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Website

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Research Article

Association of potassium and sodium parameters with the type of stroke

Importance of potassium and sodium in stroke

Şule Yakar, Necmi Baykan

Bone mineral changes in young adult females on short-term proton pump inhibitor: A retrospective cohort study

Bone mineral changes in courses of proton pump inhibitor treatment

Omer Kucukdemirci, Korhan Kapucu, Osman Mavis

Review

Stereotactic surgery and its application in Alzheimer's disease rat models

Stereotaxy in Alzheimer's rat models

Esra Tekin

Case Report

Paraneoplastic opsoclonus-myoclonus syndrome as a rare presentation of parotid adenocarcinoma

POMA syndrome with parotid adenocarcinoma

Buket Özkara Yılmaz

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Association of potassium and sodium parameters with the type of stroke

Şule Yakar, Necmi Baykan

Emergency Department, Kayseri City Education and Research Hospital, Kayseri, Turkey

ORCID of the author(s)

ŞY: https://orcid.org/0000-0002-0885-8445
NB: https://orcid.org/0000-0002-6845-9550

Corresponding Author
Şule Yakar
Kayseri City Education and Research Hospital, Emergency Department, Kayseri, Turkey
E-mail: suleeee85@hotmail.com

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The study was approved by the Ethics Committee of the Somalia Mogadishu Turkey Recep Tayyip Erdogan Training and Research Hospital (Decision No: 2022/486).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Stroke is a significant cause of death along with malignant neoplasm and cardiovascular disease. Comorbidities and laboratory abnormalities are common in stroke patients. Imaging methods are the gold standard in the differential diagnoses of stroke, but they are not used sufficiently to diagnose stroke, especially in underdeveloped countries. In this study, we aimed to examine the association between electrolytes and clinical outcomes in patients with hemorrhagic and ischemic stroke.

Methods: Patients diagnosed with a stroke in the emergency department for one year were reviewed for this retrospective cohort study. We separated the patients into two groups, hemorrhagic and ischemic stroke, according to their diagnosis. Demographic, clinical features, laboratory, and imaging results were compared for the two groups. Potassium and sodium variables and receiver operating characteristic (ROC) analysis were used to predict the stroke status of individuals.

Results: In total, we included 321 patients in our study; 114 (35.5%) patients had experienced a hemorrhagic stroke, and 207 (64.5%) patients had had an ischemic stroke. In the hemorrhagic stroke group, 64% were males, while 50.2% of the ischemic stroke group were males. The most common chronic disease was found to be hypertension in both groups (42.1% (hemorrhagic) and 33.3% (ischemic)). There was a statistically significant difference in the comparison of potassium and sodium parameters and diagnostic groups (P=0.021 and P=0.036). In addition, hypokalemia was found to be significant in the diagnosis of hemorrhagic stroke (P<0.001).

Conclusion: Using potassium levels in the differential diagnosis of ischemic and hemorrhagic stroke is especially useful in the management of patients who cannot undergo imaging.

Keywords: stroke, potassium, sodium, emergency department

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Introduction

The World Health Organization has defined stroke as a clinical condition that lasts longer than 24 hours or can result in death, resulting from sudden cessation of cerebral blood flow for various reasons and leading to neurological dysfunction [1,2]. It is classified as ischemic stroke (IS), which is caused by narrowing or occlusion of cerebral blood vessels and is more common with a rate of 85%, and hemorrhagic stroke (HS), which is caused by bleeding within the brain tissue or the membranes surrounding the brain (15%) [3]. The risk factors for stroke include age, hypertension, human immunodeficiency virus (HIV), dyslipidemia, diabetes mellitus, smoking, obesity, previous cerebral vascular disease, and heart disease [4].

Potassium (K) and sodium (Na) balance disorders have been reported as the most common electrolyte abnormalities in patients with stroke [5]. Making the differential diagnosis of IS and HS at an early stage in patients with suspected stroke is essential for the management of patient follow-up and treatment [6]. There are various studies in the literature about the relationship between hypokalemia and hyponatremia in patients diagnosed with stroke [7,8].

In this study, the demographic-clinical characteristics and laboratory results of patients diagnosed with stroke in the emergency department were examined, and the differences between the IS and HS diagnosis groups were compared. We aimed to search the usability of K and Na values in the differential diagnosis of HS and IS.

Materials and methods

For this retrospective cohort study, patients who were diagnosed with acute stroke between January 1 and December 31, 2021, in the emergency department of Somalia Mogadishu Turkey Recep Tayyip Erdogan Training and Research Hospital were analyzed. This study was approved by the Ethics Committee of Somalia Mogadishu Turkey Recep Tayyip Erdogan Training and Research Hospital (Ethics Committee Decision No: 2022/486).

A data set including demographic characteristics, chronic diseases, outcome status, laboratory tests, brain computerized tomography (CT), and diffusion magnetic resonance imaging (MRI) results of patients was created through the patient registration system. The patients who were accepted to the emergency department with a suspicion of stroke and diagnosed with acute stroke after a result of brain CT and diffusion MRI examinations were included in the study. Patients under the age of 18, and those with missing data entries in the registration system were excluded from the study.

Patients were divided into two groups, HS and IS, according to the type of stroke. Demographic data, laboratory findings, imaging results, chronic diseases, and outcomes were compared for both groups. The relationship of K and Na parameters with the diagnosis of HS and IS was investigated.

Statistical analysis

The conformity of the data to the normal distribution was evaluated with Histogram, Q-Q plots, and the Shapiro-Wilk test. The homogeneity of variance was tested with Levene's test. The Mann-Whitney U test and independent two-sample t-test were used for the comparison of quantitative variables between the two groups. Pearson $\chi 2$ analysis and Fisher exact $\chi 2$ test were used for the comparison of categorical data. Receiver operating characteristic (ROC) analysis was used to predict the stroke status of individuals with K and Na variables. The area under the curve is given with 95% confidence intervals. The Youden index was used to determine the optimum cut-off value of K and Na scores in determining the stroke status of individuals. Sensitivity and selectivity of cut-off values as well as positive and negative cut-off values were given with a 95% confidence interval. Analysis of the data was performed in software R 4.0.0 (www.r-project.org). The significance level was accepted as $P<0.05$.

Results

In total, 321 patients, who were diagnosed with acute stroke in the emergency department, were included in the study over one year. According to the results of radiological imaging, the patients were separated into two groups: HS with 114 patients (35.5%) and IS with 207 patients (64.5%). The HS group was comprised of 64% males, while the IS group had 50.2% males. The mean age of the patients was 53.40 (16.46) in the HS group and 63.35 (16.96) in the IS group. The patients were divided into three age groups: 19-44, 45-65, and >65 years. The highest number of patients in the HS group with a rate of 42.1% were between the ages of 45-65, and the highest number of patients in the IS group with a rate of 48.8% were >65 years old. Gender ($P=0.017$), mean age ($P<0.001$), and age groups ($P<0.001$) were compared, and a statistically significant difference was found. The presence of hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular disease (CVD), and chronic kidney failure (CRF) were investigated. The greatest number of comorbidities was found in the HT group (42.1% and 33.3%). Concomitant chronic diseases were compared and a statistically significant difference was only found for DM ($P=0.016$). 88.6% Of the patients in the HS group, 88.6% only had a brain CT and one patient had both a brain CT and diffusion MRI. Diffusion MRI was performed in 46.4% of the patients in the IS group, and both brain CT and diffusion MRI were performed in 30.9% of the cases. There was a statistically significant difference in the comparison of imaging methods and diagnostic groups ($P<0.001$) (Table 1). Patients were grouped according to their outcome status in the emergency department, admission to the ward, admission to the intensive care unit (ICU), leaving the hospital voluntarily, discharge, referral, and exitus in the emergency department. In both groups, it was detected that the patients were most commonly admitted to the ward (59.6% (HS) and 80.9% (IS)). Four patients tested positively for coronavirus and were referred due to the lack of space in the isolated service and intensive care units (Table 1).

Hemogram test results, glucose, creatinine, K, and Na values of the patients were compared for both groups (Table 2). There was a statistically significant difference in the comparison of K and Na parameters and diagnostic groups ($P=0.021$ and $P=0.036$). An ROC analysis graph was drawn to evaluate the relationship of K and Na parameters in the differentiation of HS and IS (Figure 1).

Figure 1: ROC analysis graph of Potassium and Sodium parameters

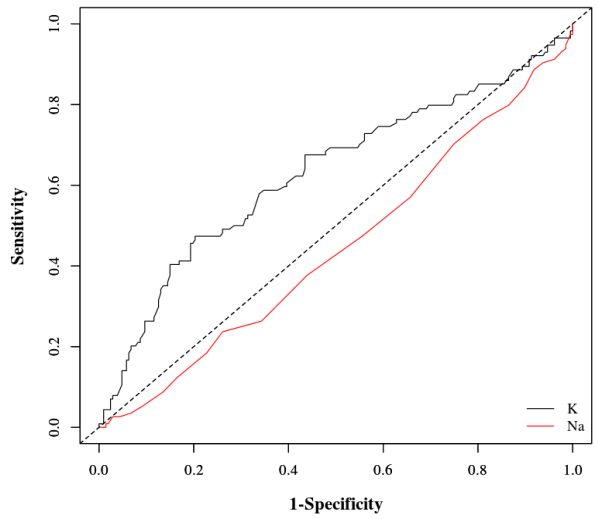

Table 1: Comparison of demographic and clinic data of patients with diagnosis groups

	Hemorrhagic Stroke n= 114 (%)	Ischemic Stroke n= 207 (%)	*P*-value
Gender			
Female	41 (36.0)	103 (49.8)	**0.017**
Male	73 (64.0)	104 (50.2)	
Age (years)	53.40 (16.46)	63.35 (16.96)	**<0.001**
Age range			
19-44	36 (31.6)	30 (14.5)	**<0.001**
45-65	48 (42.1)	76 (36.7)	
>65	30 (26.3)	101 (48.8)	
Medical history			
Hypertension	48 (42.1)	69 (33.3)	0.118
Diabetes Mellitus	8 (7.0)	36 (17.4)	**0.016**
Coronary Artery Disease	0	5 (2.4)	0.165
Cerebrovascular Disease	4 (3.5)	9 (4.3)	0.715
Chronic Kidney Disease	7 (6.1)	6 (2.9)	0.159
Radiology			
Brain CT	101 (88.6)	47 (22.7)	**<0.001**
Diffusion MRG	12 (10.5)	96 (46.4)	
Brain CT and Diffusion MRG	1 (0.9)	64 (30.9)	
Outcome			
Service	59 (59.6)	114 (80.9)	**<0.001**
ICU	40 (40.4)	27 (19.1)	
Discharged	13 (11.4)	63 (30.5)	
Referred	1 (0.9)	3 (1.4)	
Died	1 (0.9)	0	

* Data are expressed as mean (SD) and n (%).

Table 2: Comparison of laboratory results of patients with diagnosis groups

	Hemorrhagic Stroke n=114 (%)	Ischemic Stroke n=207 (%)	*P*-value
Hemoglobin (g/dL)	13.01 (2.28)	12.85 (2.39)	0.560
Hematocrit (%)	39.41 (6.63)	38.91 (6.83)	0.534
Leukocytes (x10^3/µl)	10.2 (7.4-13.5)	7.7 (5.8-10.9)	**<0.001**
Platelet (x10^3)	264 (212.8-340.3)	273 (207-348)	0.706
Glucoz (mg/dL)	126 (106.8-156.3)	123 (103-180)	0.975
Creatine (mg/dL)	0.9 (0.7-1.4)	0.9 (0.7-1.1)	0.241
Sodium (mEq/L)	141.07 (5.81)	139.75 (5.10)	**0.036**
Potassium (mEq/L)	4.22 (0.88)	4.44 (0.68)	**0.021**

***** Data are expressed as mean (standard deviation) and median (1st quartile-3rd quartile).

While the general performance of the K test level in determining the diagnosis of stroke was 0.63 by looking at the level of K and Na tests according to the area under the ROC curve, the general performance of Na level in determining the diagnosis was observed as 0.55. The cut-off value was calculated as K <4, Na >142. If the K value was less than 4, it was determined that the person had an HS with 47% sensitivity and 80% specificity (*P*<0.001). If the Na value was greater than 142, the person had an HS with 43% sensitivity and 66% specificity (*P*=0.100) (Table 3).

Table 3: ROC analysis and cut-off values of potassium and sodium

	ROC statistics		Diagnostic statistics			
	AUC (%95 GA)	*P*-value	Sensitivity (%95 GA)	Specificity (%95 GA)	PPV (%95 GA)	NPV (%95 GA)
K<4 (mEq/L)	0.63 (0.56-0.70)	**<0.001**	0.47 (0.38-0.57)	0.80 (0.74-0.85)	0.56 (0.48-0.65)	0.73 (0.65-0.80)
Na>142 (mEq/L)	0.55 (0.49-0.62)	0.100	0.43 (0.34-0.53)	0.66 (0.59-0.72)	0.41 (0.34-0.50)	0,68 (0.59-0.74)

Discussion

Approximately 15 million people worldwide are affected by stroke each year, making it the third leading cause of death after coronary artery disease and cancer [1,9]. Hypokalemia, hyponatremia, and hypernatremia are common electrolyte disturbances in patients with stroke [10,11].

The number of patients in the IS group was higher than in the HS group in our study. In previous studies, similar results were reported in which the prevalence and incidence of IS were higher than HS [12,13].

In a study conducted by Abdu et al. [3] in which types of strokes were compared, the mean age was 53 (9.6) years and most of the patients were female in the HS group. In the IS group, the mean age was 63.4 (9.6) years and the ratio of gender was equal. Similarly, in our study, the mean age was lower in the HS group than in the IS group. On the other hand, most of the patients in the HS group (64%) and in the IS group (50.2%) were male. When the diagnostic groups were compared in terms of age and gender, a significant difference was found.

Similar to the literature, hypertension is the most common risk factor for stroke in both groups [14,15]. When comorbid diseases were compared for HS and IS groups, only DM showed a significant difference, which is similar to the study of Rochemont et al. [12]. Since DM is a major factor in the development of atherosclerosis, it is thought to be detected at a higher rate in the IS group.

The non-contrast brain CT is the most commonly used diagnostic tool in the diagnosis of stroke, but it has been reported that diffusion MRI has more advantages, especially for the diagnosis of early ischemic stroke [16,17]. Consistent with our study, although the use of brain CT was common, diffusion MRI was preferred in the diagnosis of IS. Radiological imaging is important for the differential diagnosis of HS and IS, but in cases where CT and MRI are not available or the patient is not compatible with radiological imaging, laboratory findings are thought to be helpful in the differential diagnosis and patient management.

In this study; laboratory results and diagnostic groups were compared, and it was detected that the mean K value in the HS group and the mean Na value in the IS group were statistically significantly lower. In the study of Mansoor et al. [5] in which stroke diagnosis groups and laboratory results were compared, the mean Na value was low in the IS group similar to our study, but the K value was higher in the HS group. Although there are studies in the literature reporting that hyponatremia is more common in the IS group, there are also studies reporting that it is more common in the HS group [8,18]. It was thought that different results were obtained in the studies due to reasons, such as the inhomogeneity of the diagnostic groups, the late presentation of the patients, and the change in laboratory parameters as a result of chronic diseases.

In the ROC analysis performed to evaluate the use of K and Na parameters in the differential diagnosis of HS and IC, hypokalemia was significant in the diagnosis of HS in this study. Fukaguchi et al. [6] also evaluated the use of the K parameter in the differential diagnosis of stroke and reported that hypokalemia was associated with a higher risk of HS. We thought that the use of easily accessible, low-cost, and fast testing results might be beneficial in the differential diagnosis of HS and IS.

Limitations

The most important limitation of the study is that it was retrospective and employed a single-center design. Since all data could not be accessed through the registry system, a more detailed analysis could not be made regarding the time from the beginning of the complaints to the time of application.

Conclusion

Rapid differential diagnosis of stroke is important, as it will change the treatment and management of the patient. It has been shown in our study as well as many others in the literature that especially potassium and sodium parameters can be used for the differential diagnosis of stroke. Particularly in cases where radiological imaging cannot be performed, mortality and prognosis will be positively affected by rapid intervention due to the availability of laboratory tests in determining the type of stroke. Multicenter, more comprehensive, and detailed studies are needed in this regard.

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Bone mineral changes in young adult females on short-term proton pump inhibitor: A retrospective cohort study

Omer Kucukdemirci [1], Korhan Kapucu [2], Osman Mavis [2]

[1] Ondokuz Mayıs University, School of Medicine, Department of Gastroenterology and Hepatology, Samsun, Turkey
[2] University of Health Sciences, Istanbul Gaziosmanpasa Taksim Health Research Center, Department of Internal Medicine, Turkey

ORCID of the author(s)

OK: https://orcid.org/0000-0001-7642-2793
KK: https://orcid.org/0000-0002-7558-9433
OM: https://orcid.org/0000-0002-9580-6124

Corresponding Author
Omer Kucukdemirci
Ondokuz Mayıs University Faculty of Medicine, Department of Gastroenterology, Kurupelit Campus, Atakum, Samsun, Turkey
E-mail: drkucukdemirci@yahoo.com

Ethics Committee Approval
The study was approved by the Istanbul Gaziosmanpasa Taksim Health Research Hospital Ethics Committee in 2015, approval numer: 2015/6.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Proton pump inhibitors (PPIs), despite being the most prescribed medications today, have generated controversy due to their potential impact on bone metabolism. Numerous studies have emphasized the potential of prolonged PPI use to reduce bone mineral density, thereby increasing the risk of bone fractures among elderly and young individuals. However, the precise impact of PPI usage for 1 year or less on bone mineral density in young adults remains incompletely understood.
Method: In this retrospective cohort study, we conducted a comprehensive review of all dual x-ray bone densitometric examinations conducted on females under 40 years old at our tertiary care center between 2010 and 2014. Among the initial 685 patients assessed, 117 samples met the predefined inclusion criteria and were consequently enrolled in the study. Subsequently, the enrolled cases were categorized into three distinct groups: Group 1 (n=46), which received PPI treatment for less than six months; Group 2 (n=31), which received PPIs for a duration ranging from 6 to 12 months; and Group 3 (n=40), comprising individuals with no history of PPI use, thus serving as the control group. Comprehensive baseline descriptive data, encompassing bone mineral density, t-scores, and z-scores, were meticulously compared among the three groups mentioned above.
Results: The overall mean age of the study population was 32.84 (5.27) years, with an age range spanning from 20 to 40 years. No statistically significant differences in age were discerned among the three groups. Similarly, the groups exhibited no significant body mass index (BMI) variations. Noteworthy findings emerged after examining the effects of PPI usage on bone mineral density, z-scores, and t-scores across the three groups. Specifically, the data suggested that PPIs might influence t-scores (Group 1: -0.48 (0.77); Group 2: -1.25 (0.86); Group 3: -0.33 (0.78)), yielding an *F*-value of 13.28 for (2.116), signifying statistical significance at $P<0.001$. Moreover, the observed mean square error (MSE) was 64, while the effect size (eta²) was 0.19. Subsequent post-hoc Tukey tests indicated a significant distinction in the T-score of Group 2 compared to the other two groups. Furthermore, the analysis of z-scores (Group 1: 0.46 (0.79); Group 2: -1.27 (0.76); Group 3: -0.35 (0.86)) revealed a similar trend, with an *F*-value of 13.21 for (2.116) and a *P*-value below 0.001. The corresponding MSE was 0.65, and the eta² stood at 0.19. Additional post-hoc Tukey tests indicated that the Z-score of Group 2 significantly diverged from the other groups. However, it is noteworthy that both t and z-scores for Group 1 and Group 3 did not exhibit statistically significant differences.
Conclusion: Prolonged use of PPIs for durations surpassing 6 months may potentially reduce bone mineral density among young adults. Nevertheless, this observed impact does not attain clinically significant levels of osteopenia. Conversely, using PPIs for periods under 6 months did not significantly affect bone mineral density.

Keywords: proton pump inhibitor, bone mineral density, T-score, Z-score, osteopenia, osteoporosis

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Introduction

Proton pump inhibitors (PPIs) are the primary drugs for addressing conditions such as duodenal ulcers and esophageal reflux. Overall, PPIs are widely regarded as an exceedingly safe class of medications. However, variations in their metabolism can lead to specific drug interactions [1,2]. Prolonged utilization of PPIs may exert noteworthy effects on bone metabolism. Theoretically, hypochlorhydria could diminish calcium absorption and impede osteoclastic activity, potentially culminating in reduced bone density [3-5].

Measurements of bone density are conducted alongside assessments of fracture risk in osteoporosis screening. Diminished bone mineral density (BMD) correlates with heightened fracture susceptibility, irrespective of the measurement technique employed [6]. Dual-energy x-ray absorptiometry (DXA) of the spine, hip, and forearm is the singular diagnostic method for osteoporosis without a fragility fracture. It is the premier approach for monitoring BMD changes over time [7,8].

PPIs fall within a category of medications suspected to exert negative effects on the skeletal system, potentially elevating the risk of osteoporosis and fractures [9]. Epidemiological investigations have illuminated a potential link between extended PPI use and bone metabolism; however, this correlation remains controversial. Several articles propose that short-term PPI use might not impact BMD, yet the matter remains ambiguous [10-13].

Within the medical literature, multiple studies have identified baseline disparities in BMD between PPI users and non-users. Nevertheless, consistent associations have predominantly eluded longitudinal analyses across various anatomical sites. Moreover, these studies contend with notable methodological limitations that may complicate the interpretation of their findings [14]. Most publications encompass individuals aged ≥ 50 years who exhibit an escalated risk of fractures. Data concerning young adults undergoing brief or on-demand PPI treatment is lacking.

The present study assesses alterations in BMD, indicated by t and z-scores, in young female adults subjected to short-term (< 6 months or between 6–12 months) PPI treatment using DXA.

Materials and methods

This retrospective cohort study was conducted within the Internal Medicine Department of our tertiary care center, namely the University of Health Sciences, Taksim Training and Research Hospital. We collected data from female patients who had undergone DXA screening and were under 40 years of age between 2010 and 2014. Ethical approval was granted by the Ethics Committee of the same hospital, as evidenced by decision number 2015/6.

Our study aimed to encompass young adults 18 to 40 years old who had undergone BMD measurements for nonspecific reasons like trauma or bone pain. Furthermore, our scope encompassed individuals who had either used or refrained from using PPIs within the past year, excluding those with comorbidities. Hence, we meticulously reviewed the files of the 685 patients from whom we had collected data, adhering to the subsequent exclusion criteria.

All patient records underwent scrutiny in alignment with the subsequent exclusion criteria:

i) Systemic diseases: Patients diagnosed with or suspected of having endocrine disorders (such as amenorrhea, eating disorders, Cushing's syndrome, hyperthyroidism, hyperparathyroidism, hypogonadism, type 1 diabetes mellitus, deficiencies in vitamin D and calcium, hypercalciuria), gastrointestinal ailments (including Celiac disease, inflammatory bowel disease, malabsorption syndrome, severe liver disease), bone marrow disorders (such as amyloidosis, leukemia, lymphoma, multiple myeloma, hemochromatosis, sickle cell anemia, thalassemia), connective tissue disorders (e.g., osteogenesis imperfecta, Marfan Syndrome, Ehlers-Danlos Syndrome, hypophosphatasia, recipients of organ transplants), and inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, and Systemic Lupus Erythematosus [SLE]) were subject to exclusion.

ii) Individuals using medications recognized for inducing osteoporosis (such as glucocorticoids, immunosuppressive agents, anti-epileptic drugs, and chemotherapeutics), those with a history of smoking (equivalent to more than five pack-years), and excessive alcohol consumers were not considered eligible for participation in this current study.

iii) Samples displaying a body mass index (BMI) below 20 kg/m^2 or surpassing 35 kg/m^2 were omitted from the study due to their potential influence on BMD.

iv) Due to the study's design, cases involving prolonged PPI usage beyond one year were also precluded from participation.

Following the application of the exclusion criteria, a total of 409 patients were deemed ineligible for inclusion in the study. The remaining patient cohort included individuals who had employed PPIs for differing durations over the past year, from 0 to 12 months and those who had refrained from PPI use entirely. Initially, a cohort of 276 women was categorized into three distinct groups: Group 1 encompassed patients with PPI usage for less than six months; Group 2 consisted of patients who had been undergoing PPI treatment for a duration of 6 to 12 months; and Group 3 comprised cases characterized by a lack of PPI utilization.

From the initial pool of 199 cases within Group 3, a subset of 40 individuals was randomly chosen and incorporated into the study to equalize participant numbers across all groups. Consequently, data analysis encompassed 46 cases in Group 1, 31 in Group 2, and 40 in Group 3, respectively.

Dual-energy X-ray absorptiometry (DXA)

Central DXA for quantifying BMD remains the foremost standard in diagnosing osteoporosis and monitoring patient advancement, heralded as the definitive approach in this domain. This specialized x-ray technique furnishes precise evaluations of bone density at critical skeletal sites – such as the spine, hip, and forearm – while concurrently minimizing radiation exposure [15].

Bone density test results are typically presented in "T" or "Z" scores. T-scores provide a measure of the comparison

between your bone health and that of a typical young individual with healthy bones. Conversely, z-scores evaluate how your bone condition compares to your peers. Ordinarily, the T-score takes precedence in interpreting these two indicators. T-scores generally fall within the negative spectrum. A lower T-score indicates an elevated fracture risk attributed to reduced bone density.

Bone density is categorized through t-scores, which stratify various conditions. Individuals with normal bone density exhibit t-scores ranging from +1 to -1. Those with osteopenia, a precursor to osteoporosis, exhibit t-scores between -1.1 and -2.4, signifying a heightened risk of progression to osteoporosis. T-scores of -2.5 or lower characterize osteoporosis. Notably, as bone density decreases, the susceptibility to fractures escalates [16,17].

Within our study, our objective encompassed a statistical comparison of the femoral neck t and z-scores across all three groups. Furthermore, we explored whether each group's t and z-scores met the diagnostic thresholds for osteopenia or osteoporosis.

Statistical analysis

All analyses were performed utilizing IBM SPSS version 26. A one-way analysis of variance (ANOVA) was employed to assess the main effects, and for subsequent post-hoc comparisons, Tukey's HSD (honestly significant difference) test was applied. All analyses were conducted as one-tailed tests, with a significance level set at a *P*-value of 0.05.

Results

The mean age of our entire study population was 32.84 (5.27) years, ranging from 20 to 40 years. A one-way ANOVA was conducted to assess any age differences among the three groups. The means for Group 1, Group 2, and Group 3 were 32.9 (5.23), 34.26 (5.46), and 31.35 (4.93) years, respectively. The ANOVA results indicated no significant age differences among the groups ($F(2.116)=2.278$, $P=0.066$, $MSE=75.04$, $\eta_p^2=0.047$).

Similarly, a one-way ANOVA was performed to analyze potential differences in BMI among the three groups. The mean BMI for Group 1, Group 2, and Group 3 were 27.67 (7.02), 26.21 (6.47), and 25.74 (6.37), respectively. The ANOVA results showed no significant differences in BMI among the groups ($F(2.116)=0.973$, $P=0.381$, $MSE=44.35$, $\eta_p^2=0.017$). Consequently, BMI was not considered in subsequent analyses. The distribution of age and BMI can be found in Table 1.

Table 1: Baseline descriptive data in three groups under investigation

	Group 1 (n=46)	Group 2 (n=31)	Group 3 (n=40)	*P*-value
Age	32.91	34.26	31.35	0.066
BMI	**27.66**	**26.21**	**25.74**	**0.381**

BMI: body mass index, Group 1: patients had less than 6 months of PPI treatment, Group 2: patients on PPI treatment for 6-12 months, Group 3: no PPI treatment.

A comparison was made among the three groups to assess the impact of PPI use on BMD, z-scores, and t-scores. The mean t-scores for Group 1, Group 2, and Group 3 were -0.48 (0.77), -1.25 (0.86), and -0.33 (0.78), respectively. The ANOVA results indicated a significant effect of PPI on t-scores ($F(2,116)=13.28$, $P<0.001$, $MSE=64$, $\eta_p^2=0.19$). Subsequent post-hoc Tukey testing revealed that the t-score of Group 2 significantly differed from the other two groups. However, there were no significant differences in t-scores between Group 1 and Group 3 (Table 2).

Table 2: T and z-score changes in patients between Groups 1, 2, and 3

	T-score	Z-score
Group 1	-0.48	-0.46
Group 2	-1.25	-1.27
Group 3	**-0.33**	**-0.35**

Our data analysis revealed that PPI use exerted an influence on z-scores, with the mean z-scores for Group 1, Group 2, and Group 3 being 0.46 (0.79), -1.27 (0.76), and -0.35 (0.86), respectively. The ANOVA findings demonstrated a statistically significant effect of PPI use on z-scores ($F(2.116)=13.21$, $P<0.001$, $MSE=0.65$, $\eta_p^2=0.19$). Further post-hoc Tukey analysis indicated a significant disparity in z-scores between Group 2 and the other groups. Conversely, the z-scores of Group 1 and Group 3 exhibited similarity (Table 2).

Contrarily, our results did not reveal a significant impact of PPI use on BMD scores, despite observing mean BMD scores of 1.08 (0.10) for Group 1, 0.96 (0.25) for Group 2, and 1.05 (0.32) for Group 3. Notably, this result approached marginal significance ($P=0.080$). In the post-hoc Tukey test, it was suggested that this marginal *P*-value could be attributed to Group 2 ($P=0.070$).

Correlation analyses were conducted between the descriptive parameters and BMD indicators using Pearson correlation coefficients (Table 3). Additionally, it was observed that t-scores and z-scores exhibited a positive correlation with each other.

Table 3: Results of correlation analysis between descriptive parameters and bone mineral density indicators (n=31)

		Age	BMI	t-score	z-score	BMD
Age	Pearson Correlation	1	-0.177	0.014	-0.025	-0.079
	P		0.342	0.941	0.895	0.674
BMI	Pearson Correlation	0.177	1	-0.148	-0.067	0.317
	P	0.342		0.427	0.72	0.082
t-score	Pearson Correlation	0.014	-0.148	1	0.975**	0.179
	P	0.941	0.427		0	0.337
z-score	Pearson Correlation	-0.025	-0.067	0.975**	1	0.341
	P	0.895	0.72	0		0.06
	Pearson Correlation	-0.079	0.317	0.179	0.341	1
BMD	*P*	0.674	0.082	0.337	0.06	

** Correlation is significant at the 0.01 level (2-tailed), BMD: bone mineral densitometry, BMI: body mass index

Discussion

PPIs rank among the most frequently prescribed medications today, boasting an excellent short-term safety profile. These drugs find common application in acid-pepsin-associated diseases such as peptic ulcers, gastroesophageal reflux disease, Barrett's esophagus, laryngopharyngeal reflux, Zollinger-Ellison Syndrome, and functional dyspepsia [18,19]. Notably, they are recognized as highly effective and dependable medications. Despite their high reliability, it's important to acknowledge the potential side effects associated with PPIs. These encompass inducing cell differentiation to neoplasia, heightening susceptibility to infectious diseases, giving rise to gastrointestinal absorption issues, and causing a range of electrolyte imbalances and nutrient absorption deficits. Furthermore, they have been implicated in acute interstitial nephritis and may adversely affect BMD [20].

Drawing from existing literature studies and comprehensive meta-analyses, a connection has been suggested between prolonged PPI usage and an increased risk of hip fractures. However, the relationship between PPI use and

changes in BMD remains elusive, with inconsistent and conflicting outcomes [21,22].

Multiple studies have indicated that prolonged PPI use may diminish BMD and elevate the susceptibility to bone fractures across various age groups, encompassing both older and younger individuals [22]. Despite these noteworthy observations, the exact implications of PPI utilization lasting one year or less on BMD in young adults continue to elude complete understanding.

Hence, we classified the 117 patients who had used PPIs for less than one year into three distinct groups, subsequently evaluating their femoral neck t and z-scores. The connection between BMD or bone mass and specific variables such as body weight, BMI, advancing age, and female gender has been firmly established in the literature [23]. To attenuate the influence of gender and advanced age and to enhance the diversity of our study population, we exclusively included females below 40 years ols (with an average age of 32.84 [5.27]). Notably, there existed no significant variance in BMI across the three groups, with all participants maintaining a normal weight status (average BMI of 26.1 kg/m²).

Prolonged utilization of PPI therapy has been associated with a noteworthy reduction in BMD, although it falls short of constituting a diagnostic marker for osteoporosis. Furthermore, prevailing evidence indicates that chronic PPI usage does not heighten the risk of osteoporosis [24]. In this context, Targownik et al. [25] reported that patients undergoing chronic PPI therapy displayed lower BMD than non-PPI users. Nevertheless, a follow-up spanning 5 to 10 years revealed that the decline in BMD did not progress to osteoporosis. Additionally, it has been theorized that the risk of hip fractures in patients on chronic PPI therapy stems from mechanisms independent of osteoporosis [20].

Curiously, the impact of acid inhibition on calcium absorption and BMD lacks consistent effects [26]. This observation suggests that PPIs might elevate fracture risk irrespective of calcium balance and BMD, or the established connection could be erroneous. The operation of vacuolar proton pumps employed by bone osteoclasts for bone resorption can be impeded in vitro by PPIs, potentially reducing bone resorption [4]. However, as bone resorption is crucial for developing a normal bone microstructure, speculation arises that the PPI-induced hindrance of the osteoclast-associated vacuolar proton pump might elevate the risk of fractures [27].

In our investigation, the t and z-scores across the three groups proved inadequate for definitive diagnoses of osteoporosis or osteopenia (femur neck DXA scores not falling below -1.1). Concurrently, due to the unavailability of patients' x-ray records, an assessment of the relationship between fractures and PPI usage within our sample remained unattainable.

Over the past decade, numerous prospective cohorts have provided substantial evidence of declining t and z-scores in bone mineral densitometry, particularly after prolonged PPI usage spanning over 12 months [28-32]. Within our study, discernible alterations in femoral neck t and z-scores were absent among both the group abstaining from PPI usage within the last year and the group utilizing PPIs for durations less than six months. However, among participants in Group 2, who employed PPIs for periods ranging from 6 to 12 months, a reduction in both t and z-scores was noted, indicating a decline in bone density.

Parallel to our research, a prospective cohort study by Özdil et al. [29] 2013 explored bone densitometry measurements of 114 GERD patients undergoing PPI treatment. Although the subjects of their investigation were not exclusively young adults, the average age, at 37.7 (8.8) years, closely resembled our sample. This study similarly unveiled noteworthy declines in densitometric t-scores, assessed through bone densitometry of the vertebrae and femur, among patients employing PPIs for at least 6 months.

Limitations

By deliberately excluding males in our study, aimed at mitigating gender-related effects and including only a restricted male population for statistical analysis, we acknowledge that this approach could potentially curtail the broad applicability and generalizability of our findings. Given the retrospective nature of our study, we refrained from delving into the assessment of hip or other types of fractures.

Distinct from many studies that categorize PPIs based on their specific types, our study encountered a limitation. The unavailability of patients' generic medication details hindered our ability to perform such a classification. This absence of differentiation among different PPI types, including noteworthy variants like esomeprazole, which could potentially exert diverse effects on BMD compared to other PPIs, impedes a comprehensive exploration of this aspect.

Given the relatively modest sample size and the confined nature of the data sourced from a single institution's experience, we must exercise caution when extending the implications of our outcomes to the broader population.

Conclusion

Our findings propose that short-term PPI usage (less than 6 months) among females might not significantly impact BMD, whereas prolonged usage for over six months could contribute to a decline in bone mineral densitometry. This observation should be duly considered when formulating treatment plans involving PPIs. However, it's worth noting that this effect doesn't reach the diagnostic thresholds for osteopenia or osteoporosis.

It is essential to acknowledge that this retrospective cohort study is accompanied by several limitations that inevitably influence the broader applicability of our results. Further research is warranted to arrive at more precise and definitive conclusions, necessitating larger-scale, multicentric, randomized, and prospective trials.

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Stereotactic surgery and its application in Alzheimer's disease rat models

Esra Tekin

Kutahya Health Sciences University, Faculty of Medicine Department of Physiology, Kutahya, Turkey

ORCID of the author(s)

ET: https://orcid.org/0000-0002-9684-3277

Abstract

Stereotactic surgery is a technique that can be used to locate small targets in the body and administer interventions and/or treatments, such as injections, to the specific target. Stereotactic surgery is frequently used to create neurological disease models in experimental research in addition to clinical practice. The injection is administered with appropriate glass injectors using the rodent brain coordinate atlas after the specific brain region is determined. Alzheimer's disease (AD), the most common cause of dementia, has no curative treatment yet. AD models can be created in rodents through stereotactic surgery and injections of different substances. These AD models represent the disease and are frequently used especially for drug development studies. AD-like models seem to examine different and unidirectional developmental mechanisms according to the creating way. However, AD is a multidirectional disease. AD rodent models created using different methods have specific properties. This review aims to explain the basic aspects of stereotactic surgery and to discuss AD rodent models created with this surgical technique and also with alternate methods.

Keywords: stereotactic surgery, Alzheimer's disease, animal models, rat

Corresponding Author
Esra Tekin
Kutahya Health Sciences University, Faculty of Medicine Department of Physiology, Kutahya, Turkey
E-mail: esra.tekin@ksbu.edu.tr

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Introduction

Stereotactic surgery is used to locate small targets in the body and administer surgical interventions and/or treatments, such as injection, stimulation, ablation, biopsy, implantation, and/or radiosurgery, to these targets. This surgery uses a three-dimensional coordinate system to apply such interventions while causing minimal damage to the targets [1]. Stereotactic applications are frequently used in neurological research, pharmacological evaluations, and experiments on central nervous system diseases to eliminate, disrupt, or increase the function of certain regions of the brain [2].

Alzheimer's disease (AD) is a neurodegenerative disease that causes cognitive loss, personality changes, and speech disorders. AD, which is the most common cause of dementia, currently does not have a definitive treatment [3]. Rodents are the animals most often used in neuroscience studies. Studies are being conducted using the AD models created in rodents, and treatment options are being developed for the disease [4–6]. In these studies, transgenic rodents can be used, and AD models can be created using stereotactic surgery [7,8].

Stereotactic surgery is a method that is frequently used in rats to create AD models. Stereotactic methods used to create models of AD allow injections of substances to be administered to certain parts of the brain [9]. Appropriate coordinates are set in the stereotactic device to generate AD models. The injection area is determined using the brain coordinate atlas for rats. These coordinates may include the brain ventricles to ensure the distribution of the applied substance in the brain in addition to the hippocampus, which is an important brain region involved in the development of AD [10,11]. Therefore, the injection can be performed intracerebroventricularly or intrahippocampally.

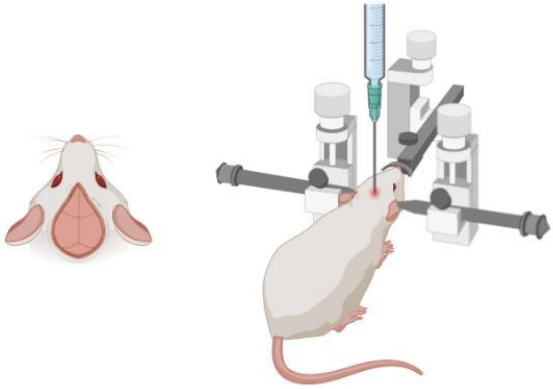
Chemicals to be injected to induce AD include various forms of amyloid or streptozotocin and also agents that will promote tau accumulation [12–14]. It is also known that metal ions play a role in AD development. Therefore, injections of substances associated with metal cations are also used to induce a model of AD [15].

In this traditional review, stereotactic surgery and its application in AD models was defined along with its basic features. This review also aims to discuss the rodent models of AD created by methods other than stereotactic surgery.

Application Steps of Stereotactic Surgery

First, the head of the experimental animal under anesthesia is shaved. The rats are placed in the stereotactic device so that the dental apparatus grasps the upper incisors, the ear bars fit into the external ear canal, and the head ceiling is in the horizontal plane. The movable apparatus of the device is compressed so as not to damage the ear and chin and to obtain a stable plane during the application (Figure 1). After this stabilization process, an incision is made in the scalp using a scalpel. After cleaning the periosteum in the skull, the lambda and bregma, which are reference points that allow us to determine the coordinates, are exposed. After the brain region to be injected with the substance is determined from the stereotaxic coordinate atlas [16], a hole is drilled into the skull in this region after which the desired coordinates are injected using a micro-injector. It is appropriate to slowly administer the chemical infusion and then remove the injector after waiting for a while (approximately 5 min) so that the chemical is absorbed after the infusion. The skin incision is then closed with sutures. Attention to maintaining asepsis during the surgical procedure positively affects the survival of the experimental animal after the procedure.

Figure 1: Stereotactic neurosurgery in rats



For example, in the rat brain atlas of Paxinos and Watson [16], the coordinates of the region we want to inject should be 3.6 mm posterior to the bregma, 2.4 mm lateral to the sagittal suture, and 2.8 mm ventral to the rat skull surface. In this case, after bringing the micro injector needle to the bregma, it should be moved 3.6 mm posterior and 2.4 mm lateral from the midline sagittal suture through the apparatus of the stereotactic device. After making a mark with a pencil perpendicular to this point, a hole is drilled into the skull at this point. The micro injector is brought to the appropriate coordinates and the syringe needle is advanced 2.4 mm ventrally in the vertical direction by means of stereotactic device apparatus after which the substance is injected.

Before starting the experiment, practicing with a preliminary study is useful. During this preliminary study, it is beneficial for experimental accuracy to inject a dye (for example, methylene blue) and then take sections from the rat brain and make sure that the stained area is the one we wish to study.

AD Models Created by Stereotactic Surgery

Since no agent is available that can provide a definitive treatment for AD, experimental models are necessary both to better understand the disease pathogenesis and develop a treatment agent. In addition to AD models created by stereotactic surgery, AD models created with transgenic animals have also been applied in recent years [17–20]. AD models created in different ways have their own distinctive features. It should be emphasized that transgenic models are established via a non-physiological process that reflects only certain pathological features. This drawback is most likely the cause of clinical failure of therapeutic agents that show positive effects in transgenic preclinical studies [21]. In addition, both transgenic and surgical AD models target only one developmental mechanism. However, since AD is a multifactorial disease, treatments targeting only one of the several developmental stages do not produce clinical success [21].

The most studied step in animal models for AD involves amyloid deposition. Triggering amyloid deposition in animals often results in cognitive impairment [22]. However, many pathways, such as neuronal loss, deterioration in both synaptic plasticity and long-term potentiation, pericyte dysfunction, metal dyshomeostasis, mitochondrial distress, blood–brain barrier

dysfunction, and pathologies associated with tau hyperphosphorylation, have been described in the development of AD [23–26]. Therefore, the reason why these models cannot fully reflect AD seems to be that they do not include the entire pathogenesis. On the other hand, the pathogenesis of AD has not yet been fully elucidated.

Stereotactic injection of amyloid derivatives is often preferred for creating a model of AD. Behavioral tests have shown that intracerebroventricular injection of amyloid β 1-42 peptide leads to impairment of learning and memory function [27]. In a previous study, it was shown that learning and memory were impaired in behavioral tests after intracerebroventricular injection of amyloid β 1-42 peptide, and hippocampal neuronal survival was impaired in histological analyses [28].

In a different study, the effect of amyloid β injected intracerebroventricularly via stereotactic surgery in rats was examined, and it was shown that infusion causes impairment of learning and memory. It was also found that amyloid β expression in the cortex and hippocampus increased in the group that received amyloid infusion compared to the control [29].

In a different rodent study in which stereotaxic injection was performed intrahippocampally, AD model was induced by amyloid β 1-40. It was shown that spatial learning and memory were impaired in rats after the injection [30].

Conclusion

AD models that are established via the use of stereotactic surgery reflect the disease in terms of learning and memory impairment and pathological accumulations of several kinds of proteins. However, models established via stereotactic surgery seem to represent the disease in terms of only one pathway depending on the substance injected and the pathway triggered. Injection of amyloid derivatives is frequently used to create an AD model via stereotactic surgery. Amyloid injection produces results that mimic AD in aspects of amyloid plaque formation and hippocampal amyloid deposition. However, the multidirectional pathogenesis of AD does not produce the expected results in pre-clinical studies conducted with AD models as these models reflect only a single pathway. Transgenic animal models of AD also present only one pathological pathway. More studies are needed to elucidate the unknown mechanisms of AD, to develop models covering the entire pathogenesis of the disease, and to develop treatment agents as a result.

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Paraneoplastic opsoclonus-myoclonus syndrome as a rare presentation of parotid adenocarcinoma

Buket Özkara Yılmaz

Department of Neurology, Nizip Hospital, Gaziantep, Turkey

ORCID of the author(s)

BÖY: https://orcid.org/0000-0002-1033-7737

Abstract

Paraneoplastic Opsoclonus-Myoclonus Ataxia Syndrome (POMA) is a rare neurological condition that affects approximately 1 in 10,000,000 people annually. This syndrome is poorly understood and can lead to long-term cognitive, behavioral, and motor complications. Opsoclonus is characterized by involuntary, rapid, repetitive, multi-vectorial oscillations of the eyes occurring in all directions of gaze. It is accompanied by diffuse or focal body myoclonus and may or may not include ataxia and other cerebellar signs. POMA is typically a paraneoplastic syndrome associated with neuroblastoma in childhood and breast carcinoma or small-cell lung carcinoma in adults. Additionally, viral or toxic agents are known to play a role in its etiology, and the immune system is involved in the pathogenesis. We report a case of a 41-year-old man with anti-Ri antibody opsoclonus-myoclonus syndrome and parotid adenocarcinoma involvement. After diagnosing opsoclonus-myoclonus syndrome, the patient underwent multimodal immunotherapy treatment, resulting in partial remission of the neurological symptoms.

Keywords: opsoclonus, myoclonus, parotid, adenocarcinoma, paraneoplastic

Introduction

Opsoclonus-myoclonus (OMS) is a rare autoimmune condition resulting from cerebellar degeneration. It often presents as a paraneoplastic syndrome, where a cancer remote from the brain induces cerebellar dysfunction unrelated to metastases [1-3]. In most adults with opsoclonus-myoclonus, the etiologies can be neoplastic, infectious, metabolic, or idiopathic in nature [5,6]. The symptoms of cerebellar dysfunction in the case presented include opsoclonus, myoclonus, and ataxia, which has led to its colloquial name, “dancing eyes, dancing feet syndrome”. Opsoclonus is characterized by rapid, dysrhythmic, and uncoordinated eye movements [3,7]. The neuronal damage is induced by antibodies typically associated with the primary pathology [4]. Treatment approaches target the underlying cause and may involve using steroids, plasmapheresis, immunosuppressive agents, or other anti-inflammatory therapies [2,4].

In children with opsoclonus-myoclonus resulting from neuroblastoma, neurological sequelae are often retained. In adult cases, opsoclonus-myoclonus can be considered an autoimmune phenomenon with idiopathic or neoplastic origins, often accompanying breast carcinoma or small-cell lung carcinoma [4,5]. There appears to be a genetic predisposition to autoimmunity in these patients, as frequent autoimmune disorders are observed in families of those with Paraneoplastic Opsoclonus-Myoclonus Ataxia Syndrome (POMA), and there is a correlation with the Human Leucocyte Antigen (HLA) class II locus DR B1*01 [7]. The pathogenesis is thought to be immune-mediated based on the paraneoplastic nature of the syndrome and its symptomatic response to immunosuppressive therapy. Therapeutic benefit has been described with the use of steroids, intravenous immunoglobulins, cyclophosphamide, azathioprine, and rituximab [4-6]. The prognosis of OMS depends on early management and successful treatment, highlighting the importance of promptly identifying the syndrome and its underlying cause [7,8].

Corresponding Author
Buket Özkara Yılmaz
Department of Neurology, Nizip Hospital, Gaziantep, Turkey
E-mail: buketozkara4188@hotmail.com

Informed Consent
The authors stated that the written consent was obtained from the patient presented in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

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In this case presentation, our objective is to underscore the significance of conducting a thorough investigation for paraneoplastic syndrome in POMA (polymyositis) and to highlight its potential association with rare types of cancer.

Case presentation

Behavioral symptoms manifested in a 41-year-old male patient, with complaints of bilateral eyeball tremor, staggering gait, and frequent falls beginning 3 weeks after the initial onset. Neurological examination revealed spontaneous, involuntary, arrhythmic, and conjugate rapid eye movements, as well as facial, axial, and appendicular myoclonus, along with gait ataxia. Motor strength and deep tendon reflexes were found to be normal. Routine blood tests, serum B12 and folate levels, erythrocyte sedimentation rate, C-reactive protein, viral scan, vasculitic scan, chest X-ray, brain CT, and MRI all showed normal results. Anti-neuronal antibodies were assessed, and the presence of anti-Ri antibodies was confirmed. The cerebrospinal fluid (CSF) analysis revealed normal cell counts and negative cytology, and viral markers, but there was an observed increase in protein (63 mg/dl) in the CSF. PET-CT did not reveal any pathological involvement. To treat the patient, intravenous methylprednisolone pulse steroid therapy was administered at a dose of 1000 mg/day for 7 days, resulting in a significant improvement in symptoms. During clinical follow-ups, a mass lesion was identified under the left ear, leading to a biopsy, which revealed polymorphous low-grade adenocarcinoma. The patient underwent surgery, and partial improvement was observed at the 6-month follow-up, coinciding with the anti-Ri antibody being reported as negative. Written consent to publish this case report was obtained from the patient.

Discussion

POMA is a rare autoimmune neurological paraneoplastic syndrome that arises from the distant effects of a tumor. Nevertheless, it is crucial to differentiate it from other neurological manifestations related to metastasis, infection, ischemia, and metabolic disturbances [5,6]. To achieve this, a comprehensive medical history is necessary to identify risk factors, clinical complaints and conduct a thorough physical examination [6]. Despite the unclear pathogenic mechanisms of POMA, specific tumor types have been linked to well-characterized anti-neural antibodies [7,8]. In particular, the presence of the anti-Ri antibody has been associated with malignant neoplasms of the breast. This antibody targets the Nova proteins Nova-1 and Nova-2, which play a role in regulating synaptic proteins in the central nervous system.

In patients with paraneoplastic OMS, surgical treatment of the underlying neoplasm has been shown to improve neurological symptoms. Immunotherapy treatment has demonstrated the potential for partial or complete recovery of POMA in some cases and can include the use of steroids, intravenous immunoglobulin, and cyclophosphamide [3,5]. Immunosuppressive therapy should be administered in the early stages of the disease. Recognizing and diagnosing paraneoplastic neurological syndromes is essential since neurological symptoms typically precede direct symptoms of the primary tumor, and early treatment offers a better chance of a favorable outcome [7,8].

Conclusion

Due to the rarity of adult POMA syndrome, only a small case series and a few case reports link it to breast and small-cell lung carcinoma exist. Currently, there are no reported cases of POMA syndrome associated with parotid adenocarcinoma in the literature.

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