSS) was negatively associated with proteins (at ADM, $r = -0.47$, $P = 0.05$; at 30 days, $r = -0.52$, $P = 0.03$) and positively with CHO/protein ratio (at ADM, $r = +0.45$, $P = 0.06$; at 30 days, $r = +0.48$, $P = 0.05$; Fig. 1). In contrast, cognitive function (MMSE) was positively associated with proteins (at ADM, $r = +0.77$, $P = 0.0003$; at 30 days, $r = +0.55$, $P = 0.02$) and negatively with CHO/protein ratio (at ADM, $r = -0.57$, $P = 0.02$; not significant at 30 days; Fig. 2). Moreover, the figures show that when the data at ADM and 30 days were pooled ($n = 34$), these relationships remained significant. There were no relationships between neurocognitive tests and energy, carbohydrate and lipid intakes.

Table 2 Macronutrient intake, neurocognitive performance, serum albumin and pre-albumin levels in patients with sub-acute strokes at admission to the rehabilitation unit and 30 days after starting the protocol

	Admission	30 days	*P*-value
Anthropometrics			
Body weight (kg)	68.7 ± 11	67.2 ± 11.3	ns
BMI (kg/m²)	22.9 ± 2.7	22.8 ± 2.5	ns
Daily energy intake			
kcal	1466 ± 482	1384 ± 465	ns
kcal/kg	21.9 ± 6.2	20.8 ± 6.1	ns
Daily protein intake			
g	59.2 ± 27.6	56.6 ± 23.6	ns
g/kg	0.87 ± 0.39	0.85 ± 0.31	ns
Daily carbohydrate intake			
g	178 ± 76	179 ± 61	ns
g/kg	2.6 ± 0.8	2.7 ± 0.8	ns
Daily lipid intake			
g	57.8 ± 10.1	49.1 ± 9.5	ns
g/kg	0.84 ± 0.1	0.73 ± 0.2	ns
Neurological deficit (NIHSS)			
Scores	10.3 ± 3.5	7.6 ± 3.8*	< 0.01
Cognitive function (MMSE)			
Scores	22.5 ± 3.3	23.8 ± 3.5*	< 0.01
Albumin			
g/dl (normal 3.5–5.0)	3.36 ± 0.57	3.4 ± 0.7	ns
Pre-albumin			
mg/dl (normal 20–40)	18.8 ± 2.7	19.1 ± 3.2	ns

Values are mean ± SD.
Statistical analysis, paired *t*-test. *$P < 0.01$, 30 days versus admission; ns, not significant.

Discussion

The study shows that the retrieval of patient neurocognitive deficits over 2–5 weeks after an acute event was positively associated with both ingested proteins and reduced carbohydrate to protein ratio, which was particularly clear for cognitive recovery 2 weeks after stroke. These results indicate that improving patient protein intake is a tool, pathophysiologically correct, to enhance neurocognitive recovery.[7,8] This can be reinforced by the study finding that body protein metabolism was mildly impaired, suggesting that protein intake of 0.8 g/kg/day may be inadequate. In addition, we can not exclude that acute phase response following index event could be responsible for the observed impaired serum protein levels.

Although correlations do not necessarily translate to a cause/effect relationship, nonetheless, on the basis of brain-nutrition relationships[15–17] and the benefits seen in

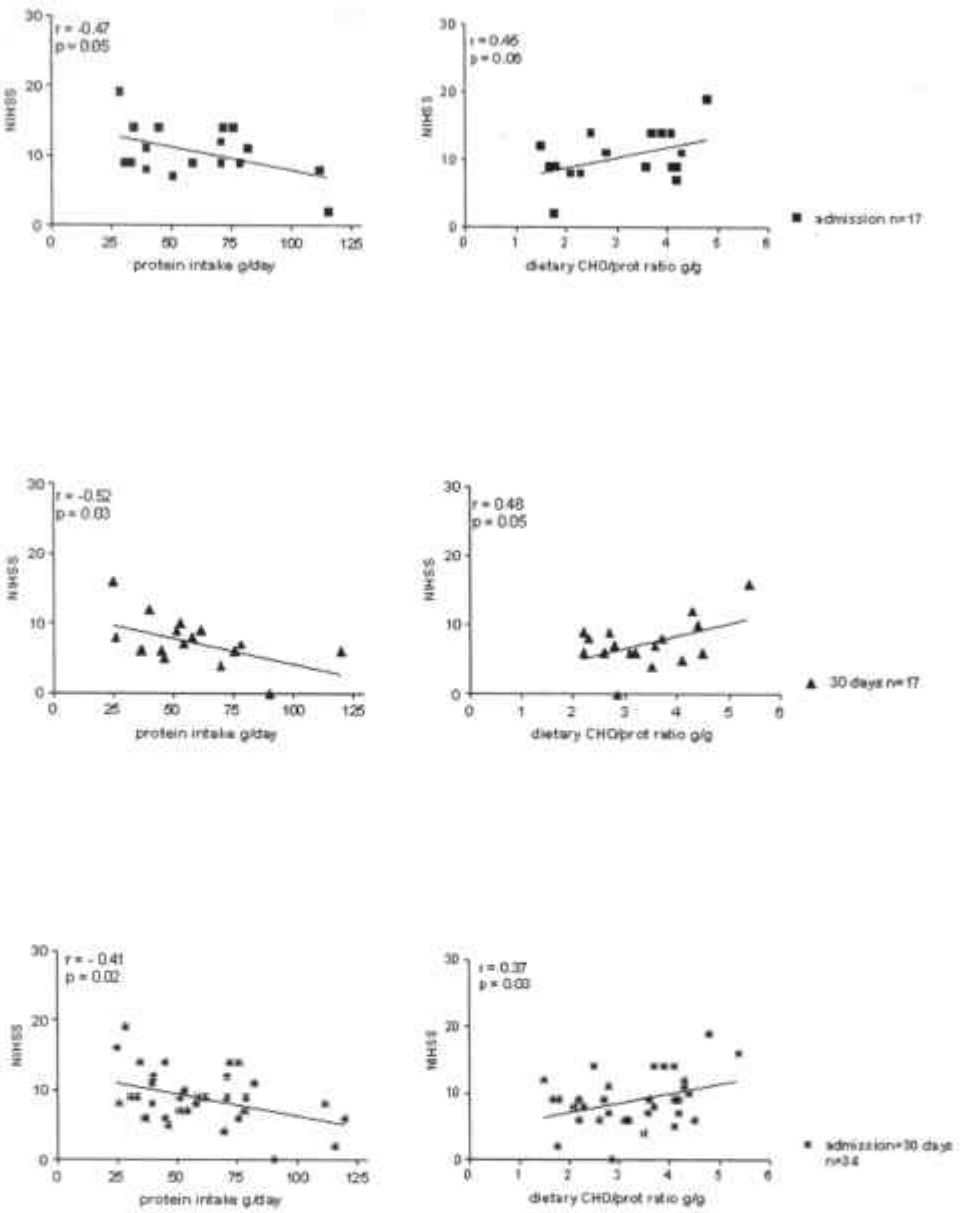

Figure 1 Correlations between neurological test (NIH Stroke Scale: NIHSS) on one hand and protein intake (g/day) and dietary CHO/protein ratio (g/g) on the other hand, both at admission (ADM) and at 30 days after ADM (30 d). The relationship remained significant even when all data were pooled together (ADM + 30 d)

stroke patients from protein supplementation,[7,8] it is reasonable to conclude that brain recovery after stroke could be aided by protein intake. Indeed, a number of experimental and clinical studies support the key role of proteins for cortical plasticity. Increased amino acid content from protein intake may re-activate protein synthesis, essential for axonal sprouting and formation of new cortical networks.[18,19] In addition, amino acids may directly improve chemical neurotransmission that occurs during the first few weeks in spared tissue near and far from an ischemic region.[20–23] Therefore, increased brain amino acids could act synergistically with rehabilitation procedures thus enhancing the efficacy of rehabilitation in the functional retrieval of ischemic patients.[24]

This study suggests the persistence of alterations in brain glucose metabolism 2 weeks after the acute event.[25–27] Nevertheless, we note that carbohydrates tended to contribute to neurological retrieval at about 40 days after the acute stroke, suggesting an initial recovery of glucose processing by the brain. In any case, the contribution of carbohydrates to brain function appears to be less important than that of proteins. This seems to be particularly clear for cognition recovery.

In synthesis, 2–5 weeks after the stroke, the biochemical strategy the brain adopts for remodelling seems to rely on amino acids rather than glucose.

We believe that the novel finding from this investigation is that protein intake, beyond its role for nitrogen balance,

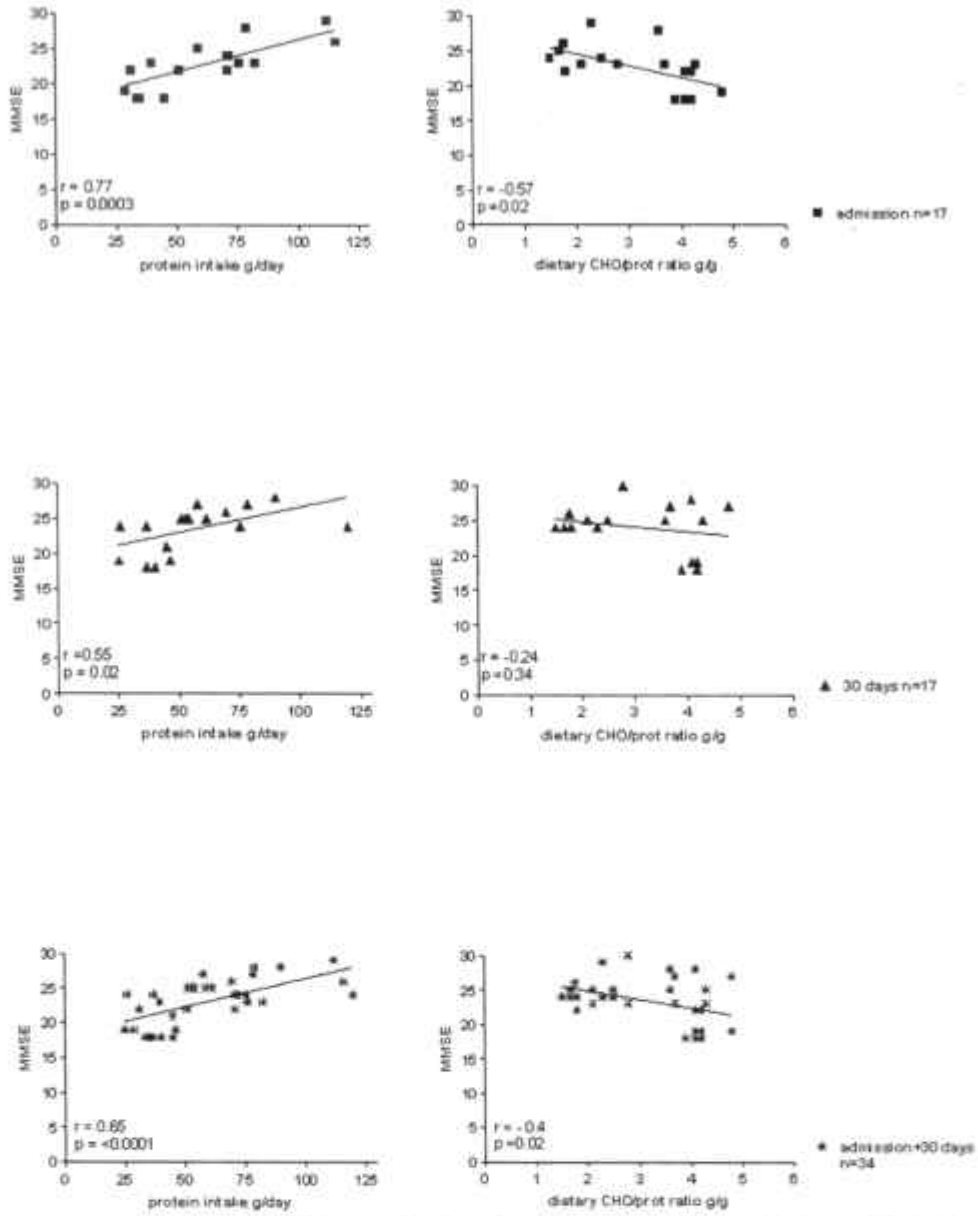

Figure 2 Correlations between cognitive test (MMSE) on one hand and protein intake (g/day) and dietary CHO/protein ratio (g/g) on the other hand, both at admission (ADM) and at 30 days after ADM (30 d). The relation remained significant even when all data were pooled together (ADM + 30 d)

seems to be directly involved in the metabolic retrieval of brain areas anatomically and/or functionally damaged by ischemia. This investigation, in line with the results of our two recent studies,[7,8] could be a premise for considering proteins as an added value for the processes of rehabilitation of patients with ischemic stroke.

Clinical considerations

The study suggests that the amount of ingested proteins could play a key role for the retrieval of neurocognitive deficits of patients with sub-acute strokes.[7,8] Our findings indirectly confirm previous studies,[7,8] in which protein supplementation improved neurocognitive dysfunctions in stroke patients in a period of time in which the potential for brain recovery is at a maximum (2–5 weeks after acute stroke).[4]

The study indicates that patient carbohydrate intakes should also be controlled over time because high CHO/protein ratio is detrimental for brain functioning,[8,13,28] as it increases the risk of acidosis in ischemic brains. Acidosis indeed may impede stroke rehabilitation by several mechanisms including increased neuronal depolarization and alterations in brain cell energy production.

Study limitations

The small population recruited did not allow us to investigate whether low CHO/protein ratio following

low spontaneous CHO ingestion might improve neurocognitive recovery. Clinically, this is relevant for at least two orders of stroke patients, those with concomitant renal insufficiency who may require low proteins, and obese/diabetic patients who may need reduced carbohydrate intake.

Patient pre-stroke diet,[29–36], smoking habit, alcohol consumption, and education were not investigated. These factors could play an important role not only for the development of stroke, but also for the quality of the retrieval of the neurocognitive deficits. For example, relevant to the present investigation is the finding of reduced dietary zinc in a large population of healthy elderly subjects in our country (Italy).[36,37] Further studies are needed to investigate the relevance of the aforementioned factors on patient quality of rehabilitation. On the other hand, this study focused on ascertaining whether patient protein intake could be associated or not with spontaneous recovery of neurocognitive alterations.

Conclusions

The study shows that the neurocognition recovery of patients suffering from ischemic strokes is positively associated with dietary proteins and negatively with a high carbohydrate to protein ratio.

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