Large Neutral Amino Acid Changes and Delirium in Febrile Elderly Medical Patients

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A hypothesized but unexplored mechanism for delirium in older persons is that changes in plasma large neutral amino acid (LNAA) concentrations alter brain serotonin levels, result in neurotoxicity, or both. Therefore we performed a prospective study of 21 acutely febrile long-term-care residents to study the relationship between LNAA changes and delirium. Plasma LNAA concentrations were measured during illness and 1 month later. Delirium was diagnosed by using the Confusion Assessment Method. Other data included age, body mass index, cognitive impairment, comorbidity, gender, maximum temperature, and medication use. Seven subjects (33%) were delirious during febrile illness. Although the phenylalanine (PHE)/LNAA ratio was higher during illness in both delirious and non-delirious groups, a two-sample t-test demonstrated that delirium was associated with a higher illness PHE/LNAA ratio (p = 0.03). The amount of change in PHE/LNAA from illness to recovery was not different between the delirious and non-delirious groups. Tryptophan/LNAA was not associated with delirium during illness or at recovery. These findings identify another potentially fruitful area of investigation for the prevention and treatment of delirium in older persons.

DELIRIUM may be the most common, and perhaps the most important, complication of illness in older persons. Although epidemiologic studies have identified important risk factors associated with the occurrence of delirium, such as advanced age, cognitive impairment, and illness severity, knowledge regarding the pathophysiology of this difficult problem is lacking (1).

One hypothesis is that changes in large neutral amino acids (LNAA), which are precursors of several neurotransmitters that are involved in arousal, attention, and cognition, may play a role in delirium (2). All LNAA (isoleucine, leucine, methionine, phenylalanine, tryptophan, tyrosine, and valine) enter the brain by using the same saturable carrier, in competition with each other. As the concentration of one LNAA increases, central nervous system entry of other LNAA decreases (3). For example, brain concentrations of serotonin may increase if the relative blood concentration of tryptophan (TRP) increases. Alternatively, serotonin concentrations may decrease if other LNAA concentrations are increased relative to TRP. Phenylalanine (PHE) has the additional interesting property of possible conversion to neurotoxic metabolites (4) and competes with TRP for entry into the brain and subsequent metabolism. This study tests the hypothesis that alterations in plasma LNAA concentrations, particularly the PHE/LNAA and TRP/LNAA ratios, are associated with delirium in febrile elderly patients.

METHODS

This study was conducted between December 1995 and December 1996, at a 725-bed long-term-care facility. Nursing staff referred residents with a recorded temperature >37.7°C for possible recruitment, and nursing units were screened daily. Non-English-speaking residents, those with advance dementia, and those whose temperature elevation lasted less than 24 hours were excluded. Fifty-six individuals were referred to the investigators, of whom 45 met inclusion criteria. Of these potential subjects, 31 were recruited for the study. Two subjects were subsequently excluded because of hospital admission. The analysis also excludes eight subjects with incomplete data, caused by refusal of follow-up (n = 4), unusable blood samples (n = 3), and death (n = 1). Thus, complete data were available for 21 subjects. Written informed consent was obtained from subjects, their proxies, or both on the first day after the initial temperature elevation.

Data Collection

On the second morning following the initial temperature elevation, a standardized interview was conducted by using the Mini-Mental State Examination (5) and Delirium Symptom Interview (6). This interview was repeated at 1 month following the febrile episode. Other data regarding population descriptive characteristics collected included the subject’s age, body mass index, cognitive function, comorbidity, gender, maximal temperature elevation, and medication use. All potentially absorbed medications used by the subjects were counted (including vitamins, metered-dose inhalers, and optic preparations) if used in the 24 hours before blood sampling.

Baseline cognitive function was assessed with the Cognitive Performance Scale (CPS) score derived from the most recent Minimum Data Set assessment. The Minimum Data Set is a database of medical, psychiatric, and functional measures performed on all nursing home residents in the United States (7). The CPS is scored on a scale of 0–6, with higher numbers indicative of greater amounts of cognitive impairment (8); the range of 0–3 selected for this study includes residents with no more than moderate dementia. Delirium was diagnosed by utilizing the Confusion Assessment Method (CAM), a validated instrument known to be...
both sensitive and specific for detecting delirium in elderly patients (9). Comorbidity at enrollment was quantified by using the Cumulative Illness Rating Scale (CIRS), a validated measure of physical disease burden in the elderly (10). PHE/LNAA and TRP/LNAA ratios were calculated by dividing PHE or TRP respectively by the sum of the levels of the other LNAA s. The change in PHE/LNAA ratio was calculated by subtracting the recovery PHE/LNAA ratio from the illness PHE/LNAA ratio.

On the mornings of the febrile illness and follow-up interviews, a fasting blood sample was drawn and centrifuged, and the plasma was separated and stored at −80°C. All LNAA concentrations except TRP were measured by high-pressure liquid chromatography, using ion-exchange chromatography and postcolumn derivatization (11). Total plasma TRP was measured fluorometrically (12).

Statistical Analysis

Data were analyzed by using SPSS (Chicago, IL) statistical software (13). Mean and standard deviations for all subjects, and those with and without delirium, were generated to describe the population characteristics. A two-sample t test was used to evaluate differences between the delirious and nondelirious groups with respect to these characteristics.

The mean and standard deviation of each LNAA concentration and the TRP/LNAA and PHE/LNAA ratios were determined for all subjects, and subjects with and without delirium. A paired t test was used to evaluate the difference between PHE/LNAA and TRP/LNAA during illness and at recovery in delirious and nondelirious groups. A two-sample t test was used to evaluate the difference between PHE/LNAA and TRP/LNAA, among the delirious and nondelirious groups during illness and at recovery. An independent measures t test was also used to evaluate the difference between the change in PHE/LNAA from illness to recovery in the delirious and nondelirious groups. Linear regression was used to examine the relationship between the CPS score and LNAA levels and ratios during illness and at recovery following log transformation of the data to account for skewness.

RESULTS

Seven of the 21 subjects (33%) met the criteria for delirium. No subject was still delirious at recovery. Descriptive characteristics of the delirious and nondelirious residents are reported in Table 1. Compared with residents who did not develop delirium, the delirious individuals were more cognitively impaired (p = .01). With respect to the study hypothesis, Figure 1 demonstrates that delirious individuals had a significantly higher PHE/LNAA ratio during illness than nondelirious individuals (p = .03). Delirious individuals also had a higher PHE/LNAA ratio at recovery than nondelirious individuals, but this difference did not reach statistical significance. As Table 2 demonstrates, neither the PHE concentration nor the non-PHE LNAA concentration was statistically different between the delirious and nondelirious groups during illness, and there was a trend toward a lower non-PHE LNAA concentration in delirious subjects at recovery (p = .08).

PHE concentrations were higher during illness than recovery in both delirious and nondelirious groups. Interestingly, non-PHE LNAA concentrations increased in the nondelirious group from illness to recovery, whereas they declined in the delirious group. There was no significant difference between delirious and nondelirious individuals with respect to overall change in the PHE/LNAA ratio from illness to recovery. There was no difference in the TRP/LNAA ratio between delirious and nondelirious individual during illness or recovery. Greater impairment on the CPS (higher scores) was associated with a higher PHE/LNAA ratio (raw regression coefficient = 13.95; p = .02) during illness, but not during recovery (raw regression coefficient = 7.21; p = .50).

DISCUSSION

The present study suggests that delirium is associated with an elevated PHE/LNAA ratio during acute febrile ill-
ness in frail elderly cognitively impaired medical patients. The magnitude of change in the PHE/LNAA ratio was not associated with delirium, suggesting that the increase in the PHE/LNAA ratio might be a generalized response to illness, and delirium associated with higher illness PHE/LNAA ratios. This higher PHE/LNAA ratio during illness in the delirious group occurred because the modestly higher mean non-PHE LNAA concentration during illness was more than offset by an increase in mean PHE concentration. This is in contrast to the nondelirious group, in which the mean PHE concentration was not as high during illness as in the delirious group, and the non-PHE LNAA concentration was lower during illness than recovery. Had the mean non-PHE LNAA concentration been lower during illness than recovery in the delirious group, as it was in the nondelirious group, the overall PHE/LNAA ratios for the delirious group would have been even higher.

Interestingly, the delirious individuals had a higher PHE/LNAA ratio at recovery than nondelirious individuals, although this difference did not reach statistical significance. This difference, if borne out by larger studies, might suggest that baseline differences in PHE/LNAA ratios may predispose to delirium during illness. This may simply be because starting with a higher PHE/LNAA ratio makes it easier to reach a hypothetical threshold level of the PHE/LNAA ratio at which delirium may be precipitated. The observation that the magnitudes of the change in mean PHE concentration, as well as the actual direction of the mean non-PHE LNAA concentration changes, were different in the delirious and nondelirious groups suggests that the answer maybe more complex. Whether other factors related to an elevated PHE/LNAA ratio at baseline may predispose to delirium is unknown. In one prior study of 87 nursing home residents, the serum concentrations of individual LNAAAs were not associated with the Blessed Dementia Scale score, and although the PHE/LNAA ratio was not reported, an elevated PHE concentration was associated with depression (14).

The plausibility of a relationship between elevated PHE/LNAA ratios and delirium is supported by several prior studies. In one recent study of 296 postcardiac surgery patients, elevations of the PHE/LNAA ratio were independently associated with postoperative delirium (15). Prior studies of patients with septic encephalopathy have also reported increased levels of PHE and PHE metabolites in the plasma and cerebrospinal fluid of those with encephalopathy (16,17). Further, elevated levels of PHE have been shown to prolong performance time, impair higher integrative function (18), and reduce electroencephalogram mean power frequency (19) in older treated patients with phenylketonuria. The cognitive effects of PHE elevation or changes in PHE/LNAA ratios in normal older persons has not been studied.

Because tyrosine hydroxylase is rate limiting for the production of dopamine, excess dopamine production is unlikely to be a mechanism whereby excessive PHE entry into the brain may effect cognition. PHE’s primary effects might occur following entry in the brain, where it also competes with TRP and tyrosine for hydroxylation. Elevated PHE levels in treated patients with phenylketonuria have been reported to reduce plasma dihydroxyphenylalanine (L-DOPA) concentrations and urinary serotonin excretion (18,19). Furthermore, in phenylketonuria, PHE undergoes alternate metabolism, and these metabolites of PHE or PHE itself may be neurotoxic (4). In contrast to a previously reported study of postcardiac surgery patients (15), in these elderly medical patients no association between delirium and lower TRP/LNAA ratios was found.

There are a few limitations to the present study. The sample size may have been too small to detect important differences in some of the study variables between the residents with and without delirium. The subjects had mild illnesses not requiring hospitalization, and therefore these findings may not hold true for sicker individuals. It is also possible that the changes in LNAA concentrations and ratios observed in this study are an epiphenomenon and not causally related to delirium itself. Diet was not rigorously controlled

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**Table 2. Changes in PHE and LNAA During Illness Among Subjects With and Without Delirium**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 21)</th>
<th>Not Delirious (n = 14)</th>
<th>Delirious (n = 7)</th>
<th>p Value* (Not delirious vs delirious)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHE/LNAA Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness</td>
<td>0.161 (0.009)</td>
<td>0.148 (0.008)</td>
<td>0.186 (0.016)</td>
<td>0.03</td>
</tr>
<tr>
<td>Recovery</td>
<td>0.113 (0.005)</td>
<td>0.106 (0.003)</td>
<td>0.126 (0.012)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>0.048 (0.009)</td>
<td>0.042 (0.008)</td>
<td>0.060 (0.023)</td>
<td></td>
</tr>
<tr>
<td>TRP/LNAA Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness</td>
<td>0.065 (0.003)</td>
<td>0.065 (0.004)</td>
<td>0.065 (0.006)</td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>0.073 (0.003)</td>
<td>0.073 (0.03)</td>
<td>0.072 (0.004)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Values represent the mean (SEM). PHE = phenylalanine; LNAA = large neutral amino acids; TRP = tryptophan. PHE and non-PHE LNAA concentrations are in micromoles per liter.

*This is determined by t test.
and can have marked effects on plasma LNAA concentrations. However, the drawing of plasma samples before the morning meal may have attenuated diet-related differences in amino acid levels.

Because cognitive impairment was so prevalent in this population, it cannot be definitively concluded that PHE/LNAA changes were associated with delirium, independent of dementia. The lack of association between cognitive impairment and PHE ratios at recovery suggests that the relationship between PHE/LNAA changes and delirium may not be related to cognitive impairment per se. Indeed, if an elevated PHE/LNAA ratio does negatively affect brain function, these effects may be more likely to precipitate delirium in those with prior cognitive impairments.

The present study found that an elevated plasma PHE/LNAA ratio during acute febrile illness is associated with delirium in elderly medical patients. Because the PHE/LNAA ratio can be influenced by diet and intravenous solutions, the potential for being able to counter illness-related changes in PHE/LNAA exists. These findings, if borne out by future studies, identify another potentially fruitful area of investigation for the prevention and treatment of this common and morbid condition.

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