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Plasma Tryptophan and Tyrosine levels are Independent Risk Factors for Transitioning to Delirium in Critically Ill Mechanically Ventilated Patients: a pilot investigation

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Abstract

The pathophysiology of delirium remains elusive though neurotransmitters and their precursor large neutral amino acids (LNAAs) may play a role. This pilot study investigated whether alterations of tryptophan (Trp), phenylalanine (Phe), and tyrosine (Tyr), plasma levels were associated with a higher risk of transitioning to delirium in critically ill patients.

Methods—Plasma LNAA concentrations were determined on days 1 and 3 in mechanically ventilated (MV) patients from the MENDS randomized controlled trial (dexmedetomidine vs. lorazepam sedation). Three independent variables were calculated by dividing the plasma concentrations of Trp, Phe, and Tyr by the sum of all other LNAA concentrations. Delirium was assessed daily using the Confusion Assessment Method in ICU (CAM-ICU). Markov regression models were used to analyze the independent associations between plasma LNAA ratios and transition to delirium after adjusting for important covariates.

Results—The 97 patients included in the analysis had a high severity of illness (median APACHE II, 28; IQR, 24 to 32). Patients with either high or very low tryptophan to LNAA ratios (p=0.0003), and tyrosine to LNAA ratios (p=0.02) were at increased risk of transitioning to delirium, after adjusting for potential confounders. Phenylalanine levels were not associated with transition to delirium (p=0.27). Older age and exposure to fentanyl were also associated with a higher probability of transitioning to delirium.

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Conclusions—In this pilot study, plasma tryptophan/LNAA (via serotonin or tryptophan metabolites) and tyrosine/LNAA ratios (via dopamine or its downstream neurotransmitter norepinephrine) were associated with transition to delirium in MV patients, suggesting that alterations of amino acids may be important in the pathogenesis of ICU delirium. Future studies studying the role of amino acid precursors of neurotransmitters are warranted in critically ill patients.

Keywords

delirium; amino acids; tryptophan; phenylalanine; tyrosine; large neutral amino acids; blood brain barrier; LAT-1 transporter; risk factor for delirium

Introduction

Delirium is highly prevalent among patients in the intensive care unit (ICU) with reported rates varying from approximately 20–80%, depending upon the severity of illness and the diagnostic method [1–3]. Delirium in the ICU setting is associated with prolonged hospitalization [4–6], increased costs [7], mortality [8–10], and potentially long term cognitive impairment [11, 12]. Despite previous efforts, a firm understanding of the pathophysiology of delirium remains elusive, and delirium is thought to occur due to alterations in neurotransmission [13–15], inflammation [16, 17], and/or cerebral blood flow [18, 19].

Theories associating changes in neurotransmission with delirium focus upon the effects of serotonin (5HT), dopamine (DA), acetylcholine (ACh) and norepinephrine (NE) pathways [14, 15, 20–22]. No technique currently exists to measure neurotransmitter concentrations *in vivo* in critically ill patients without the performance of invasive procedures such as lumbar punctures. However, the rate limiting step for synthesis and release of these neurotransmitters is the availability of the respective plasma precursor large neutral amino acids (LNAA), which can easily be measured [23]. Serotonin synthesis depends upon the availability of tryptophan (Trp). In contrast, DA and NE production require tyrosine (Tyr) and phenylalanine (Phe), as both are part of the same metabolic pathway. Cerebral uptake of these circulating amino acids involves transport through two membranes: the brain capillary endothelial wall, forming the blood brain barrier (BBB) *in vivo*, and the brain cell plasma membrane [23]. The entry of the LNAA across the BBB occurs via the sodium independent LNAA transporter type 1 (LAT1) [24, 25]. The LAT1 transporter in the BBB has a much higher affinity for the LNAAs than similar transporters in peripheral tissue [24], underlying the brain's selective vulnerability to pathological effects of hyper/hypo-aminoacidemias. Given this high affinity, the LAT1 transporters are normally highly saturated, so a selective increase in one amino acid will reduce the entry of the other LNAAs (tryptophan, phenylalanine, tyrosine, lysine, methionine, valine, leucine and isoleucine) [23–25]. Thus, if the plasma Trp concentration increases in comparison to other LNAAs, an increased Trp to other LNAA ratio will result, and more Trp will pass through the BBB via the LAT-1 transporter to provide the opportunity for increased serotonin synthesis. Alternatively, an increase in the plasma concentration of Phe or Tyr would result in an increase in central DA and NE.

Plasma levels of Phe have been implicated in delirium in febrile hospitalized patients and cardiac surgery patients [20–22, 26], while Trp increases have been seen in patients with hepatic encephalopathy [27]. No prior study, however, has evaluated the relationship of amino acid precursors for neurotransmitters and delirium in critically ill mechanically ventilated patients. This pilot investigation was designed to study the temporal association of

Trp, Phe, and Tyr levels as risk factors for transitioning into delirium, in order to offer insight into potential pathophysiological mechanisms of delirium among ICU patients.

Materials and methods

The institutional review board (IRB) at Vanderbilt University Medical Center, Nashville, Tennessee approved this study. Plasma levels of Trp, Tyr, Phe and the other LNAAs (lysine, methionine, valine, leucine and isoleucine) were prospectively collected from subjects enrolled in the MENDS double blind, randomized controlled trial comparing sedation with dexmedetomidine versus lorazepam [28]. The patient population has previously been described in detail: 103 adult mechanically ventilated medical and surgical ICU patients from two tertiary care centers, enrolled between August 2004 and April 2006, excluding those with neurological disease (previous stroke, cerebral palsy, etc), active seizure disorders, Child-Pugh class B or C cirrhosis, alcohol abuse, active myocardial ischemia, second- or third-degree heart block, severe dementia, pregnancy, and severe hearing disabilities or inability to understand English, which would prevent delirium evaluations [28].

At enrollment, baseline cognitive abilities were assessed through surrogate interview using the validated Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [29], and demographics were collected via data accessed from the computerized medical record.

Delirium was assessed until hospital discharge or for up to 12 days using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [1, 2]. The sedation level was measured via the Richmond Agitation-Sedation Scale (RASS) [30, 31]. Patients were categorized as delirious if they had a RASS score of −3 or greater (i.e. −3 to + 4) and a positive CAM-ICU score. Coma was defined as a RASS score of −4 (responsive only to physical stimulus) or −5 (unresponsive to physical stimulus). A more comprehensive description and training manual for the CAM-ICU and RASS scale are available at: http://www.icudelirium.org.

Patient blood samples were collected and centrifuged on study days 1 and 3. Plasma was separated and stored at −80° Celsius (C). Plasma amino acids were analyzed using high performance liquid chromatography (HPLC) [32]. To examine the independent relationship of the amino acid precursors for serotonin, DA and NE, plasma ratios of Trp, Phe, and Tyr were calculated by dividing the plasma concentration for each by the sum of the concentrations of all the remaining LNAAs (e.g the Trp/LNAA ratio is the concentration of Trp divided by the sum of tyrosine, phenylalanine, lysine, methionine, valine, leucine, and isoleucine), as previously reported [20–22]. Plasma ratios for these precursors were used as peripheral indices of their cerebral availability for neurotransmitter synthesis following transport across the BBB.

Statistical Analysis

Patients' baseline demographic and clinical variables are presented using medians and interquartile ranges for continuous variables, and proportions for categorical variables. This study's primary outcome was to determine the temporal association of Trp, Phe and Tyr in transition to delirium. Markov regression models [33] were used to determine the probability of transitioning to delirium as a function of the LNAA ratios from the previous 24 hours and pre-determined clinically relevant covariates: age, IQCODE, APACHE II at enrollment, sedation regimen (dexmedetomidine, lorazepam, or fentanyl) and mental status on the previous day. Generalized Estimation Equations (GEE) [34] were used to account for correlations among patient observations. Three separate models were evaluated, with Trp/LNAA, Phe/LNAA and Tyr/LNAA studied as the independent variables of interest. Given

that sedatives are so closely tied with coma, we excluded all transitions to coma in our Markov model, so that the model examined transitions from normal, delirious or comatose mental state to either normal or delirious states. For this analysis, the outcome variable was binary; thus, the logit link function and a binomial distribution were specified in GEE. Since amino acids samples were collected on study days 1 and 3 and cognitive status data was recorded more frequently, we only used those cognitive assessments that had amino acid levels measured the previous day as the dependent variables. Restricted cubic splines were used to assess any nonlinear effect of amino acids. All statistical analyses were performed using R version 2.7 (www.r-project.org).

Results

Among the available 103 patients, 96 were included in this study's analyses, following exclusions based upon the lack of sufficient amino acid specimens or at least two cognitive status evaluations for the computation of Markov model transitions (total 7 patients). Baseline demographic characteristics are described in Table 1. Patients presented a high severity of illness with a median (interquartile range, IQR) APACHE-II score of 28 (24, 32), with sepsis and acute respiratory distress syndrome being the most common admission diagnosis.

In the Markov model, both Trp/LNAA (p=0.0003) and Tyr/LNAA (p=0.02) ratios were independent risk factor for transitioning to delirium (Tables 2 and 3). The relationship between Trp/LNAA ratios and Tyr/LNAA ratios and transitioning to delirium are graphically shown in Figures 1 and 2 respectively, and indicate that both low and high levels of tryptophan and tyrosine were associated with an increased risk of delirium. The Phe/LNAA ratio was not associated with an increased risk of transitioning to delirium (p=0.27) (Tables 4). In keeping with results of our previous studies [35, 36], increasing age, APACHE II scores and exposure to fentanyl was associated with an increased probability of transitioning to delirium in all 3 models (Trp/LNAA, Tyr/LNAA and Phe/LNAA) (Tables 2, 3 and 4).

Discussion

To our knowledge, this is the first study evaluating the relationship between plasma amino acid ratios and transitioning to delirium in a cohort of mechanically ventilated critically ill patients. In this pilot study, extremely low and high levels of Trp/LNAA and Tyr/LNAA were significantly associated with transitioning to delirium. Furthermore, our study was consistent with previous studies in that it showed that age, APACHE II scores and exposure to fentanyl were risk factors for delirium [35, 36].

Our findings of the association of high levels of Trp with delirium are in accordance with clinical studies that have suggested that excess serotonin activity is responsible for the development of psychosis associated with hepatic encephalopathy and serotonin syndrome [20, 37]. Our data also suggest that very low levels of tryptophan are associated with an increased risk of transitioning into delirium. Low Trp levels (thus presumably low serotonin) have been associated with neuropsychiatric complications among patients with severe alcohol withdrawal, individuals treated with levodopa for Parkinson's disease, and postoperative patients [20]. Potentially these low Trp levels, however, must be sufficiently decreased past a threshold value in order to decrease serotonin efflux [38], which could possibly explain the lack of increased risk among patients with intermediate Trp ratio levels. Unfortunately, it is unclear whether the symptoms of delirium associated with alterations in Trp concentrations are due to the production of neurotoxic metabolites of tryptophan,

fluctuations of serotonin or its down steam neurotransmitter, melatonin, or a combination of both.

A possible mechanism for Trp associated delirium is through the production of metabolites that are neurotoxic. Following activation of the immune and inflammatory response systems as seen in critical illness, Trp undergoes metabolism via the kynurenine pathway through the induction of indoleamine-2,3-dioxygenase (IDO) (Figure 3). This leads to an increased production of kynurenine and additional metabolites in both central [38] and peripheral tissues [39]. In the presence of inflammation, kynurenine is further metabolized to quinolinic acid, an *N*-methyl-D-aspartate (NMDA) receptor agonist and neurotoxin, while to a lesser extent Trp is metabolized to the neuroprotective NMDA antagonist, kynurenic acid. Potentially enhancing the detrimental effects of inflammation, kynurenine also makes the blood brain barrier more susceptible to the neurotoxic effects of quinolinic acid [40]. Of note, the kynurenine pathway of Trp metabolism is quantitatively more prominent in comparison to the pathways for serotonin and melatonin production, and it has even been described as occurring ten times more frequently [41], with approximately only 1% of Trp metabolism undergoing the serotonin pathway [42]. Potentially, such metabolites in increased amounts could lead to the excitatory neuropsychiatric complications found among patients with delirium [38, 40, 41].

A second possible mechanism by which tryptophan may lead to delirium is via alteration of melatonin production secondary to changes in serotonin levels. The production of melatonin from serotonin is controlled by serotonin-N-acetyltransferase (NAT), which is the rate limiting step (Figure 3). Melatonin is responsible for sleep-wake cycle modulation and may similarly increase or decrease in concentration depending upon Trp levels [26]. A high Trp concentration (or increased serotonin breakdown) can potentially lead to increased production of melatonin, thereby causing the somnolent symptoms of hypoactive delirium, while a low Trp ratio could be responsible for decreased melatonin, sleep dysregulation, and the development of hyperactive delirium [43]. This pattern of abnormal plasma melatonin levels has been noted among peri- and post-operative patients with delirium [43]. In support of these theories, Balan et al. [44] have found high levels of the melatonin metabolite 6-sulphatoxymelatonin (6-SMT) in the urine of patients with hypoactive delirium, with much lower levels in those with hyperactive delirium [44]. We were not able to evaluate the relationship between tryptophan levels and the hypoactive and hyperactive subtypes of delirium, because pure hyperactive delirium occurs in <5% of ICU patients [45, 46], limiting the ability to study this relationship.

The other notable finding in our study was that the Tyr/LNAA ratio was also an independent risk factor for transitioning to delirium in critically ill mechanically ventilated patients, such that both low and high levels were associated with increased risk of developing delirium. It can be hypothesized that patients with high levels of tyrosine are more likely to have excess dopamine or its down stream neurotransmitter, norepinephrine, both of which have been implicated in the pathogenesis of delirium [23]. On the other hand given that both tryptophan and tyrosine compete to cross the blood brain barrier, it is also plausible that the reason low levels of both tyrosine and tryptophan are associated with delirium is because this infact is a reflection of higher levels of the other amino acid. [23–25].

In concordance with our previous investigation [35], both age and APACHE II scores were risk factors for development of delirium. Additionally the previous day's mental status (delirium or normal) was a strong predictor of the mental status the next day. Exposure to fentanyl was also associated with transition to delirium in the three models. These findings are consistent with the fact that delirium is often due to multiple risk factors. In our study, exposure to the alpha$_2$ agonist, dexmedetomidine, was not associated with delirium in all

three models. The mechanisms via which dexmedetomidine alters delirium risk are not known, though it possibly modulates neurotransmission (by noradrenergic blockage at the locus ceruleus), attenuates inflammation and may improve natural sleep. Therefore the relationships between LNAA levels, sedative choice and delirium risk should remain an important component of this line or research, as they have not been clearly elucidated in this pilot investigation.

Our study presents several strengths and limitations. First, the samples used to test the levels of the LNAA were drawn on study days 1 and 3, and therefore differences in the relationship between transitioning to delirium and LNAA might have been altered had we collected these samples daily, especially if major dietary changes occurred during this period, such as the start of parenteral nutrition. If important dietary changes did occur, it is unlikely that they were influenced by delirium status. Therefore, any misclassification resulting from dietary changes and the lack of daily sample collection would be non-differential and would bias our results toward showing less of an association than truly exists. To further reduce the potential for any systematic bias, we utilized only those cognitive assessments on the day following the plasma amino acid levels. This limitation highlights the difficulty in conducting research involving daily blood collections from critically ill patients. Second, we did not monitor dietary information that may have had a role in altering the levels of LNAA. While dietary supplementation may be a method by which to manipulate these levels towards therapeutic goals when these relationships are better understood, the main purpose of this study was to assess whether Trp, Phe, and Tyr levels were associated with increased risk of the development of delirium, regardless of the source of excess or depletion. Future studies will be needed to further characterize the etiology of Trp or Tyr excess (or significant insufficiency, as evident with our patient data) and to design interventional trials to ascertain if optimizing LNAA ratio levels of Trp and Tyr improve delirium outcomes. Third, we did not detect an association between levels of Phe with delirium, as seen in previous studies in cardiac surgery patients and long-term care patients [20, 22, 47]. This may be due to the different patient population utilized (ICU mechanically ventilated critically ill patients versus elective cardiac surgical/hospitalized), which is also reflected with the higher rate of delirium found in our patient population compared to the non-ICU cohort (80% versus 13.5%). Addressing these limitations in future work will provide opportunities by which to build on the knowledge gained via this pilot study in order to advance our understanding of the role of amino acids and neurotransmitters in delirium in the critically ill.

Conclusions

This pilot investigation found that high and extremely low levels of plasma tryptophan/LNAA (via serotonin or tryptophan metabolites) and tyrosine/LNAA ratios (via dopamine or its downstream neurotransmitter norepinephrine) were associated with transition to delirium in MV patients, suggesting that alterations of amino acids may be important in the pathogenesis of ICU delirium. The mechanisms postulated in this report provide insight into potential pathogenesis of delirium and indicate potential areas for future research into the modifiable causes and treatments for delirium during critical illness.

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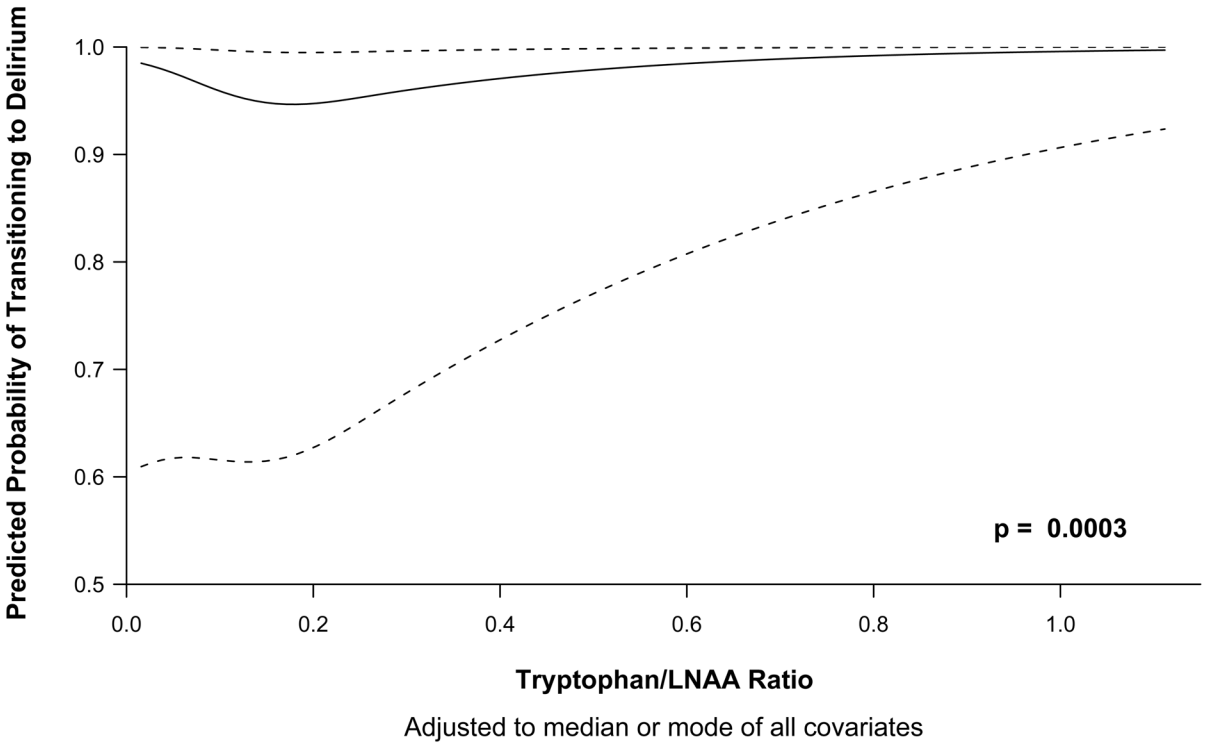

Figure 1.
Odds of transitioning to delirium according to tryptophan/large neutral amino acids ratio. The odds of transitioning from any mental state (normal, delirious, or comatose) to delirium are higher at very small Trp/LNAA ratios, lower when the ratio is approximately 0.2 and then increase as the Trp/LNAA ratio increases.

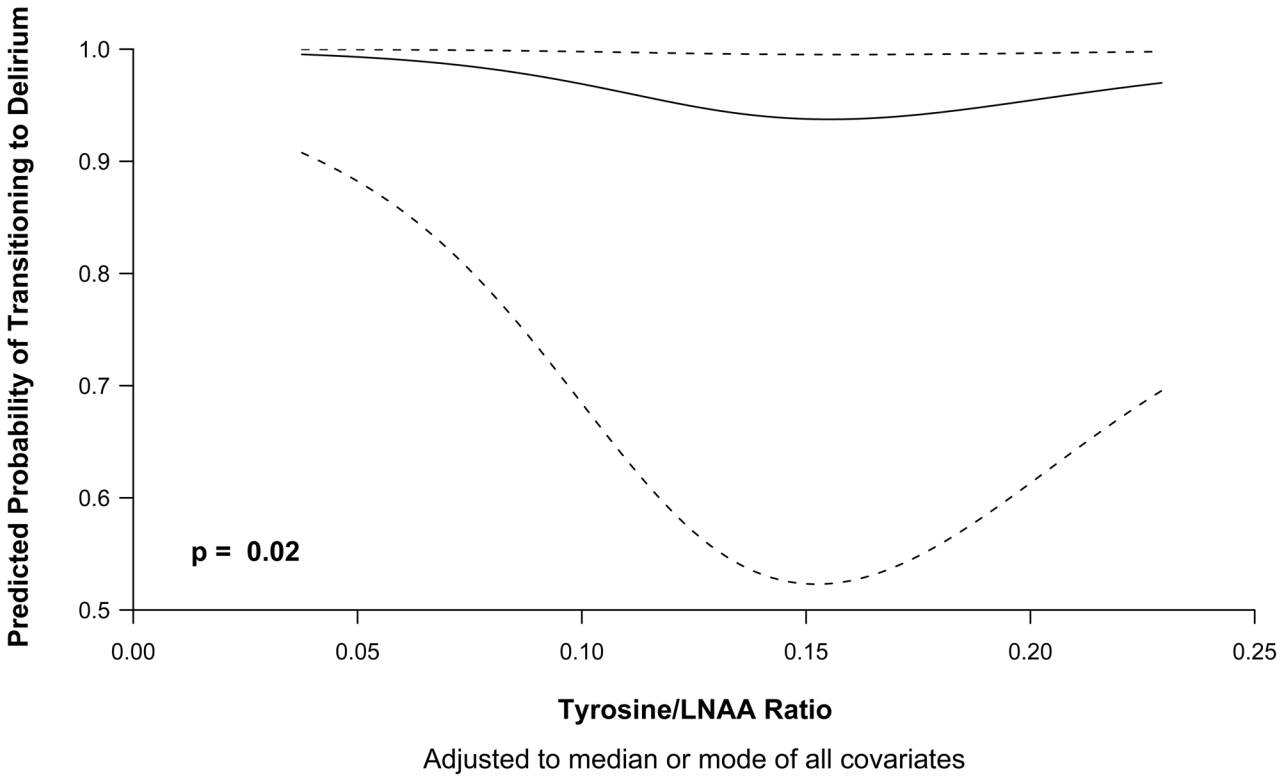

Figure 2.
Odds of transitioning to delirium according to tyrosine/large neutral amino acids ratio. The odds of transitioning from any mental state (normal, delirious, or comatose) to delirium are higher at very small Tyr/LNAA ratios, lower when the ratio is approximately 0.15 and then increase as the Tyr/LNAA ratio increases.

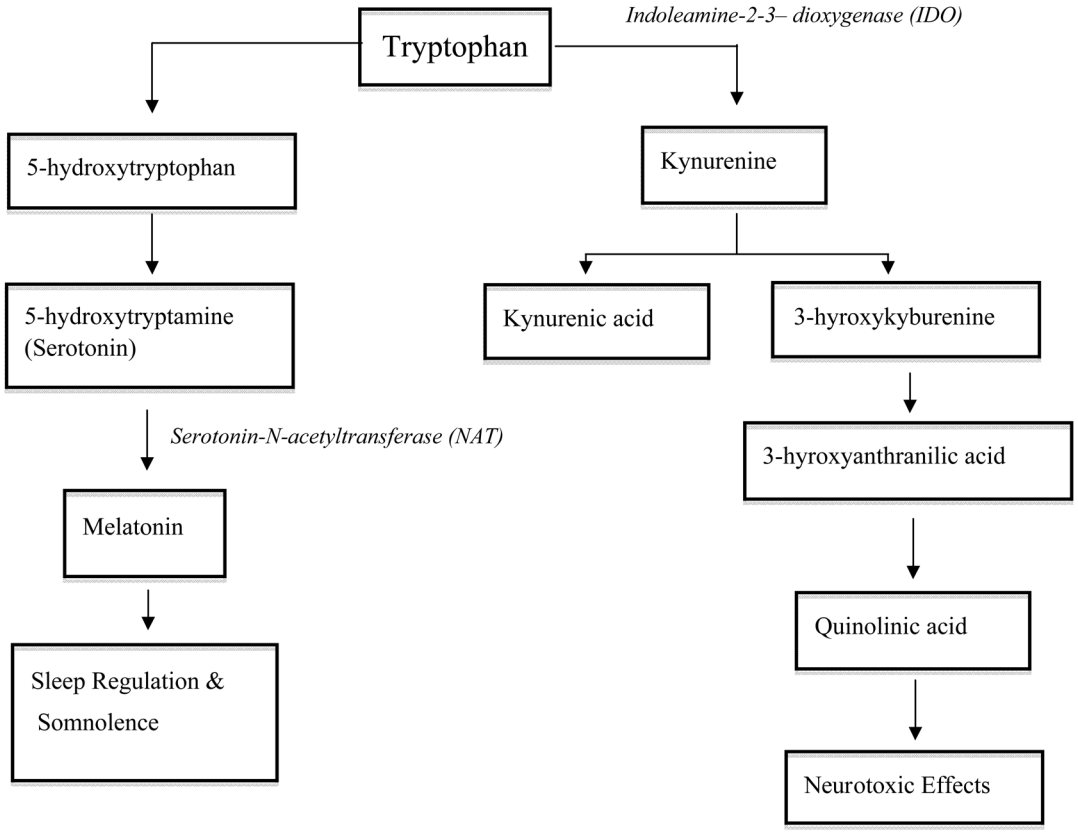

Figure 3.
Schematic of tryptophan metabolism via the kynurenine pathways or through the synthesis of serotonin. Note that this is not representative of all intermediates and enzymes for the purpose of simplicity.

Table 1

Demographics of patients.[a]

Variable	(N= 96)
Age, y	60 (47 to 66)
Men, No. (%)	51 (53)
APACHE II	28 (24 to 32)
IQCODE at enrollment	3 (3 to 3)
ICU type, No. (%)	
Medical ICU	70 (72)
Surgical ICU	27 (28)
Admission diagnoses, No. (%)	
Sepsis/acute respiratory distress syndrome	41 (42)
Pulmonary (other)[b]	22 (23)
Malignancies	8 (8)
Chronic obstructive pulmonary disease	4 (4)
Cardiogenic shock	2 (2)
Hemorrhagic shock	1 (1)
Renal Failure	1 (1)
Other[c]	34 (35)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

[a] Median (interquartile range) unless otherwise noted

[b] Pulmonary (other) included admissions due to pulmonary hypertension, cystic fibrosis, hemoptysis, pulmonary embolism, and pulmonary fibrosis.

[c] Included admission diagnoses due to gastric and colonic surgery, urological surgery, vascular surgery, cardiac surgery, transplant surgery (except liver); neuromuscular disease; reasons other than sepsis.

Table 2

Transition to Delirium and Tryptophan/Large Neutral Amino Acids Ratio.

Variables	Chi-Square	*P* Value
Tryptophan/LNAA ratio	16.1	0.0003
Age	8.1	0.005
Modified APACHE II at enrollment	4.9	0.02
IQCODE	0.1	0.73
Previous day's mental status	15.6	0.0004
Dexmedetomidine on previous day	0.2	0.67
Lorazepam on previous day	0.3	0.58
Fentanyl on previous day	5.23	0.02

Abbreviations: LNAA, Large Neutral Amino Acids; Modified APACHE II, Acute Physiology and Chronic Health Evaluation II excluding Glasgow coma scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

Table 3

Transition to Delirium and Tyrosine/Large Neutral Amino Acids Ratio.

Variables	Chi-Square	*P* Value
Tyrosine/LNAA ratio	8.3	0.02
Age	7.3	0.007
Modified APACHE II at enrollment	8.2	0.004
IQCODE	0.2	0.65
Previous day's mental status	18.8	<0.0001
Dexmedetomidine on previous day	0.72	0.39
Lorazepam on previous day	1.71	0.19
Fentanyl on previous day	3.3	0.07

Abbreviations: LNAA, Large Neutral Amino Acids; Modified APACHE II, Acute Physiology and Chronic Health Evaluation II excluding Glasgow coma scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

Table 4

Transition to Delirium and Phenylalanine/Large Neutral Amino Acids Ratio.

Variables	Chi-Square	*P* Value
Phenylalanine/LNAA ratio	2.6	0.27
Age	8.1	0.004
Modified APACHE II at enrollment	3.9	0.05
IQCODE	0.08	0.78
Previous day's mental status	19.4	<0.0001
Dexmedetomidine on previous day	0.24	0.62
Lorazepam on previous day	1.2	0.28
Fentanyl on previous day	3.7	0.05

Abbreviations: LNAA, Large Neutral Amino Acids; Modified APACHE II, Acute Physiology and Chronic Health Evaluation II excluding Glasgow coma scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.