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Investigation of metabolic disorders in the etiology of delirium in geriatric patients

Metabolic disorders in the etiology of delirium

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Abstract

Aim: The aim of this study was to examine metabolic parameters, which are among the factors that promote delirium, in geriatric patients pre-diagnosed with delirium by the Consultation-Liaison Psychiatry Unit of our medical school.

Material and Methods: The diagnosis and treatment records of 1435 patients over 65 years of age were retrospectively screened. For patients diagnosed with delirium, demographic data, mode of presentation, leukocyte count, and levels of hematocrit, sodium, potassium, albumin, C-reactive protein (CRP), urea, creatinine, glucose, vitamin B12, TSH, and T4 were recorded.

Results: Of the 1435 patients screened, 1147 patients with available survival and laboratory data were included in the study. Of these, 285 patients were diagnosed with delirium and 861 patients were not. In the delirium group, 63% of the patients had anemia, 33% had leukocytosis, 28% had hyponatremia, 47% had elevated serum creatinine, 90% had elevated CRP, 60% had hypoalbuminemia, and 53% had hyperglycemia.

Discussion: Our comparison of patients with and without delirium indicates that metabolic disorders such as hyponatremia, hypopotassemia, hypoalbuminemia, impaired renal function, hyperglycemia, presence of infection, and anemia are contributing factors in delirium. Delirium is a serious and common problem that increases morbidity and mortality in geriatric patients. Identifying metabolic markers of delirium can help diagnose delirium and predict mortality.

Keywords

Delirium, Geriatric, Mortality, Metabolic Disorder

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Introduction

Delirium is a neuropsychiatric syndrome common among the elderly. It is serious and often fatal, involving severe cognitive impairment, changes in the sleep-wake cycle, and perceptual disturbances. Its diagnosis requires a cognitive assessment and a history of the onset of acute symptoms [1]. It is a clinical diagnosis, made with no laboratory measurements, imaging methods, or testing instruments. The diagnosis can only be made by careful clinical evaluation following thorough history-taking, behavioral observations, and assessment of cognitive functions [2]. Delirium is considered a warning sign that the patient's medical condition may be leading to morbidity or mortality [3].

The prevalence of delirium in the elderly varies among different populations. It has been observed at rates of 10% in emergency rooms, 10-30% in hospitalized patients, and 40% in terminal patients, while it may be as high as 80% among intensive care patients [4].

Generally, delirium is the direct result of a physiological stressor. There are many possible causes of delirium and it is not always possible to identify the underlying cause. The main goal of treatment is to determine and eliminate the underlying cause; therefore, it is critical to identify factors that may be involved in the etiology.

In brief, whenever a patient is diagnosed with delirium, the underlying cause should be investigated. A diagnosis of delirium should be rapidly confirmed by further assessment and examination. Most patients with delirium require hospitalization. A diagnosis of delirium also leads to prolonged hospital stays and increased mortality.

In this study, we aimed to determine the metabolic disorders and precipitating factors that may be associated with delirium in patients over 65 years of age who were referred to the Consultation-Liaison Psychiatry (CLP) Unit of our hospital between 2005 and 2013, to determine the prevalence of these metabolic disorders, and to evaluate their relationships with mortality.

Material and Methods

The files of all patients who were evaluated and diagnosed with a psychological disorder (n=12962) in the CLP Unit between January 2005 and December 2013 were accessed. The records were reviewed by two physicians and patients aged 65 years or older (n=1435) were selected for the study. Patients with available survival data (n=1147) constituted the study sample.

These patients' files were reviewed and they were divided into two groups: those who were diagnosed with delirium and those who were not. The study was approved by the Clinical Research Ethics Committee of Ege University (decision dated 03/04/2014, committee number 14-3.1/5). This retrospective evaluation was carried out in İzmir, the third largest city in Turkey.

The CLP records used in the diagnosis process comprised files structured as symptom checklists regarding cognitive disorders, mood disorders, psychotic disorders, anxiety disorders, and somatoform disorders according to the DSM-IV (Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision Criteria). Previous investigation of the reliability of these forms demonstrated high concordance of double-blind diagnoses based on file data.

After receiving the necessary permission, survival data were obtained from the Death Notification System of the Turkish Ministry of Health's Public Health Agency using the patients' citizenship numbers. Data regarding metabolic parameters were obtained from hospital records using hospital protocol numbers and the patients' Turkish citizenship numbers. Laboratory results from the date on which CLP consultation was requested for the patients were also included in the study.

Statistical Analysis

The data were analyzed using SPSS 22 (IBM Corp., Armonk, NY, USA). Descriptive results pertaining to numerical variables were expressed as mean ± standard deviation and those of categorical variables were expressed as frequency and percentage. Chi-square analysis and pairwise comparisons (Student's t-test, Mann-Whitney test) were performed in accordance with variable type.

Results

From the files of a total of 12962 patients who were evaluated and diagnosed with a psychological disorder by the CLP Unit between January 2005 and December 2013, the data of 1435 patients aged 65 years or older were obtained. Because survival data were not available for 288 of these patients, a total of 1147 patients constituted the study sample.

The prevalence of delirium among the 1435 elderly patients screened was 25.5%. The patients' mean age was 74.18±6.2 years (range: 65-96 years), 53.4% were female and 46.6% were male, and most were young-old (65-74 years old, 56.3%) or middle-old (75-84 years old, 36.1%). The mean age of patients diagnosed with delirium was 73.53±5.91 years.

Laboratory results and survival data were available for a total of 1147 patients (285 patients with delirium and 861

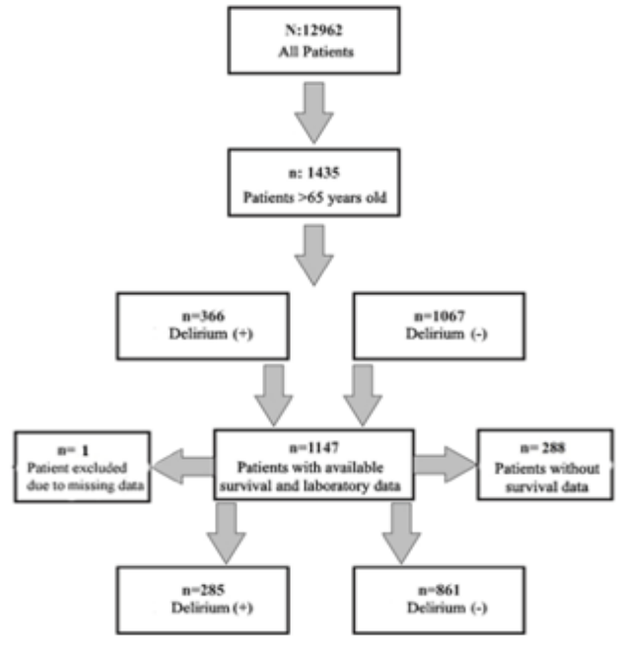

Figure 1. Patient sample

without delirium). The most commonly evaluated biomarkers were creatinine, urea, sodium, potassium, and complete blood count variables, while thyroid function tests and vitamin B12 were least commonly requested by physicians on the date of consultation. Uric acid and complete urine analysis were not included in the study because they were not evaluated for many patients at the time of diagnosis. Table 1 presents the percentage distributions of laboratory variables requested for the patients on the date of consultation based on the presence of delirium.

Table 1. Distribution of laboratory values according to presence of delirium

Variable		Delirium		p
Biomarkers		Yes (n=285)	No (n=861)	
Na (mEq/L)	<136	68 (28.5%)	101 (18.8%)	<0.001*
	>145	26 (10.9%)	33 (6.1%)	
	136-145	145 (60.7%)	404 (75.1%)	
K (mEq/L)	<3.5	30 (12.7%)	22 (4.1%)	<0.001*
	>5	9 (3.8%)	17 (3.2%)	
	3.05.2005	197 (83.5%)	488 (92.7%)	
Ca (mg/dL)	<8.6	107 (51.9%)	96 (20.7%)	<0.001*
	>10.2	7 (3.4%)	20 (4.3%)	
	8.6-10.2	92 (44.7%)	334 (74.9%)	
Cre (mg/dL)	≤1.2	125 (52.5%)	409 (73.7%)	<0.001*
	>1.2	113 (47.5%)	146 (26.3%)	
Urea (mg/dL)	≤50	92 (38.7%)	358 (65.0%)	<0.001*
	>50	146 (61.3%)	193 (35.0%)	
CRP (mg/dL)	≤0.5	12 (9.7%)	89 (31.3%)	<0.001*
	>0.5	112 (90.3%)	195 (68.7%)	
Albumin (g/dL)	<3.5	120 (60.6%)	112 (23.8%)	<0.001*
	≥3.5	78 (39.4%)	359 (76.2%)	
Vitamin B12 (pg/mL)	<197	3 (100.0%)	38 (95.0%)	0.864**
	≥197	-	2 (5.0%)	
TSH (IU/mL)	>5.5	6 (12.5%)	4 (4.0%)	0.496**
	0.35-5.5	31 (64.6%)	86 (86.9%)	
	<0.35	11 (22.9%)	9 (9.1%)	
WBC count (103/µL)	<4.5	12 (5.1%)	39 (7.5%)	<0.001*
	4.5-11.0	144 (61.3%)	400 (77.1%)	
	>11.0	79 (33.6%)	80 (15.4%)	
Hemoglobin (g/dL)	<11.7	150 (63.3%)	203 (38.8%)	<0.001*
	≥11.7	87 (36.7%)	320 (61.2%)	
Hematocrit (%)	<35	138 (58.2%)	185 (35.2%)	<0.001*
	≥35	99 (41.8%)	341 (64.8%)	

*: Pearson's chi-square test; **Fisher's exact test.

Table 2. Comparison of mean laboratory values of patients with and without delirium

Laboratory variables	Delirium group, mean values	Non-delirium group, mean values	p
Alb (g/dL)	3.28±0.7	3.8±0.6	<0.001
Na (mEq/L)	138.3±7.2	139.1±5.3	>0.05
K (mEq/L)	4.22±0.7	4.3±0.6	<0.001
Ca (mEq/L)	8.56±1.02	9.09±0.79	<0.001
Cre (mg/dL)	1.68±1.6	1.2±1.1	<0.001
Glucose (mg/dL)	131.4±85	119.3±60	<0.05
CRP (mg/dL)	9.49±10	5.25±8.1	<0.001

In summary, metabolic evaluation of laboratory values in the delirium group revealed that 63% of the delirium patients had anemia, 33% had leukocytosis, 28% had hyponatremia, 47% had high serum creatinine, 90% had elevated CRP, 60% had hypoalbuminemia, 51% had hypocalcemia, and 53% had hyperglycemia.

In the logistic regression model created with laboratory variables statistically associated with the presence of delirium (Na, K, Ca, creatinine, urea, CRP, albumin, sedimentation rate, leukocyte count, hemoglobin, hematocrit), hypernatremia was found to be an independent risk factor increasing the likelihood of delirium by 31.45 times (p=0.032).

The survival data of 1114 (79%) patients were evaluated from their public records. While 209 (75%) of delirium cases resulted in death, 68 (25%) patients with delirium survived. The mortality rate was significantly higher among patients with delirium than those without (p<0.001).

In comparisons of the prevalence of metabolic disorders in patients with and without delirium, hypoalbuminemia, hyponatremia, hypernatremia, hypopotassemia, hyperpotassemia, hypocalcemia, elevated creatinine, hyperglycemia, CRP elevation, anemia, and leukocytosis were found to be significantly more common in patients with delirium (p<0.001). On the other hand, there was no significant difference in terms of vitamin B12 deficiency or hypothyroidism (Table 2).

Discussion

Delirium is one of the geriatric emergencies frequently encountered in old age. However, there are few studies conducted in the general elderly population evaluating mortality and metabolic conditions in older adults diagnosed with delirium based on psychiatric evaluation.

The most commonly used inflammatory marker in clinical practice is CRP. Therefore, we retrospectively evaluated patients' CRP levels in the present study in order to investigate the relationship between delirium and inflammation. The difference between the two groups was statistically significant. In another study investigating the relationship between levels of CRP and insulin-like growth factor and rates of delirium in preoperative hip fracture patients, no relationship could be established between CRP values and the development of delirium. Postoperative CRP values were significantly higher in both the control group and the group of patients who developed delirium compared to preoperative values. Patients with delirium demonstrated a more marked change in CRP postoperatively than the control group. The lack of different CRP values in the delirium group compared to the control group makes it difficult to consider CRP as an independent risk factor in the development of delirium. On the other hand, the significant difference in the change in CRP in the delirium patients suggests that the inflammatory response has a role in the pathophysiology of delirium [5]. CRP is an important biomarker for the interpretation of these infectious and inflammatory processes [6].

Hyponatremia is the most common electrolyte imbalance, and advanced age is a risk factor for hyponatremia [7]. At 28%, the prevalence of hyponatremia among patients with delirium in the

present study was found to be comparable to that seen among hospital inpatients. Although the prevalence of hyponatremia was higher in patients diagnosed with delirium compared to patients without delirium, the two groups had similar mean sodium values. The difference between hyponatremic patients with and without delirium in terms of increased risk of mortality was insignificant. This may be due to the fact that hyponatremia is itself a risk factor for mortality.

Hypernatremia is another common disorder in the elderly [8]. In the present study, the logistic regression model including laboratory variables statistically associated with delirium revealed hypernatremia to be an independent risk factor that increased the likelihood of delirium by 31.45 times. Older adults are also prone to hypokalemia and hyperkalemia [9].

In the present study, uremia and potassium imbalance significantly reduced survival time in the presence of delirium, while diabetes mellitus was not found to have a statistically significant effect on survival. However, hyperglycemia alone is regarded as a factor that precipitates delirium. It may also be associated with complications related to DM and increased mortality.

Hypo/hyperthyroidism is known to be one of the precipitating factors of delirium. Although thyroid hormones are responsible for regulating metabolism, a decrease in thyroid hormone levels also causes significant changes in the receptors of noradrenaline, serotonin, and GABAergic agents. However, the mechanism by which thyroid hormones lead to psychiatric disorders is not clear. Accordingly, in addition to variations of thyroid hormones, changes in the function of neurotransmitters can cause delirium [10]. We noted that thyroid hormone levels were generally overlooked when the current metabolic status of patients with a pre-diagnosis of delirium was evaluated on the date of consultation. When patients with and without delirium were compared, the difference between them was not significant, but this may be due to inadequate assessment during laboratory studies.

The prevalence of vitamin B12 deficiency in adults over 60 years of age is reported as 5-20%. The elderly are the group most at risk of vitamin B12 deficiency [11]. In a study of patients who underwent coronary artery bypass surgery, it was emphasized that cobalamin deficiency may be associated with an increased risk of delirium. In addition, preoperative cobalamin levels were found to be associated with delirium severity [12]. The relationship between vitamin B12 deficiency and delirium is usually presented in case reports; large-scale studies on the topic are extremely limited in number. Similarly, in the present study, we observed that analysis of vitamin B12 level was requested for very few patients during metabolic evaluations of patients on the date of consultation for a pre-diagnosis of delirium. Vitamin B12 was evaluated for a total of 205 patients, of whom only 3 had both delirium and vitamin B12 deficiency. Further studies evaluating the relationship between vitamin B12 and delirium in larger numbers of patients are needed.

The threshold hemoglobin level for identifying anemia in the elderly is controversial. The generally accepted practice is to use the same limit as in the young population. Older adults with hemoglobin concentrations below 11 g/dL were found to have poorer performance and higher mortality rates from myocardial infarction and heart failure [13]. Joosten et al. determined that anemia was an independent risk factor for delirium [14]. In the present study, anemia was detected in 63% of patients with delirium. The fact that cardiac disease was not a determinant of mortality due to delirium in our study may be attributed to the very high prevalence of anemia. However, further analyses are needed to elucidate this issue.

According to a recent meta-analysis, in addition to older age, diabetes, blood transfusion, preoperative albumin, postoperative albumin, preoperative hematocrit, postoperative hematocrit, preoperative hemoglobin, postoperative hemoglobin, preoperative sodium, postoperative sodium, and living in an institution were found to be significant in cases of delirium [15]. Delirium is common in elderly inpatients. A number of models have been proposed to calculate the risk of developing delirium during hospitalization. Inouye et al. stated that a simple predictive model based on four risk factors can be used at patient admission to identify the elderly individuals at greatest risk. The four main components in this predictive model are low vision, cognitive impairment, severe disease (evaluation by APACHE score), and high blood urea nitrogen/serum creatinine ratio (>18), each being worth 1 point [16]. Our aim in the present study was to contribute to the literature in terms of diagnosing delirium and predicting mortality by more comprehensively determining metabolic markers. We hope that more practical metabolic scales will be developed in future meta-analyses.

According to studies in the literature, inflammation and oxidative stress contribute to the pathophysiology of delirium. However, it remains unclear whether the neutrophil-to-lymphocyte ratio (NLR), an indicator of systemic inflammation, is associated with delirium. Results from multivariate logistic regression models showed that NLR was independently associated with delirium in elderly internal medicine patients and we think that future studies will show us the importance of NLR in predicting metabolic disorders [17].

In summary, delirium in elderly patients leads to higher mortality independently of all risk factors. Although metabolic disorders that lead to delirium have been investigated in different studies, not many of those studies had large patient samples. There is no standardization of laboratory tests to be requested for the diagnosis of delirium. We believe that a standardized laboratory testing pathway for determining metabolic status would reduce the likelihood of missing a delirium diagnosis and would facilitate early diagnosis and treatment. In this study, we identified many metabolic disorders in patients with delirium, but only potassium metabolism disorders and uremia were found to be associated with mortality. Due to inconsistent and insufficient laboratory testing of the patients, we may not have been able to detect all metabolic problems that influence mortality.

A limitation of the present study is that some laboratory data were missing and the type of delirium could not be determined due to the retrospective nature of the study. In addition, laboratory reference intervals specific to geriatric patients were not available and factors that may affect long-term mortality were not evaluated. The strengths of our study are that it identified metabolic problems that precipitate delirium in geriatric patients in a CLP Unit and investigated their

associations with mortality. Moreover, this study can serve as a reference due to the high number of cases included in our analysis.

Conclusion

Delirium is a serious and common problem in geriatric patients that increases morbidity and mortality if not diagnosed and treated. The causes, diagnosis, and outcomes of delirium should be well known. Psychiatric consultation should be requested for all patients suspected of having delirium. All clinicians, and especially geriatricians and psychiatrists, should have a high awareness of delirium. Determining the metabolic markers of delirium may help diagnose delirium and predict mortality. Metabolic scales can be developed for this purpose.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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