Breakfast improves cognitive function in cirrhotic patients with cognitive impairment

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ABSTRACT

Background: Cognitive disturbances are relatively common in patients with liver disease. High protein load precipitates hepatic encephalopathy in cirrhotic patients. Minimal hepatic encephalopathy (MHE) is a prevalent neurocognitive complication of cirrhosis.

Objective: Because the influence of nutritional factors on the progression of cognitive impairment has not been explored in depth, this study aimed to investigate the effect on cognition of acute metabolic changes induced by breakfast consumption.

Design: Twenty-one subjects (10 women) with Child A cirrhosis and 21 age- and sex-matched healthy controls were enrolled. Patients and controls were divided into 2 groups: those receiving a breakfast of 500 kcal and 21 g protein and those receiving no breakfast. Serum ammonia concentrations and cognitive functions were studied (Mindstreams; NeuroTrax, Fresh Meadows, NY) before and 2 h after breakfast. A mixed model was used to analyze the data.

Results: At baseline, cirrhotic patients had significantly lower total scores and significantly lower subscores (P < 0.015 global cognitive score) in 4 of 7 cognitive categories, which is indicative of MHE. Patients with hyperammonemia (>85 μg/dL) scored significantly lower for attention than did patients with normal serum ammonia concentrations (P < 0.003). After 2 h, MHE patients and controls responded differently to breakfast consumption with regard to attention and executive functions (P < 0.003 and P < 0.04, respectively). Although patients’ scores improved after breakfast consumption, despite an increase in serum ammonia, healthy controls who continued to fast performed better.

Conclusions: Chronic hyperammonemia may negatively affect attention. Eating breakfast improves attention and executive functions of patients with MHE. Prolonged periods of starvation may be partly responsible for these changes. This trial was registered at clinicaltrials.gov as NCT01083446. Am J Clin Nutr 2010;92:137–40.

INTRODUCTION

Cognitive disturbances are relatively common in patients with liver disease, and they may vary widely from minimal neurological changes detectable only by specific tests to deep coma (1). Cirrhosis is the most frequent liver disease that causes hepatic encephalopathy. Minimal hepatic encephalopathy (MHE) is one of the prevalent neuro-cognitive complications of cirrhosis that is diagnosed in up to 80% of cirrhotic patients (2). MHE is characterized mainly by a subtle impairment of neurocognitive status and is not readily detectable by standard tests for mental status or neurological examinations. The condition was shown to predict the eventual development of overt hepatic encephalopathy (3) and to impair daily functioning (4). Drivers with MHE were recently shown as being more likely to be involved in motor vehicle crashes and violations (5). For the most part, the changes in cognitive functions are attributed to an increase in blood ammonia concentrations and/or other intestinal neurotoxins and neurotransmitters of the benzodiazepine/γ-aminobutyric acid system (1). Encephalopathy, especially in its mild forms, may have a fluctuating nature, depending on changes in blood ammonia or neurotoxin concentrations. Different factors, among them a high protein load, were shown to precipitate the induction of hepatic encephalopathy (1).

We hypothesized that, due to an acute increase in blood ammonia concentrations, breakfast may have an effect on cognitive functions of patients with Child A cirrhosis with and without concurrent impaired neurocognitive functions.

SUBJECTS AND METHODS

The study population included 21 subjects (10 women) with Child A cirrhosis who were being followed in our liver outpatients clinic and 21 age- and sex-matched healthy controls.

Inclusion criteria for the cirrhotic patients were as follows: age ≥18 y, diagnosis of Child A cirrhosis with a Mayo End-Stage Liver Disease score of <10, diagnosis of liver cirrhosis by liver biopsy (stage IV) and/or a fibroscan score ≥12 kPa or a fibrotest score ≥0.74, or imaging evidence (eg, computerized tomography or magnetic resonance). Exclusion criteria were a history of grade II or greater hepatic encephalopathy; a diagnosis of dementia, Parkinson’s disease, or schizophrenia; use of sedatives, tranquilizers, or antipsychotic medication during and/or 2 wk before enrolling in the study; current use of lactulose or neomycin; and use of alcohol or illicit drugs during and/or 6 mo before study entry. Study patient characteristics are given in Table 1. The effect of breakfast on cognitive functions was
studied in the cirrhotic patients and healthy controls after an overnight fast. All the subjects were admitted to the Unit of Clinical Nutrition at 0800–0900, venous blood was drawn for determination of ammonia concentrations, and each subject completed a computerized test (NeuroTrax, Fresh Meadows, NY) for assessing performance across an array of cognitive domains, including memory, executive functions, visual spatial perception, verbal functions, attention, information processing speed, and motor skills. Each subject was then randomly assigned to eating a breakfast meal (30% of daily calories and 21 g of protein) or to fasting. Two hours later, all subjects repeated the tests, and venous blood was drawn again for measuring ammonia concentrations.

All participants completed a battery of tests (Mindstreams; NeuroTrax) designed to detect mild impairment in their primary cognition of language. The computerized assessment system has been described in detail elsewhere (6). Briefly, it consists of commercial software installed in a computer and serves as a basis for interactive cognitive tests that produce data on accuracy and reaction time (millisecond timescale). Once tests are run on the local computer, data are automatically uploaded to a central server that calculates outcome variables from raw single-trial data, normalizes data, and generates a report of the findings. The cognitive domains assessed by the computerized battery include memory (verbal and nonverbal), executive function, visual spatial skills, verbal function, attention, information processing, and motor skills (6). The tests that compose the battery have been shown to detect cognitive impairment in the elderly in multiple cognitive domains (7). All responses are made by clicking the computer mouse or by means of a number pad. Patients were familiarized with these devices and undergo practice sessions before the individual tests so that they will correctly provide the kind of responses required for each test. They are administered in the same fixed order for all participants. Outcome variables vary according to the test. To minimize differences in age and levels of education and to permit the averaging of performances across different types of outcome variables (eg, accuracy, reaction time), each outcome variable is normalized according to stratifications of age and education. Normalization for the current study was based on the 1569 cognitively healthy participants of the Mindstreams normative database. Normalized subsets of the various outcome variables were averaged to produce 7 summarized scores as follows, each indexing a different putative cognitive domain: The 7 scores serve as the primary dependent variables for the analysis. A Global Cognitive Score is computed as the average of these index scores and serves as a secondary dependent measure. Institutional review board approval from the Tel Aviv Sourasky Medical Center (Tel Aviv, Israel) was obtained to conduct this study.

The relative change between tests was calculated for each subtotal score as the difference between test grades divided by the grade in the first test ($t_2 - t_1/t_1$). The same procedure was performed for ammonia concentrations. All test results at baseline were compared between patients and controls by the $t$ test for independent samples. An analysis of variance was performed with repeated measures by using the mixed model, which was applied to the relative change in each test and compared patients to their healthy matched controls and to the 2 treatment groups (breakfast, nonbreakfast), taking into account the ammonia concentration at baseline (below or above 85 µg/dL). Pearson’s correlation coefficient was used to assess the correlation between ammonia concentrations and the NeuroTrax results at baseline. All statistical analyses were performed by using the SAS for Windows version 9.1.3 (SAS Institute, Cary, NC).

### RESULTS

A total of 21 subjects with MHE (age range 31–83 y, 10 women) and 21 age- and sex-matched healthy controls were recruited into the study after they signed informed consent forms. Patient characteristics are described in Table 1. At baseline, blood ammonia concentrations were significantly higher in the patient group compared with the control group (71.8 ± 49.0 compared with 45.8 ± 16.4 µg/dL, $P < 0.03$). Six of the patients had ammonia concentrations >85 µg/dL at baseline. After 2 h, mean ammonia concentrations increased in cirrhotic patients who ate and decreased in those who continued to fast (56.7 ± 28.9 to 87.2 ± 47.4 compared with 85.5 ± 60.1 to 79.4 ± 61.3 µg/dL, respectively). Ammonia concentrations increased >85 µg/dL in 5 cirrhotic patients who ate breakfast and stayed above normal in another patient. In the patients who continued to fast, in one patient ammonia blood concentration increased >85 µg/dL whereas in 3 others blood ammonia concentrations decreased to <85 µg/dL. No significant changes in blood ammonia concentrations were observed in the controls who ate breakfast (48.3 ± 11.9 compared with 54.6 ± 22.3 µg/dL) and those who fasted (43.3 ± 20.3 compared with 47.6 ± 26.8 µg/dL).

Patients with liver cirrhosis generally had lower baseline scores compared with the controls for the cognitive tests. These findings mirror those described in MHE. Global score, memory, informed processing speed, attention, and executive functions differed significantly between the groups (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient characteristics *</th>
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<td>Patient no.</td>
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* CC, cardiac cirrhosis; CT, computerized tomography; PBC, primary biliary cirrhosis; HCV, hepatic C virus; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
attention was significantly lower in cirrhotic patients with high ammonia concentrations (>85 µg/dL) compared with those with ammonia concentrations within the normal range.

The results of the mixed model indicate that there is no overall effect of either disease (cirrhosis) or food (breakfast) on the different cognitive scores. Yet the significant interactions between disease and food and their effect on the attention (P = 0.003) and executive functions (P = 0.04) point to a different effect of food in each one of the groups. In cirrhotic patients, the attention and executive functions increased with breakfast whereas, in the healthy controls, those who continued to fast for 2 additional hours achieved higher scores (Table 3).

**DISCUSSION**

Our results indicate that patients with Child A cirrhosis and MHE may improve their attention and executive functions by eating breakfast even with an increase in ammonia concentrations. By using the mixed model, we learned that patients responded differently to breakfast than did healthy individuals. Yet patients with abnormally high ammonia concentrations scored lower for attention at baseline. This may indicate factors other than hyperammonemia; for example, higher glucose utilization may be of importance. Improvement in cognitive functions after eating breakfast had also previously been shown in other situations, eg, among elementary school children (8) and elderly subjects (9), and had been attributed to the increase in glucose concentrations.

Actually, protein-calorie malnutrition is highly prevalent in all clinical stages of liver disease (10). Sufficient caloric and adequate protein intake therefore are crucial for affected individuals. The influence of nutritional factors on the progression of liver cirrhosis and hepatic encephalopathy has been extensively investigated (11). For example, precipitation of hepatic encephalopathy by a high protein load is a well-established phenomenon (1). The influence of prolonged starvation or protein supplementation on cognitive function of patients with MHE, on the other hand, is less clear.

A number of earlier studies had shown that cirrhotic patients seem to handle substrates differently from the healthy control subjects. When 8 patients with cirrhosis were measured in a respiratory chamber, the measured respiratory quotient was significantly lower during the morning preprandial period (0900–1200), reflecting a higher oxidation rate of fat to carbohydrate that is compatible with a more catabolic state (12). A similar metabolic pattern was also shown by Owen et al (13). After an overnight fast, the hepatic glucose production in patients with cirrhosis diminished as a result of low-rate glycolysis whereas hepatic gluconeogenesis and ketogenesis increased. Owen et al (13) concluded that this pattern of hepatic metabolism mimics that seen in healthy subjects after more advanced stages of starvation. The calculated calorie equivalents of substrates in the bloodstream, which could potentially be oxidized by peripheral tissues, were significantly lower in cirrhotic patients compared with healthy controls, both after an overnight and after a 3-d fast. On the basis of the above findings, it was suggested that a late evening snack of carbohydrate be recommended (14) or that an oral branched-chain amino-acid–enriched nutrient mixture be given to these patients (15). Finally, Weissenberg et al (16) observed that deficits in memory and attention in patients with cirrhosis were accompanied by a decrease of cerebral glucose utilization in the cingulated gyrus, the dorsolateral prefrontal cortex, and the parietal cortex on the basis of 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography studies. The brain is the main organ consumer of glucose in the body during regular metabolism and switches to usage of ketone bodies only after a few days of starvation. All of these findings taken together serve to explain why prolonged starvation may affect the

<table>
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<th>Variable</th>
<th>Cirrhotic patients (n = 21)</th>
<th>Healthy controls (n = 21)</th>
<th>Model effects (P values)</th>
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<tbody>
<tr>
<td></td>
<td>With breakfast</td>
<td>Without breakfast</td>
<td>With breakfast</td>
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</table>
| Global cognitive score    | 3.6 ± 10.6  
4.09 ± 2.93 | 5.51 ± 4.68  
3.10 ± 4.38 | 0.92  
0.64 | 0.38  
0.94 |
| Memory                    | 3.24 ± 25.24  
10.35 ± 16.56 | 10.75 ± 18.13  
1.08 ± 5.50 | 0.73  
0.96 | 0.14  
0.61 |
| Executive functions       | 6.38 ± 9.06  
−0.63 ± 4.11 | 0.67 ± 8.59  
6.47 ± 12.68 | 0.50  
0.12 | 0.04  
0.10 |
| Visual spatial            | 4.02 ± 10.57  
1.53 ± 9.36 | 7.71 ± 18.83  
4.79 ± 13.86 | 0.08  
0.61 | 0.30  
0.84 |
| Verbal function           | 53.96 ± 11.13  
3.12 ± 5.79 | 12.20 ± 16.57  
−2.92 ± 17.20 | 0.22  
0.11 | 0.35  
0.99 |
| Attention                 | 6.91 ± 12.41  
0.35 ± 7.67 | 0.22 ± 4.33  
7.50 ± 13.48 | 0.20  
0.21 | 0.003  
0.019 |
| Information process speed | 10.32 ± 7.30  
9.14 ± 7.57 | 7.08 ± 6.96  
5.16 ± 7.84 | 0.22  
0.47 | 0.87  
0.96 |
| Motor skills              | 1.66 ± 5.82  
7.95 ± 5.66 | 6.46 ± 14.8  
2.00 ± 4.50 | 0.93  
0.77 | 0.16  
0.95 |

ootnote{Mean ± SD (all such values).}
cognitive functions of cirrhotic patients and why eating breakfast may improve the cognitive functions most probably by increasing glucose utilization.

We propose that our cirrhotic patient group may be considered as having MHE. None of the members of this group had any signs of encephalopathy on the day of the exams, and their results at baseline (Table 2) indicate that they scored lower in all the tests compared with age- and sex-matched healthy controls. In addition, 4 of the 7 variables as well as the global score were significantly lower in our patient group compared with normal controls.

Two of the 7 subcategories of the cognitive scores of our cirrhotic patients—attention and executive functions, both of which are related to everyday activities, including driving skills—improved after eating. As such and based on the difference in metabolic handling of substrates, we reason that eating breakfast may also improve driving skills that were recently observed to be impaired in patients with MHE (5, 17). This may also affect fatigue, which was also recently reported in these patients (18). Thus, on the basis of our study, we can conclude that a regular breakfast that supplies 25% of daily calories and 21 g of protein may improve cognitive functions.

Ammonia was suggested to play a central role in the pathogenesis of hepatic encephalopathy due to a direct neurotoxic effect and brain swelling causing hypoxia (19). We studied the effect of acute hyperammonemia in our patients after they had eaten breakfast. We expected that changes in blood ammonia concentrations would be correlated with deterioration in the neuro-cognitive scores, but this was not the case. The acute increase in blood ammonia concentrations after breakfast seems not to affect their cognitive functions, which improved in spite of an increase in blood ammonia concentrations >85 μM/dL. On the other hand, the baseline attention level was significantly lower in the patients with fasting hyperammonemia (P < 0.003). This may indicate that breakfast (glucose consumption?) may override the effects of hyperammonemia. Similar results were observed by others in the past and were reportedly related to a difference in the brain uptake of ammonia, which is increased in hepatic encephalopathy independently of blood ammonia concentrations (20). Differences in cerebral microcirculation and blood-brain abnormalities may also contribute to the lack of correlation. In the studies that did suggest some correlation, the relation was nonlinear, especially for the lower grades of encephalopathy (21). Our results indicate that eating breakfast has a beneficial effect that masks any deterioration due to a further increase in ammonia concentrations. This may shed some light on the role of ammonia in the pathogenesis of hepatic encephalopathy (21).

In conclusion, we have shown that eating a regular breakfast improves the attention and executive functions of patients with cognitive impairment consistent with MHE. On the basis of the metabolic characteristics of these patients and the recent publications on high rates of accidents, traffic violations, and fatigue among patients with MHE, we believe that prolonged periods of starvation may be partly responsible for these outcomes and suggest that patients with MHE be encouraged to diligently incorporate breakfast into their daily routine.

We thank Esther Eshkol for editorial assistance.

The authors’ responsibilities were as follows—NV: design of the experiment, collection of data, analysis of data, and writing of the manuscript; HK: collection of data, analysis of data, and writing of the manuscript; MC-H: design of the experiment and collection of data; and ML and EN: collection and analysis of data. None of the authors had a conflict of interest.

REFERENCES