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Low Tryptophan Levels Are Associated with Post-Operative Delirium in the Elderly

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Abstract

Background—Post-operative delirium is a common complication in geriatric patients. Tryptophan is an amino acid precursor to the mood stabilizing neurotransmitters serotonin and melatonin. We hypothesized that tryptophan levels are lower in elderly subjects who develop post-operative delirium.

Methods—A prospective observational study was performed. Subjects older than 50 years undergoing an operation with an anticipated post-operative ICU admission were recruited. Post-operative delirium assessment occurred daily using the Confusion Assessment Method-ICU. Peripheral serum tryptophan levels were measured two days following surgery.

Results—Forty-nine subjects (46 male) were enrolled with an age of 64 ± 7 years. The incidence of delirium was 43% (21/49). The average duration of delirium was 2.9 ± 3.0 days. Tryptophan was lower in the subjects who developed delirium (29.9 ± 13.3 versus 48.5 ± 19.8 $\mu\text{g/ml}$, $*p < 0.001$)

Conclusion—Lower levels of tryptophan post-operatively were associated with the development of delirium in the elderly.

Keywords

Tryptophan; Delirium; Surgery; Post-Operative; Geriatric

INTRODUCTION

Delirium is the most common post-operative complication in geriatric patients.¹ In 2004, patients aged 65 years and older accounted for 55% of all operations in the United States.² With an aging population, the understanding of the etiology and pathophysiology of delirium becomes increasingly relevant.

The etiology of post-operative delirium in elderly patients is unclear. Factors implicated in the pathogenesis of delirium include alterations in neurotransmission and inflammation.³ Tryptophan is a large neutral amino acid which is able to cross the blood brain barrier.⁴ Once

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inside the central nervous system, tryptophan acts as a precursor to the neurotransmitters serotonin and melatonin.⁴ The neurotransmitters serotonin and melatonin improve adaptation to stress, prevent the deterioration of mood and improve emotional processing.^{5,6} Post-operative delirium has been linked to low levels of tryptophan, serotonin and melatonin.^{4,7} Previous research found tryptophan levels were reduced on post-operative day number one following elective cardiac surgery.⁴ Alterations in tryptophan and other amino acids have been recognized as a potential mechanism for delirium which warrants further investigation.⁸

The purpose of our study was (1) to determine the baseline demographics of elderly subjects who did and did not develop post-operative delirium and (2) to compare tryptophan levels in elderly subjects who did and did not develop post-operative delirium. We hypothesized that tryptophan levels would be lower in elderly subjects who developed post-operative delirium.

METHODS

Prior to patient recruitment, approval was obtained from the Colorado Multiple Institutional Review Board (05-0281). Written informed consent was obtained from all participants. Inclusion criteria included: (1) age of 50 years or older, (2) undergoing an elective operation with an anticipated post-operative intensive care unit (ICU) admission and (3) able to undergo informed consent. Exclusion criteria included: (1) non-English speaking (in whom delirium assessment may be inaccurate because of a language barrier), and (2) vision/hearing impaired (in whom the delirium assessment tool cannot be administered).

Between April and September 2007, 62 patients were screened for enrollment. Exclusion criteria made 7 patients ineligible (6-operation on the brain, 1-vision impairment) and 3 patients refused to participate. Of the 52 subjects enrolled, three participants did not have tryptophan levels assessed (1-not admitted to ICU after the operation, 1-death prior to blood draw for tryptophan level, and 1-subject request to withdraw from study).

Relevant pre- and intra-operative variables were recorded. Pre-operatively, each participant underwent assessment of cognitive function, functional status and burden of co-morbidities. Cognitive function was determined with the validated Mini-Cog Test which combines a three item recall with a clock drawing task to determine level of cognitive impairment.⁹ Functional status was assessed with the Barthel Index which rates the ability to perform activities of daily living.¹⁰ Burden of co-morbidities was defined by the Charlson Index which provides a risk of one year mortality based on the sum of co-morbidities.¹¹

Delirium assessment was performed daily in the ICU with the Confusion Assessment Method-ICU (CAM-ICU).¹² This reliable and valid assessment tool checks for fluctuations in mental status, inattention, altered level of consciousness, and disorganized thinking to determine the presence or absence of delirium.¹² Because delirium is a transient clinical event and the fluctuations in and out of delirium can be missed by a single daily evaluation, a previously described validated chart review for the presence of delirium over each 24-hour period was performed which looked for key words (for example; agitation, confusion, disorientation) and descriptors which described fluctuations in mental status.¹³ Delirium was determined to be present if either the CAM-ICU or the validated chart review were positive as previously described.¹³

Blood was drawn on the morning of post-operative day number two in all patients and assessed for the level of tryptophan and phenylalanine. Post-operative day number two was chosen because this was the most common day of initial presentation of delirium in both our pilot study and in the literature.² Plasma was separated by centrifugation and the serum was stored at -20°C in a polypropylene tube. Plasma tryptophan was measured with liquid chromatography and mass spectrometry.¹⁴

Inter-rater reliability was established prior to study initiation. A pilot study of 100 patient encounters was completed to determine inter-rater reliability between researchers (T.N.R., C.D.R. and E.M.A.) administering the CAM-ICU for delirium assessment. A high inter-rater reliability with a concordance rate = 98% and a kappa statistic = 0.96 (95% confidence interval, 0.91 to 1.00) was established. Subjects in the pilot study were not included in the data analysis.

Statistical analyses were performed using univariate student's t-test for continuous variables and either chi-squared or Fischer's exact for dichotomous variables. Results are reported as mean±standard deviation and * denotes significance set at $p<0.05$.

RESULTS

Forty-nine subjects (46 male) were studied with an average age of 64 ± 7 years. The incidence of delirium was 43% (21/49). The average duration of delirium was 2.9 ± 3.0 days. The average time following the operation to the initial presentation of delirium was 2.9 ± 2.6 days (range 1 to 12 days). Length of intensive care unit stay for the entire group was 6.3 ± 4.3 days (range 3 to 35 days).

Subjects enrolled in the study underwent operations including: abdominal 23 (47%), cardiac 19 (39%), non-cardiac thoracic 5 (10%) and vascular 2 (4%). The number of each type of operation was similar in the groups that did and did not develop delirium. (see Table 1) Other intra-operative variables including type of anesthesia and length of operation were similar in the groups that did and did not develop delirium.(see Table 1)

Pre-operative clinical variables were recorded. Delirium was associated with older age, increased cognitive dysfunction, increased burden of co-morbidities and impaired functional status.(see Table 1) Pre-operative laboratory variables revealed delirium was associated with lower albumin levels. Other pre-operative laboratory variables including sodium, potassium, creatinine and glucose were similar in the two groups. (see Table 1) The coefficient of variance for each variable was: age 11%, co-morbidities (Charlson Index) 68%, cognitive function (Mini-Cog) 41%, functional status (Barthel Index) 8%, albumin 16%, sodium 2%, potassium 12%, creatinine 27%, glucose 36%, length of operation 37%, tryptophan 48% and phenylalanine 19%.

Peripheral blood drawn on the morning of post-operative day number two revealed the tryptophan level in subjects who developed delirium (30 ± 13 µg/ml, median 31 µg) to be lower in comparison to subjects who did not develop delirium (49 ± 20 µg/ml, median 44 µg, * $p=0.001$). (see Figure 1) Individual tryptophan levels of participants with and without post-operative delirium are presented on figure 2. Retrospective analysis of tryptophan data revealed a cutoff value of ≤ 40 µg/ml predicted post-operative delirium with a sensitivity of 81% and a specificity of 68%. The initial presentation of delirium in subjects with low tryptophan levels (≤ 40 µg/ml) was 3.0 ± 2.9 days following the operation which was similar in comparison to subjects with high tryptophan levels (>40 µg/ml) 2.2 ± 1.1 days ($p=0.527$) following the operation.

Peripheral blood drawn on the morning of post-operative day number two revealed the phenylalanine level in subjects who developed delirium (74 ± 17 µg/ml, median 76 µg) to be similar in comparison to subjects who did not develop delirium (75 ± 13 µg/ml, median 77 µg, $p=0.671$)

DISCUSSION

The purpose of our study was to compare the post-operative levels of tryptophan in elderly subjects who did and did not develop post-operative delirium. Subjects older than 50 years

with a planned post-operative ICU admission were enrolled. Pre-operative and intra-operative variables typical of patients who develop delirium in comparison to patients who do not develop delirium were found. Pre-operative clinical variables related to the delirium group included older age, cognitive impairment, impaired functional status and increased burden of co-morbidities. Pre-operative laboratory values were similar in the delirium and no delirium groups with the one exception of albumin which was lower in the delirious group. Types of operations, anesthesia technique and the length of the operations were similar in the two groups. Tryptophan levels on post-operative day number two were lower in the elderly group of patients who developed delirium in comparison to the group who did not develop delirium.

The relationship between altered tryptophan levels and delirium has been studied previously in both surgical and medical hospitalized patients. In surgical patients, van der Mast et al studied the relationship of tryptophan and delirium following cardiac surgery.⁴ Serum levels of tryptophan were found to be reduced in the patients who developed post-operative delirium compared to control.⁴ The authors suggested that decreased tryptophan peripherally might create alterations in central neurotransmitters, particularly serotonin, resulting in delirium.⁴ In febrile medical patients, Flacker et al studied the relationship of tryptophan levels and delirium in febrile medical patients.¹⁵ No relationship was identified between delirium and tryptophan levels during the acute illness or during recovery in elderly febrile medical patients.¹⁵

The importance of our finding that tryptophan levels were lower in elderly subjects who develop post-operative delirium is to provide insight into the underlying pathophysiology of post-operative delirium. The pathogenesis of post-operative delirium is likely multi-factorial and is poorly understood. A minority of post-operative delirium is attributed to metabolic abnormalities such as hypoxia, hypoglycemia, electrolyte abnormalities and sepsis. The majority of post-operative delirium in the elderly is not accompanied by an underlying organic abnormality. The "Threshold Theory" hypothesizes that changes in the aged brain's milieu of neurotransmitters and neurons account for the increased susceptibility of the geriatric patient to develop post-operative delirium.¹⁶ Senile dementia has been associated with multiple nutritional deficiencies, including lower tryptophan levels.¹⁷ The association of lower tryptophan levels and delirium could provide support for the "Threshold Theory." Our finding of decreased tryptophan levels in elderly patients with post-operative delirium suggests potential central nervous system deficiency of the neurotransmitter products of tryptophan which include both serotonin and melatonin.

Three competing theories could explain the differences in tryptophan levels: (1) a pre-operative baseline condition that predisposes to delirium; (2) an effect of other post-operative physiologic derangements that then in turn predisposes to delirium; or (3) low tryptophan levels and delirium are an epiphenomenon. The first theory of a lower baseline pre-operative tryptophan levels is less likely because van der Mast et al previously described similar pre-operative levels of tryptophan even though their post-operative group of delirious patients had lower levels of tryptophan.⁴ The second theory that the physiologic response to surgery alters tryptophan levels which then predisposes to delirium has been speculated to be the problem by authors who suggest that a catabolic post-operative state results in lowered tryptophan levels.¹⁸ And finally, the third theory that low tryptophan levels and post-operative delirium are an epiphenomena is less likely given that this finding has been described previously.⁴

The limitations of our project were threefold. First, the major limitation of this study is that pre-operative tryptophan values were not performed. The value of pre-operative levels would be to exclude pre-operative differences in tryptophan levels which might account for the differences found in the post-operative levels. Van der Mast et al found similar pre-operative levels of tryptophan even though their post-operative group of delirious patients had lower levels of tryptophan.⁴ Future studies should include pre-operative tryptophan level

measurements. Second, the operations in the study included abdominal, cardiac, non-cardiac thoracic and vascular. The variety of operative approaches may lead to differences in tryptophan metabolism which are not understood. However, the benefit of including a range of operations allows the results to be generalized to all post-operative patients admitted to the ICU. And third, male subjects accounted for 94% of the study group. While this reflects the gender ratio of patients at the Denver VA Medical Center and not selection bias, the lack of female participants may not take into account gender differences in tryptophan metabolism.

In summary, our project found that post-operative tryptophan levels were lower in elderly subjects who developed post-operative delirium in comparison to elderly subjects who did not develop post-operative delirium. The operative variables and the pre-operative laboratory data for the delirium and non-delirium groups were similar. The differences found in the pre-operative clinical variables were typical of risk factors related to development of post-operative delirium. This study provides background evidence to support a trial supplementing tryptophan in post-operative patients who are at high risk for developing delirium with the goal of reducing the incidence of delirium.

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Figure 1.
Post-operative Tryptophan Levels in Elderly Subjects with and without Delirium

Figure 2.
Individual Post-operative Tryptophan Levels in Elderly Subjects with and without Delirium

TABLE 1

BASELINE DEMOGRAPHICS OF STUDY POPULATION

Results reported as mean±standard deviation. Statistical analysis compared subjects in whom delirium was present to subjects in whom delirium was absent.

	All Subjects n=49	Present n=21	DELIRIUM Absent n=28	
PRE-OPERATIVE VARIABLES				
Clinical				
Age (years)	64±7	67.2±8.0	61.8±5.9	*p=0.009
Co-Morbidities (Charlson Index ^a) ¹	3.1±2.1	4.5±2.0	2.0±1.3	*p<0.001
Cognitive Function (Mini-Cog ^b)	3.7±1.5	2.5±1.6	4.6±0.5	*p<0.001
Functional Status (Barthel Index ^c)	96±8	92±10	99±4	*p<0.001
Laboratory				
Albumin (g/dL)	3.7±0.6	3.4±0.6	4.0±0.4	*p<0.001
Sodium (mEq/L)	139±3	138±3	140±4	p=0.147
Potassium (mEq/L)	4.2±0.5	4.1±0.6	4.3±0.4	p=0.166
Creatinine (mg/dL)	1.1±0.3	1.2±0.5	1.1±0.2	p=0.185
Glucose (mg/dL)	114±41	118±47	111±37	p=0.531
INTRA-OPERATIVE VARIABLES				
Type of Operation				
Abdominal Operations	23 (47%)	11 (32%)	12 (43%)	p=0.572
Cardiac Operations	19 (39%)	6 (29%)	13 (32%)	p=0.247
Non-Cardiac Thoracic Operations	5 (10%)	3 (14%)	2 (7%)	p=0.639
Vascular Operations	2 (4%)	1 (5%)	1 (4%)	p=0.835
Operating Room Variables				
GETA	43 (88%)	19 (90%)	24 (86%)	p=0.688
GETA + Epidural	6 (12%)	2 (10%)	4 (14%)	p=0.688
Time in Operating Room (minutes)	262±97	258±107	264±89	p=0.840

(a) Charlson's Index determines burden of co-morbidities from 0 (no comorbidities) to 17 (severe co-morbidities).

(b) Mini-Cog Test assesses cognitive dysfunction from 0 (severe cognitive dysfunction) to 5 (no cognitive dysfunction).

(c) Barthel Index describes functional status from 0 (severe functional impairment) to 100 (no functional impairment).

GETA = General-endotracheal anesthesia.