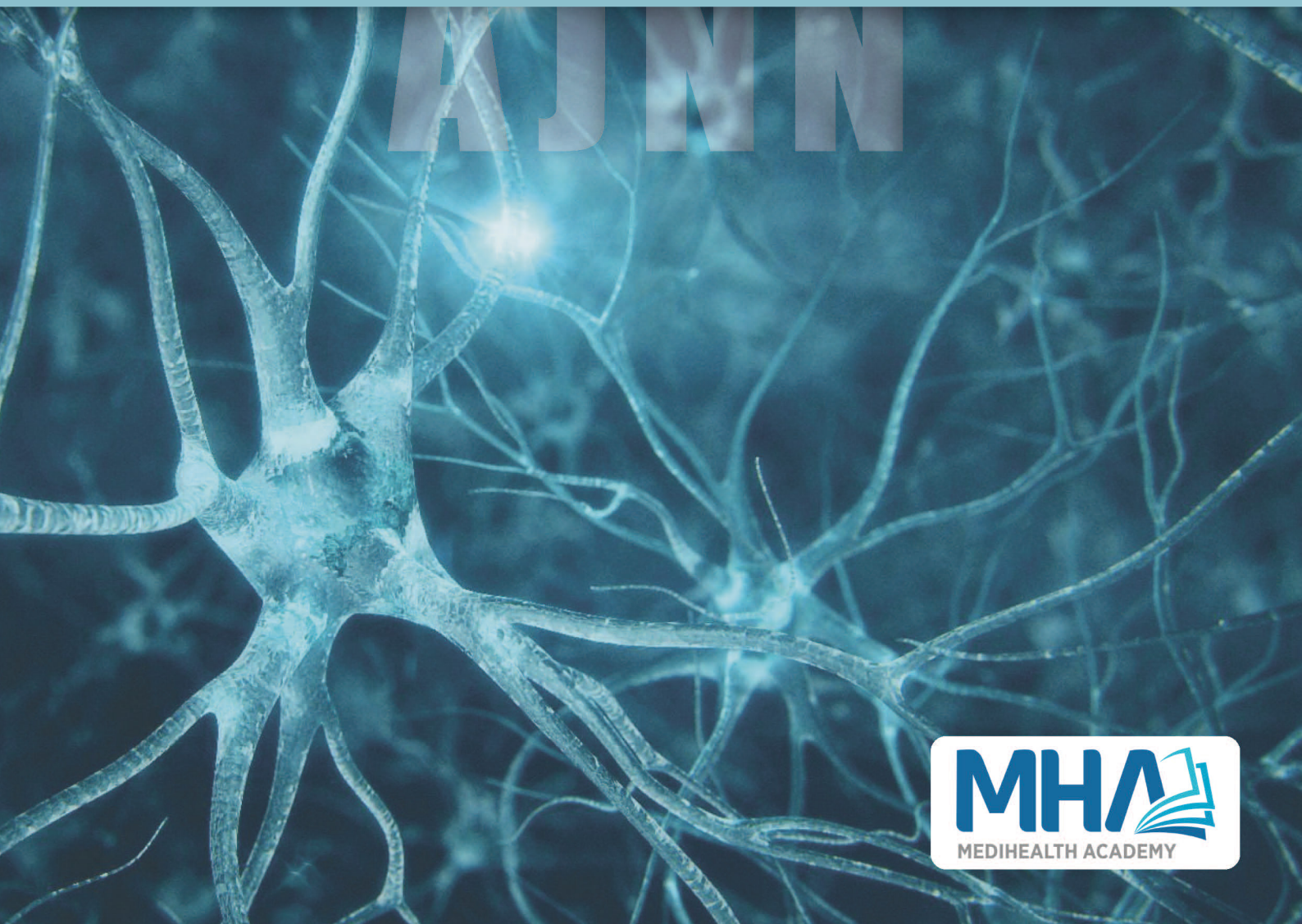
e-ISSN: 3023-6517

Volume: 2 Issue: 1 Year: 2025

Academic Journal of

Neurology & Neurosurgery

AJNN



MHA
MEDIHEALTH ACADEMY

EDITORS-IN-CHIEF

ASSOCIATE EDITOR-IN-CHIEF

EDITORIAL BOARD

Dear Colleagues,

We are happy to publish the first issue of 2025 of the Academic Journal of Neurology and Neurosurgery, which is published four times a year. In this respect, we would like to thank both our authors who prepared and sent their scientific studies that required intensive effort, and our valuable referees who put forward their experiences, knowledge and devotion without any other motivating factor other than academic responsibility and the happiness of contributing to the field, so that these studies turn into more qualified and scientific studies. In addition, I would like to thank all members of our journal team who, as the third pillar of the tripod, ensure that the articles meet the relevant readership.

Kind regards,

Prof. Yeşim GÜZEY ARAS

Editor-in-Chief

Academic Journal of
Neurology & Neurosurgery

Contents

Volume: 2 Issue: 1 Year: 2025

ORIGINAL ARTICLES

REVIEW

CASE REPORTS

Academic Journal of Neurology & Neurosurgery

Original Article

DOI: 10.51271/AJNN-0021

The impact of asymptomatic carotid stenosis on cognition

Şeyda Çankaya[1], Shair Shah Safa[1], Ayşe Karakuş[1], Ceyhun Sayman[1], Hatice Lakadamyalı[2], Burak Yuluğ[1]

[1]Department of Neurology, Faculty of Medicine, Alanya Alaaddin Keykubat University, Alanya, Turkiye
[2]Department of Radiology, Faculty of Medicine, Alanya Alaaddin Keykubat University, Alanya, Turkiye

Received: 27/01/2025 ◆ Accepted: 03/03/2025 ◆ Published: 21/03/2025

Cite this article: Çankaya Ş, Safa SS, Karakuş A, Sayman C, Lakadamyalı H, Yuluğ B. The impact of asymptomatic carotid stenosis on cognition. *Acad J Neurol Neurosurg.* 2025;2(1):1-4.

Corresponding Author: Şeyda Çankaya, seyda.cankaya@alanya.edu.tr

ABSTRACT

Aims: Asymptomatic carotid stenosis (ACS), characterized by the narrowing of carotid arteries without evident symptoms, has been increasingly associated with cognitive decline, particularly in memory and executive functions. This study investigates the cognitive implications of ACS by evaluating cognitive performance using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

Methods: This retrospective study included 20 ACS patients, and 15 matched healthy controls. Participants were recorded for cognitive status, age, gender, and educational background to ensure group comparability. MMSE and MoCA were used for cognitive assessment.

Results: The findings revealed that while MMSE scores did not differ significantly between groups, MoCA scores were notably lower in ACS patients (19.85 ± 4.68) compared to controls (23.07±3.01, p=0.027), suggesting pronounced cognitive deficits in domains such as visuospatial ability and delayed recall. These results align with existing literature indicating that ACS may impair cerebral blood flow and disrupt connectivity in key neural networks, thereby contributing to cognitive impairment. Additionally, while the ACS group tended to be older and have fewer years of formal education, these factors did not significantly confound the observed cognitive differences (p<0.05).

Conclusion: Our results underscore the importance of routine cognitive evaluations in patients with ACS, as traditional assessments may underestimate their impact on brain health. Future research should explore the efficacy of interventions such as carotid endarterectomy or stenting in mitigating cognitive decline associated with ACS. These findings advocate for a holistic approach to managing ACS, integrating cognitive assessments alongside traditional cardiovascular risk evaluations to enhance patient outcomes and quality of life.

Keywords: Asymptomatic carotid stenosis, cognition, MOCA, MMSE

INTRODUCTION

Asymptomatic carotid stenosis (ACS), characterized by the narrowing of the carotid arteries without significant symptoms, poses a substantial risk not only for cerebrovascular events but also for cognitive decline.[1] This phenomenon has garnered attention in recent research due to its potential implications for memory and overall cognitive function. Understanding the relationship between ACS and memory is crucial as it highlights the intricacies of vascular health and neurocognitive processes. The absence of overt symptoms can lead to a troubling underestimation with moderate to severe stenosis found notable deficits in cognitive functions, particularly in domains such as the executive functions independent of the vascular stenosis condition's seriousness, allowing it to progress unchecked.[2] The cognitive importance of ACS makes investigating the underlying mechanisms that connect arterial blockages to cognitive impairments substantial, especially regarding the impacts of silent vascular changes on memory, which is vital for developing effective treatment and preventive interventions.[1]

Current research suggests that individuals with this condition may experience subtle cognitive impairments, such as deficits in memory and information processing speed. For instance, a study indicated that cognitive impairment was prevalent among patients with severe ACS, with 72% suffering from memory issues before intervention.[3] This result is not only seen in carotid stenosis but also in carotid plaques, which are strongly linked with significant cognitive decline, especially in memory and visuospatial abilities assessed through standardized neuropsychological tests.[4] Furthermore,

this decline in cognitive function occurs independently of clinically evident cerebrovascular incidents, positioning ACS as a potential risk factor for dementia.[5] In addition, declines in working memory linked to both severe carotid stenosis and conditions like Alzheimer's disease (AD)[6] underscore the critical relationship between cerebral health and cognitive capacity. Moreover, recent studies indicate that also patients with no AD but with significant stenosis exhibit notable impairments in executive functions, memory, and emotional state, underscoring a correlation between high-grade and bilateral stenosis with cognitive deterioration.[2,7,8] Advanced carotid disease is not only linked to a heightened risk of cerebrovascular events. Still, it may also precipitate cognitive decline independent of symptomatic occurrences, suggesting clinicians need to evaluate cognitive status routinely during assessments.[5,7] Within that context, utilizing functional magnetic resonance imaging (fMRI) to investigate these dynamics has shown that cognitive interventions may yield improvements in brain activation patterns, suggesting that targeted treatments could mitigate some cognitive deficits associated with carotid stenosis.[8] Besides the high-tool imaging tools, evaluating the clinical memory impairment in patients with ACS is critical, given the potential above-mentioned cognitive deficits associated with this condition.[4,9]

Among the most widely used cognitive screening tools, the Montreal Cognitive Assessment (MoCA)[10] and the Mini-Mental State Examination (MMSE)[11] provide valuable insights into different cognitive domains. The MoCA is a 30-point test designed to assess visuospatial and executive function, attention, language, memory, and orientation, with a strong sensitivity for detecting mild cognitive impairment. In contrast, the MMSE is an 11-question screening tool that evaluates five key cognitive areas: orientation, registration, attention and calculation, recall, and language. A total score below 24 on the MMSE is generally indicative of cognitive impairment. These tests, commonly used in research and clinical practice, allow for early detection of cognitive decline and facilitate monitoring disease progression, making them critical in studies assessing cognitive function in ACS patients.

To raise clinicians' awareness, incorporating comprehensive assessments that measure these cognitive domains along with imaging methods allows for a better understanding of the cognitive implications of ACS. This approach ultimately guides therapeutic interventions and improves patient outcomes. In the present study, we aimed to evaluate the relationship between ACS and cognition.

METHODS

We searched the hospital database for a group sample with a carotid Doppler ultrasound report and cognitive tests performed. A total of 20 patients were enrolled with sociodemographic factors (age, gender, and years of education). Additionally, 15 healthy subjects were matched for cognitive assessment and demographic variables. Alanya Training and Research Hospital Ethical Committee approved the study (Date: 22.01.2025, Decision No: 02-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with ≥50% carotid stenosis on carotid Doppler ultrasound were included in the study. Exclusion criteria were: 1) history of brain trauma or operation; 2) accompanying neuropsychiatric diseases and being used drugs which may affect the cognitive status (e.g., antidepressants); 3) electrolyte or metabolic imbalance (e.g., vitamin B12, vitamin B9, thyroid functions); 4) a history of stroke, transient ischemic attack, or carotid endarterectomy.

The MoCA, a 30-point test, evaluates various cognitive domains, including visuospatial and executive function, abstraction, and delayed recall.[12] The MMSE, another widely used cognitive screening tool, was also administered to all participants. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30 points. A score of 23 or lower is indicative of cognitive impairment.[13]

Statistical Analysis

IBM SPSS Statistics software (version 22) was used in the data analysis. Continuous parameters are expressed as the mean and the standard deviation (SD), and categorical parameters are shown as numbers and frequencies (%). Data were tested for normal distribution using the Shapiro-Wilk test. Normally distributed data were analyzed with one-way ANOVA, Student's t-test, and Pearson's correlation, while non-normally distributed data were analyzed with a Mann–Whitney U test, Kruskal Wallis, and Spearman's test. Also, categoric variables were analyzed using Fisher's exact test. Two-sided p-values and 95% CIs were used in SPSS software. Significance was determined at $p<0.05$.

RESULTS

This study compared patient and control groups' cognitive performance, age, and educational background. Twenty patients and 15 healthy individuals participated in the study. Ten female patients were in the patient group, and five were in the control group (χ^2:0.972, p= 0.324, Table 1).

Table 1. Demographic and clinical variables in the participants

Variables	ACS (n=20)	Controls (n=15)	p
Gender (female, n, %)	10 (50)	5 (33)	0.324 (χ^2: 0.972)
Age	66.15±12.15	60±9.17	0.11
Years of education	6.15±4.21	8.73±5.18	0.16
MMSE	25.85±2.28	26.8± .93	0.19
MoCA	19.85±4.48	23.07±3.01	0.028*

MMSE: Mini-Mental State Examination, MoCA: The Montreal Cognitive Assessment, n: Number. Results have been presented as mean±standard deviation, p significance level: <0.05

The MMSE scores were slightly lower in the patient group (25.85±2.28) compared to the control group (26.80±2.93); however, this difference was not statistically significant (p=0.28, Table 1). In contrast, the MoCA scores, which provide a more detailed evaluation of cognitive abilities, were significantly lower in the patient group (19.85±4.68) than in the control group (23.07±3.01; p=0.027, Table 1). This finding highlights a distinct disparity in MoCA, suggesting that carotid stenosis exhibited more significant impairments in cognitive performance.

There was no correlation between right or left carotid stenosis and cognitive tests in the patient group (Table 2). Patients'

Table 2. The correlation analyses in individuals with asymptomatic carotid stenosis

	2	3	4	5	6 (MoCA)
(1) right carotid stenosis (%)	-0.239 0.310	-0.017 0.943	-0.052 0.827	-0.074 0.756	-0.219 0.353
(2) left carotid stenosis (%)		0.328 0.158	-0.472 0.035*	-0.122 0.607	-0.181 0.446
(3) Age			-0.428 0.060	-0.496 0.026*	-0.665 0.001*
(4) Education years				0.381 0.097	0.634 0.003*
(5) MMSE					0.615 0.004*

MMSE: Mini-Mental State Examination; MoCA: The Montreal Cognitive Assessment; n: Number. The results have been presented as r (correlation coefficient) and p values*p<0.05: significance level

ages were negatively correlated with cognitive tests, as expected.

Although the patient group was nonsignificant (p=0.11, Table 1), it was, on average, older (66.15±12.15) than the control group (60±9.17).

Educational background, assessed through years of formal education, showed a trend toward lower values in the patient group (6.15±4.21) compared to the control group (8.73±5.18). However, this difference was not statistically significant (p=0.113, Table 1), indicating that the groups were relatively comparable in terms of educational attainment.

DISCUSSION

We have found that patients with ACS had lower cognitive function than controls. The findings from our study contribute to the growing body of evidence suggesting that ACS may not be as clinically silent as previously thought, particularly in relation to cognitive function. Our results align with several recent studies demonstrating a significant association between ACS and cognitive impairment.[14-16]

Interestingly, our findings reveal that patients with ACS exhibit poorer performance in global cognition, memory, and executive function compared to healthy controls.[16] The MoCA scores were significantly lower in the ACS group, suggesting more pronounced impairments in cognitive domains such as visuospatial ability, executive function, and delayed recall. In contrast, while MMSE scores were lower in the patient group, the difference was not statistically significant. This discrepancy may be attributed to the greater sensitivity of the MoCA test in detecting mild cognitive impairment, particularly in executive functions, which are often affected early in vascular cognitive decline. The MMSE, while widely used, primarily assesses orientation, memory, and basic cognitive functions and may not be as effective in capturing subtle cognitive deficits associated with ACS. This cognitive decline appears to be linked to cerebral hemodynamic impairment, as evidenced by decreased cerebral blood flow in specific brain regions and reduced connectivity in the default mode network.[16] These observations are further supported by studies showing that patients with ACS and impaired cerebrovascular reserve demonstrate significant cognitive impairment compared to those with normal reserve.[14] However, it is essential to note that the relationship between ACS and cognitive impairment is complex and may involve multiple mechanisms. While some studies have identified older age and cerebral hypoperfusion as additional factors contributing to cognitive decline in ACS patients[15], others have observed diffuse white matter abnormalities and localized grey matter atrophy in the ipsilateral hemisphere.[17] Furthermore, although differences in age and educational background between groups were not statistically significant, the trends observed suggest that these factors may still play a role in cognitive performance. Older age and lower educational attainment, both more prevalent in the ACS group, are well-established risk factors for cognitive decline and may have influenced the observed cognitive differences.

Under the our findings, it would be assumed that the cognitive effects of ACS may be more widespread than previously thought and not limited to the territory of the stenosed artery. This has important implications for the management of ACS patients, as cognitive function may need to be considered alongside traditional stroke risk factors when making treatment decisions.[18,19] Future research should focus on longitudinal studies to better understand the progression of cognitive decline in ACS and evaluate the potential cognitive benefits of interventions such as carotid endarterectomy or stenting.[16,20]

CONCLUSION

In conclusion, the exploration of ACS reveals critical insights into its potential impact on cognitive function and overall patient well-being. Our results, in conjunction with existing literature, strongly suggest that ACS is associated with cognitive impairment and should not be considered truly asymptomatic. While initially deemed benign, research indicates that individuals with ACS may experience notable cognitive impairments affecting memory, executive functions, and psychological dimensions. All of the complexity suggests that asymptomatic status may be misleading, warranting a re-evaluation of how these patients are assessed and managed. As the relationships between vascular health, cognition, and emotional states become clearer, clinicians must consider comprehensive evaluations for ACS patients to address cognitive decline and mental health effectively, ultimately improving patient outcomes.

To sum up, our results suggest that while the patient group demonstrated significantly poorer cognitive performance on the MoCA test, other factors such as age and education may also play a role, albeit somewhat. Further studies are needed to disentangle these factors and their impact on cognitive function. These findings suggest that cognitive assessment should be integrated into managing patients with carotid stenosis, as ignoring these cognitive impairments could overlook critical aspects of patient health and impede appropriate intervention strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

Alanya Training and Research Hospital Ethical Committee approved the study (Date: 22.01.2025, Decision No: 02-02).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Johnston SC, O'Meara ES, Manolio TA, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Ann Intern Med*. 2004;140(4):237-247. doi:10.7326/0003-4819-140-4-200402170-00005
2. Everts R, Wapp M, Burren Y, et al. Cognitive and emotional effects of carotid stenosis. *Swiss Med Wkly*. 2014;144:w13970. doi:10.4414/smw.2014.13970
3. Ortega G, Alvarez B, Quintana M, Yugueros X, Alvarez-Sabin J, Matas M. Asymptomatic carotid stenosis and cognitive improvement using transcervical stenting with protective flow reversal technique. *Eur J Vasc Endovasc Surg*. 2014;47(6):585-592. doi:10.1016/j.ejvs.2014.02.022
4. Landgraff NC. Cognitive and physical performance in patients with asymptomatic carotid artery stenosis and occlusion. University of Pittsburgh; 2004.
5. Martinic-Popovic I, Lovrencic-Huzjan A, Demarin V. Advanced asymptomatic carotid disease and cognitive impairment: an understated link? *Stroke Res Treat*. 2012;2012(1):981416. doi:10.1155/2012/981416
6. Vitali F, Torrandell-Haro G, Branigan G, et al. Asymptomatic carotid artery stenosis is associated with increased Alzheimer's disease and non-Alzheimer's disease dementia risk. *Stroke Vasc Neurol*. 2024:svn-2024-003164. doi:10.1136/svn-2024-003164
7. Sztriha LK, Nemeth D, Sefcsik T, Vecsei L. Carotid stenosis and the cognitive function. *J Neurol Sci*. 2009;283(1-2):36-40. doi:10.1016/j.jns.2009.02.307
8. Chinda B. Task-phase fMRI in detection of improvements in working memory post-interventions for carotid stenosis and early Alzheimer's disease. 2021.
9. Durmaz Çelik FN, Aykaç Ö. The effect of asymptomatic carotid artery stenosis on cognitive functions. *Turkish J Cerebrovasc Dis*. 2019;25(3):140-144. doi:10.5505/tbdhd.2019.14890
10. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
11. Cockrell JR, Folstein MF. Mini-mental state examination. Principles and Practice of Geriatric Psychiatry. 2nd Edition. 2002.
12. Nasreddine ZS, Phillips NA, Bédirian V, et al. Montreal cognitive assessment. *Am J Geriatr Psychiatry*. 2011;53(4):695-699. doi:10.1037/t27279-000
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6
14. Bhandari A, Feridooni T, Pikula A, Styra R, Mikulis DJ, Howe KL. Evaluating the influence of altered cerebral hemodynamics on cognitive performance in asymptomatic carotid artery stenosis: a systematic review. *J Vasc Surg*. 2024;79(2):436-447. doi:10.1016/j.jvs.2023.08.111
15. Chang X-L, Zhou H-Q, Lei C-Y, et al. Association between asymptomatic carotid stenosis and cognitive function: a systematic review. *Neurosci Biobehav Rev*. 2013;37(8):1493-1499. doi:10.1016/j.neubiorev.2013.05.011
16. Wang T, Sun D, Liu Y, et al. The impact of carotid artery stenting on cerebral perfusion, functional connectivity, and cognition in severe asymptomatic carotid stenosis patients. *Front Neurol*. 2017;8:403. doi:10.3389/fneur.2017.0040317
17. Avelar WM, D'Abreu A, Coan AC, et al. Asymptomatic carotid stenosis is associated with gray and white matter damage. *Int J Stroke*. 2015;10(8):1197-1203. doi:10.1111/ijs.12574
18. AbuRahma AF. The new 2023 European Society for Vascular Surgery (ESVS) carotid guidelines: the transatlantic perspective. *Eur J Vasc Endovasc Surg*. 2023;65(1):5-6. doi:10.1016/j.ejvs.2022.06.001
19. Kim J-G, Kang C-H, Choi JC, Song Y, Suh DC, Lee DH. Clinical outcomes of endovascular treatment for carotid artery dissection without intracranial large vessel occlusion in patients with cerebral ischemia presentation. *Front Neurol*. 2022;12:713190. doi:10.3389/fneur.2021.713190
20. Gaba K, Ringleb PA, Halliday A. Asymptomatic carotid stenosis: intervention or best medical therapy? *Curr Neurol Neurosci Rep*. 2018;18(11):80. doi:10.1007/s11910-018-0888-5

Academic Journal of Neurology & Neurosurgery

Original Article

DOI: 10.51271/AJNN-0022

Evaluation of post-traumatic stress disorder in ischemic stroke patients

Şennur Delibaş Katı[1], Ufuk Boran Özdemir[1], Gizem Günaydın[1], Eylem Özaydın Göksu[1], Süleyman Korkut[2]

[1]Department of Neurology, Antalya Training and Research Hospital, Antalya, Turkiye
[2]Department of Psychiatry, Antalya Training and Research Hospital, Antalya, Turkiye

Received: 01/03/2025 • Accepted: 17/03/2025 • Published: 21/03/2025

Cite this article: Delibaş Katı Ş, Özdemir UB, Günaydın G, Özaydın Göksu E, Korkut S. Evaluation of post-traumatic stress disorder in ischemic stroke patients. *Acad J Neurol Neurosurg.* 2025;2(1):5-8.

Corresponding Author: Şennur Delibaş Katı, sennurdelibaskati@gmail.com

ABSTRACT

Aims: Post-traumatic stress disorder (PTSD) is most commonly seen in cases such as actual death or threat of death, a severe injury, or experiencing a threat to the physical integrity of oneself or others. Stroke was defined to be related to PTSD as well. For this purpose, we aimed to evaluate acute and chronic PTSD after stroke with this test in our hospital, which is also a stroke center and has many different stroke patient profiles.

Methods: 25 patients hospitalized for stroke in the neurology clinics of our hospital and 25 patients in outpatient follow-up were included in the study. Inpatients were in the first 1-month period after stroke. These patients were accepted as acute PTSD. Patients who took the test from the outpatient clinic were in the follow-up period of at least 6 months after stroke.

Results: Patients were included in the study as 1-month post-stroke group and 6 months or more post-stroke group. In group 1, the test score was significantly higher ($p<0.001$). No significant difference was found in the comparison of these parameters.

Conclusion: In our study, a significant difference was found especially in terms of acute and chronic PTSD. The scores in the acute PTSD group were significantly higher than the chronic PTSD group ($p<0.001$). This suggests that this effect of stroke, especially in the acute period, may affect the course of treatment of the disease. However, multicenter studies including randomized controlled and long-term follow-up are needed.

Keywords: Stroke, post-traumatic stress disorder, life quality

INTRODUCTION

Stroke is one of the most important causes of mortality and morbidity worldwide. In the post-stroke period, return to social life may become difficult in relation to the remaining sequelae.[1] Many different problems may be encountered in adaptation to daily life in post-stroke patients. Psychiatric complaints may also accompany the patient's adaptation process. Clinicians should be especially vigilant in terms of conditions such as post-traumatic stress disorder, depression and anxiety.[2] Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops after a life-threatening event.[3] Although it has been associated with traumatic brain injury for a long time, in the last 30 years studies have proven that it has also been observed after stroke.[4] In the post-stroke period due to PTSD, symptoms such as problems in compliance with medications, decreased participation in activities of daily living and slowdown in mental capacity may be observed.[5] These may undermine the patient's recovery process and worsen his/her current condition.[6] Therefore, it is important to recognize PTSD after stroke.

PTSD is most commonly seen in cases such as actual death or threat of death, a severe injury, or experiencing a threat to the physical integrity of oneself or others.[3] It is classified as acute PTSD if the symptoms last less than 3 months and chronic PTSD if they last longer than 3 months.[3,7] The PTSD Checklist (PCL) is a self-report questionnaire that measures symptoms of PTSD according to the diagnostic and statistical manual of mental disorders (DSM). The PCL was first developed in 1993 by Weathers and colleagues[8] at the National Center for PTSD. The current version (PCL-5; Blevins et al.[10]; Weathers et al.[7]) is a 20-item questionnaire that includes items corresponding to the 20 PTSD symptoms (Criteria B-E) in the DSM-5 (American Psychiatric Association 2013). Items 1-5 reflect involuntary re-experiencing symptoms (Criterion B), items 6-7 reflect avoidance symptoms (Criterion C), items 8-14 reflect negative

mood and cognition symptoms (Criterion D), and items 15-20 reflect hyperarousal symptoms (Criterion E).[10] It has also been emphasized that the PCL-5 is a powerful test in the assessment of PTSD.[9,10]

Many different tests have been used in previous studies: post-traumatic stress disorder checklist-5 (PCL-5), patient health questionnaire-9 (PHQ-9), stroke specific quality of life scale (SS-QOL-12) are the most commonly used ones.[11,12] The post-traumatic stress disorder questionnaire (Civilian Version (PCL-C)) was validated in Turkish in 2005 and it was observed that there were very few studies on its use after stroke in the literature.[13] For this purpose, we aimed to evaluate acute and chronic PTSD after stroke with this test in our hospital, which is also a stroke center and has many different stroke patient profiles.

METHODS

The study was carried out with the permission of the Antalya Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 4/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, 25 patients hospitalized due to stroke in the neurology service of our hospital and 25 patients in outpatient clinic follow-up were included. The study was conducted with patients admitted with stroke between August 2024 and January 2025. Inpatients were planned as an acute group and patients in the first 1-month period after stroke were included in the study. Patients who were in outpatient follow-up after stroke and in the follow-up period of at least 6 months after stroke were included in the study as the chronic patient group. Informed consent was prepared for the study and patients who agreed to participate were tested. Aphasic patients, patients with advanced hearing loss, patients with multiple medication use due to diseases such as dementia, bipolar disorder, psychotic disorder before stroke, and patients with traumatic brain injury or brain surgery were excluded.

Statistical Analysis

The study data were analyzed with SPSS (Statistical Package fort he Social Sciences) 16.0 (SPSS Inc., Chicago, IL). Study data were expressed as mean±standard deviation for continuous variables and percentage (%) for categorical variables. Interquartile range (IQR) was used. Kolmogorov-Smirnov test was used for normality analysis of the data. Since the data did not fit the normal distribution, Independent simple t-test and Chi-square test were used to compare the two groups and $p<0.05$ was considered statistically significant.

RESULTS

Demographic data and stroke-related information of the patients are as follows. The mean age for group–1 was calculated as 71.28±12.98 and group–2 was 64.56±10.72 years. Thirteen patients were female (26%) and 37 were male (74%). Forty patients were married (80%) and 10 were single or divorced (20%). 40 (80%) patients had a history of first stroke, 6 (12%) patients had 2 strokes, 3 (6%) patients had 3 strokes and 1 (2%) patient had 4 strokes. 5 patients had a history of monopharmacy drug use for depression. 4 patients had mild motor aphasia that did not interfere with communication and had no comprehension disorder. 1 patient was receiving treatment for epilepsy.

23 patients (46%) had a history of left-sided stroke, 21 (42%) had a history of right-sided stroke and 6 (12%) had a history of bilateral stroke. 36 patients (72%) had anterior system stroke and 14 patients (28%) had posterior system stroke. In 41 patients (82%) modifed Rankle score(mRs) was 0-1, while in 9 patients (18%) it was 2 or more.

According to demographic data between the groups, the acute group was significantly higher than the chronic group according to age ($p=0.024$) and number of previous strokes ($p=0.041$). Again, in terms of mRS results ($p=0.010$), this time the chronic group had statistically more significant results than the acute group. Patients were included in the study as the first 1-month post-stroke group and the group with 6 months or more after stroke. Group 1 had a significantly higher test score ($p<0.001$) [acute 25 IQR (21.5-30.5), chronic 17 IQR (17-24)] (Table).

Table. Demographic data and (PCL-C) test results

	Group–1 (acute)	Group–2 (chronic)	p*
Age	71.28±12.98	64.56±10.72	0.052[1]
Sex			0.024[2]
Male	15	22	
Female	10	3	
Marital status			0.111[2]
Married	18	22	
Single	3	3	
Divorced	4	-	
Stroke number			0.041[2]
First time	17	23	
Second time	6	-	
Third time	1	2	
Fourth time	1	-	
Chronic disease (n=10)			0.700[2]
Depression	3	2	
Aphasia	3	1	
Epilepsy	1	0	
Laterlization			0.149[2]
Left	14	9	
Right	10	11	
Bilateral	1	5	
Localization			0.208[2]
Front	16	20	
Back	9	5	
mRS			0.010[2]
Good (0-1)	17	24	
Bad (>1)	8	1	
PCL-C*	25	17	<0.005

* PCL-C: Post-traumatic stress disorder checklist: civilian scale, [1] Independent simple t-test, [2] Chi-square test

DISCUSSION

Stroke is a disease with a heavy social burden and is still one of the diseases causing the highest mortality and morbidity in

the world. In general, problems related to physical capacity are more prominent after stroke. However, psychosomatic complaints similar to those in patients with head trauma may occur after stroke.[1-2] Since stroke is a serious life-threatening condition, these patients should also be questioned in terms of posttraumatic stress disorder.[5-6] This condition, which remains in the background in the clinic, actually affects patients' compliance with treatment and quality of life in the long term.[6,11,12] There is no test to evaluate posttraumatic stress disorder especially in stroke patients. Tests used for similar conditions have been used for this patient group in various studies and meta-analyses.[11-14] There may not always be enough time to administer these tests to patients by physicians or healthcare personnel in neurology outpatient clinic conditions. For this reason, the PTSD Checklist-Civilian Version" (PCL-C) is particularly important as it provides information to the physician about the patient's condition by answering the questionnaire in a short time. There is no data on the use of this test especially in Turkish stroke patients. Our study is important as it is one of the first in this respect.

In our study, a significant difference was found especially in terms of acute and chronic PTSD. The scores in the acute PTSD group were significantly higher than the chronic PTSD group ($p<0.001$). This suggests that this effect of stroke, especially in the acute period, may affect the course of treatment of the disease. However, multicenter studies including randomized controlled and long-term follow-up are needed.

Since there are very few studies in which this test was applied in stroke, our study is important in this respect. Fear of progression (FoP) is closely related to PTSD, perceived social support and coping styles in stroke patients. PTSD may directly or indirectly affect FoP through perceived social support, confrontation and submissive coping styles.[15] Therefore, it is important to encourage patients to reasonably use social support and coping styles to enhance their well-being and strive to alleviate the ongoing impact of PTSD symptoms and reduce the risk of FoP. In terms of PTSD risk factors, no significant difference was found in terms of gender, mRS, anterior or posterior system stroke. However, different results may be obtained by increasing the number of patients and increasing the sample size. Because there were not enough patients in our study to perform subgroup analysis. There were 5 patients who were previously taking medication for depression. No significant difference was found in the scores of these patients compared to other patients. Although the number of patients was very small, this result is still important in terms of showing that stroke can be a cause of PTSD in itself. In another study, delirium, previous psychiatric history, younger age, female gender and unemployment status were found to be more highly associated with PTSD symptoms after hemorrhagic stroke in patients evaluated with the PCL-C test.[16] More prominent PTSD symptoms were also associated with greater functional impairment. However, unlike our study, it was applied in patients with non-traumatic hemorrhage, not ischemic stroke, and 205 patients were included in the study. In another study, a significant relationship was found between younger age, female gender and previous PTSD history and post-stroke PTSD.[17] Similarly, in another study, PTSD caused by stroke was associated with younger age, recurrent strokes, more disability and comorbidities.[18] PTSD was associated with significantly increased physical, mental and quality of life burden in this already vulnerable population. Having social support was protective and indicated a potential target for intervention. A review shows that PTSD is common after stroke and even more common after subarachnoid hemorrhage. This underlines the importance of awareness and screening for PTSD after stroke, even after the first year post-stroke.[19] Feely et al.[29] evaluated both acute stress disorder and PTSD as a prospective cohort in their study and emphasized the importance of early assessment and identification of acute stress symptoms in stroke survivors as a risk factor for subsequent PTSD.

Different findings were obtained in studies comparing National institutes of health stroke scale (NIHSS) with PTSD. Müller et al.[20] found no relationship between anxiety and depression developing after stroke and NIHSS, whereas Pedowitz et al.[21] found that both acute stress disorder and PTSD increased as stroke disability increased. Rutovic et al.[22] showed that mRS was associated with PTSD. In our study, such a relationship with mRS was not detected. However, different results may be obtained in more patients and multicenter studies.

Although PTSD is generally thought to be triggered by external events such as war or sexual assault, studies have shown that PTSD symptoms develop in one out of every 4 patients after transient ischemic attack (TIA) and stroke.[23] PTSD is also frequently observed after myocard infarctus (MI).[24] In other words, experiencing MI, TIA or stroke means facing a life-threatening event. Therefore, early screening, diagnosis and treatment of PTSD in patients with somatic diseases is important. Because PTSD may both mislead the clinician about the underlying disease and challenge the clinician with problems such as compliance with treatment.[6]

PTSD after stroke is a clinical entity that needs to be examined more. There are a considerable number of studies on migraine in the literature.[25-27] However, self-assessment tests have been applied in stroke patients in a limited way. One reason for this may be that patients do not have the capacity to perform self-assessment after stroke. The use of these tests in neurological diseases both prevents confusion with stroke or stroke worsening by recognizing functional neurological symptoms and helps to understand the prevalence of PTSD.[28,29]

Limitations

Our study has some limitations. We think that the small number of patients is an important limitation especially in determining the factors predisposing to PTSD. Although the tests were administered prospectively, it was not possible to perform subgroup analyses. It can be predicted that the effectiveness of the study will increase if we can reach a sample size where subgroup analysis can be performed. The fact that it was a single-center study is another limiting factor. For future studies, a study design that includes a larger pre-sample and subgroups is planned.

CONCLUSION

Recognizing and treating PTSD after stroke affects the patient's acceptance of the disease, compliance with treatment and suitability for rehabilitation. In addition, it should be kept in mind that some symptoms perceived as worsening of stroke symptoms may be due to PTSD. Thus, unnecessary further examinations can be prevented each time. Therefore, multicenter randomized controlled studies with long-term follow-up are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Antalya Training and Research Hospital Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 4/8).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tang WK, Wang L, F Tsoi Kelvin KF, Rutovic Stela, Kim Jong S. Post-traumatic stress disorder after stroke: a systematic review. *Neurol India*. 2022;70(5):p1887-1895, doi:10.4103/0028-3886.359285
2. Kutlubaev MA, Akhmetova AI, Ozerova AI. Emotsional'nye rasstroistva posle insul'ta [Emotional disorders after stroke]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2023;123(12. Vyp. 2):30-35. doi:10.17116/jnevro202312312230
3. Amerikan Psikiyatri Birliği, (2014). Ruhsal bozuklukların tanısal ve sayımsal el kitabı (DSM-5), Tanı ölçütleri el kitabı. (Çev: Köroğlu,E.) Ankara: Hekimler Yayın Birliği. (Özgün çalışma 2013).
4. Bombardier CH, Fann JR, Temkin N, et al. Posttraumatic stress disorder symptoms during the first six months after traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2006;18(4):501-508. doi:10.1176/jnp.2006.18.4.501
5. Sembi S, Tarrier N, O'Neill P, Burns A, Faragher B. Does post-traumatic stress disorder occur after stroke: a preliminary study. *Int J Geriatr Psychiatry*. 1998;13(5):315-322. doi:10.1002/(sici)1099-1166(199805)13:5<315::aid-gps766>3.0.co;2-p
6. Kronish IM, Edmondson D, Goldfinger JZ, Fei K, Horowitz CR. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. *Stroke*. 2012;43(8):2192-2197. doi:10.1161/STROKEAHA.112.655209
7. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD checklist for DSM-5 (PCL-5). In National center for PTSD. 2013.
8. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. Paper presented at the annual meeting of the International Society for Traumatic Stress Studies, San Antonio. 1993.
9. American Psychiatric Association. Diagnostic and statistical manual of mental health disorders (5th ed.). Washington DC: Author. 2013.
10. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress*. 2015;28(6):489-498. doi:10.1002/jts.22059
11. Palmisano C, O'Neal M, Bautista MA, O'Neil CA, Fitzpatrick S. Assessing adherence to posttraumatic stress disorder screening in young stroke survivors. *J Neurosci Nurs*. 2025;57(1):31-36. doi:10.1097/JNN.0000000000000808
12. Renati S, Raju S, Makarova A, et al. Impact of post-stroke post-traumatic stress disorder. *Neurohospitalist*. 2025:19418744251315201. doi:10.1177/19418744251315201
13. Kocabaşoğlu N, Çorapçıoğlu Özdemir A, Yargıç İ, Geyran, P. Türkçe "PTSD Checklist - Civilian Version" (PCL-C) geçerliği ve güvenilirliği. Yeni Symposium. 2005.
14. Kutlubaev MA, Sabitova ÉR, Voevodin VA, Akhmadeeva LR. Simptomy posttravmaticheskogo stressovogo rasstroĭstva u patsientov s tserebral'nym insul'tom [Posttraumatic stress disorder in patients after stroke]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2014;114(12 Pt 2):16-18. doi:10.17116/jnevro201411412216-18
15. Guan X, Zhu Q, Qian H. Relationship between post-traumatic stress disorder and fear of progression in stroke patients: the mediating role of perceived social support and coping styles. *Top Stroke Rehabil*. 2024:1-9. doi:10.1080/10749357.2024.2417646
16. Griffin TT, Bhave V, McNulty J, Christophe BR, Garton ALA, Sander Connolly E Jr. Delirium and previous psychiatric history independently predict poststroke posttraumatic stress disorder. *Neurologist*. 2023;28(6):362-366. doi:10.1097/NRL.0000000000000495
17. Kronenberg G, Schöner J, Levitanus M, et al. The importance of previous lifetime trauma in stroke-induced PTSD symptoms and mental health outcomes. *J Psychiatr Res*. 2021;136:589-594. doi:10.1016/j.jpsychires.2020.10.033
18. Calderbank A, Gray C, Morgan-Boon A, Reuber M. Changes in posttraumatic stress disorder symptoms with integrative psychotherapy for functional neurological symptom disorder. *J Neuropsychiatry Clin Neurosci*. 2023;35(4):398-403. doi:10.1176/appi.neuropsych.21070184
19. Janssen EPJ, Spauwen PJJ, Bus BAA, Rijnen SJM, Ponds RWHM. Prevalence of posttraumatic stress disorder after stroke: a systematic literature review. *J Psychosom Res*. 2024;187:111914. doi:10.1016/j.jpsychores.2024.111914
20. Müller HHO, Czwalinna K, Wang R, et al. Occurence of post-traumatic stress symptoms, anxiety and depression in the acute phase of transient ischemic attack and stroke. *Psychiatr Q*. 2021;92(3):905-915. doi:10.1007/s11126-020-09873-9
21. Pedowitz E, Derby L, Cruz GJ, Trainor A, Edmondson D, Cornelius T. Relationship between NIH stroke symptoms and post-traumatic stress disorder in patients evaluated for transient ischemic attack/stroke. *Gen Hosp Psychiatry*. 2021;70:98-102. doi:10.1016/j.genhosppsych.2021.03.004
22. Rutovic S, Kadojic D, Dikanovic M, Solic K, Malojcic B. Prevalence and correlates of post-traumatic stress disorder after ischaemic stroke. *Acta Neurol Belg*. 2021;121(2):437-442. doi:10.1007/s13760-019-01200-9
23. Edmondson D, Richardson S, Fausett JK, Falzon L, Howard VJ, Kronish IM. Prevalence of PTSD in survivors of stroke and transient ischemic attack: a meta-analytic review. *PLoS One*. 2013;8(6):e66435. doi:10.1371/journal.pone.0066435
24. Dollenberg A, Moeller S, Lücke C, et al. Prevalence and influencing factors of chronic post-traumatic stress disorder in patients with myocardial infarction, transient ischemic attack (TIA) and stroke- an exploratory, descriptive study. *BMC Psychiatry*. 2021;21(1):295. doi:10.1186/s12888-021-03303-1
25. Balaban H, Semiz M, Şentürk IA, et al. Migraine prevalence, alexithymia, and post-traumatic stress disorder among medical students in Turkey. *J Headache Pain*. 2012;13(6):459-467. doi:10.1007/s10194-012-0452-7
26. Peterlin BL, Tietjen GE, Brandes JL, et al. Posttraumatic stress disorder in migraine. *Headache*. 2009;49(4):541-551. doi:10.1111/j.1526-4610.2009.01368.x
27. Peterlin BL, Tietjen G, Meng S, Lidicker J, Bigal M. Post-traumatic stress disorder in episodic and chronic migraine. *Headache*. 2008;48(4):517-522. doi:10.1111/j.1526-4610.2008.00917.x
28. Goldfinger JZ, Edmondson D, Kronish IM, et al. Correlates of post-traumatic stress disorder in stroke survivors. *J Stroke Cerebrovasc Dis*. 2014;23(5):1099-1105. doi:10.1016/j.jstrokecerebrovasdis.2013.09.019
29. Feely D, Slattery B, Walsh T, et al. Acute stress symptoms 1-2 weeks after stroke predict the subsequent development of post-traumatic stress symptoms: a prospective cohort study. *PLoS One*. 2023;18(10):e0286220. doi:10.1371/journal.pone.0286220

Academic Journal of Neurology & Neurosurgery

Review

DOI: 10.51271/AJNN-0023

Are gabapentinoids addictive?

Ceyda Tanoğlu[1], Ruhsen Öcal[2]

[1]Department of Neurology, İzmir Tepecik Training and Research Hospital, İzmir, Turkiye
[2]Department of Neurology, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkiye

Received: 29/10/2024 ◆ Accepted: 27/01/2025 ◆ Published: 21/03/2025

Cite this article: Tanoğlu C, Öcal R. Are gabapentinoids addictive? *Acad J Neurol Neurosurg.* 2025;2(1):9-12.

Corresponding Author: Ceyda Tanoğlu, ceydatanoglu@gmail.com

ABSTRACT

Gabapentinoids (GBPs) are highly effective drugs used in the treatment of epilepsy, anxiety disorders, and particularly neuropathic pain. In recent years, their use has become a cause for concern as reports on their misuse have increased. Studies have been conducted to identify the patient groups that are prone to the drug's misuse. Additionally, the drug's use has been restricted in some countries. While GBPs are favored due to their efficacy in pain management, their potential for addiction has made them a drug that physicians are increasingly hesitant to prescribe. The aim of this study is to review the research on the addictive effects of GBPs, providing physicians with information on predictive tests and anamnesis data regarding the risk of addiction.

Keywords: Pain management, substance-related disorders, neuralgia, epilepsy, anxiety disorders, physicians

INTRODUCTION

The use of gabapentinoids (GBPs) has been increasing in recent years because of their broad indications and success in pain management. The consumption of GBPs has increased more than fourfold in the last decade. In high-income countries, the drug's consumption is six times higher than that in low-income countries.[1] However, because of the drug's potential for addiction, its use has been restricted in some countries. Substance dependence, which was considered a sin or crime in the 19th century, was classified as a disease by the World Health Organization in 1952, following scientific advancements. For the first time in 1980, with the diagnostic and statistical manual of mental disorders (DSM)-III, a distinction was made between substance abuse and substance dependence, emphasizing that physiological dependence symptoms are necessary for a diagnosis of addiction. In the DSM-IV, substance abuse was defined as a milder disorder compared with substance dependence and was considered an early stage of addiction. Moreover, tolerance and withdrawal were no longer required for a diagnosis of addiction. The category "disorders related to substance use" in DSM-IV was changed to "substance-related and addictive disorders" in DSM-V.[2] Substances associated with use disorders are categorized as alcohol, caffeine, cannabis, hallucinogens (phencyclidine and other hallucinogens), inhalants, opioids, sedative-hypnotics and anxiolytics, stimulants (amphetamines, cocaine, and other stimulants), nicotine, and other (or unknown) substances.[2,3] GBPs are in the sedative, hypnotic, and anxiolytic group.

As addiction progresses, not using the addictive substance leads to symptoms, such as anhedonia, anxiety, depression, dysphoria, and irritability, and the urge to consume the substance increases to alleviate these negative symptoms rather than for the primary reinforcement.[3]

Substance use does not necessarily result in addiction. The development of addiction is associated with environmental, neurodevelopmental, and genetic factors. Approximately 15–17 out of every 100 individuals who begin using a substance will develop an addiction.[3,4] Conversely, abuse refers to using a substance for purposes other than its intended use without necessarily developing an addiction.

In the literature, although the term addiction has been used in relation to GBPs in recent years, the term abuse has been used for a much longer period.

Gabapentin (GBP) and pregabalin (PGB) belong to the group of GBPs. GBP was approved by the United States food and drug administration (FDA) in 1993 for the treatment of post-herpetic neuralgia and epilepsy, and the drug holds an indication for neuropathic pain according to the European medicines agency (EMA). PGB was approved by the FDA in 2004 for the treatment of neuropathic pain, post-herpetic neuralgia, seizures, and fibromyalgia, and it holds an indication from the EMA for generalized anxiety disorder.[5] Moreover, the off-label use of GBPs is common. Off-label uses include

headache, trigeminal neuralgia, acute or chronic postoperative pain, chronic non-specific low back pain, fibromyalgia, anxiety disorder, attention deficit hyperactivity disorder, bipolar disorder, alcohol withdrawal, opioid withdrawal, sleep disorders (insomnia and restless legs syndrome), and pruritus.[6,7]

GBPs share a similar mechanism of action but differ in their pharmacokinetic and pharmacodynamic properties.[7] Although structurally similar to gamma-aminobutyric acid (GABA), GBPs do not bind to the same receptor. They bind with high affinity to the α2δ-1 subunit of voltage-gated calcium channels (VGCCs) as well as to the N-methyl-D-aspartate receptor, inhibiting both. This likely inhibits the release of excitatory neurotransmitters and synaptogenesis, possibly through thrombospondins. The α2δ-1 subunits of VGCCs play a role in nociception. Following injury, the number of α2δ-1 subunits increases. However, their reduction can take several months. In transgenic mice that express high levels of α2δ-1, neuropathic pain has been shown to develop even in the absence of nerve damage.[7,8]

MECHANISM OF ADDICTION FOR GABAPENTINOIDS

The frequent prescription of GBPs because of their broad indication profile has been accompanied by increasing reports of abuse and mortality.[9] Gabapentinoid-related mortality was first recorded in the United Kingdom's database in 2006.[9] GBPs exhibit GABA-mimetic properties and likely exert effects on the dopaminergic reward system.[9] Deficits in glutamate clearance and postsynaptic glutamatergic receptor activation are thought to be associated with drug-seeking behavior and chronic drug use.[10] Glutamate transporter type-1 (GLT-1) plays a crucial role in the reuptake of synaptically released glutamate and in drug-seeking behavior.[10] Althobaiti et al.[10] showed that the drug-seeking behavior induced in mice administrated with 60 and 90 mg doses of PGB was blocked by ceftriaxone, a potent GLT-1 upregulator, which was reported as concrete evidence of PGB's addictive potential.

GABAPENTINOID ABUSE

Not everyone who uses GBPs develops an addiction. However, a history of psychiatric illness and substance abuse increases the likelihood of GBPs abuse.[11] When taken intravenously, intranasally, or orally at doses higher than the therapeutic range, GBPs can cause euphoric and dissociative effects.[12]

Relaxation and euphoria, especially at the beginning of drug treatment and at overdose, are due to the weak GABA-mimetic properties of GBPs and may lead to tolerance.[13]

Individuals with substance use disorder (SUD) tend to use GBPs at doses higher than that recommended, often taking very high doses at once. Although GBPs are most commonly abused orally, they can also be used rectally to increase absorption or administered via injection, inhalation, or smoking after crushing the tablets. To enhance absorption, individuals may also wrap crushed GBP tablets in a pouch, such as toilet paper, before swallowing them.[5]

The euphoric side effect associated with GBP use becomes more pronounced when combined with central nervous system (CNS) depressants, leading to a significant synergistic effect that increases the likelihood of abuse.[14] PGB is absorbed more rapidly than GBP and binds with higher affinity to the α2δ-1 subunit. Therefore, PGB has a greater potential for abuse compared to GBP.[9,15]

Most patients with a history of gabapentinoid abuse have also been found to have a history of other substance abuse.[9,13] The presence of a history of current or past substance abuse as well as psychiatric comorbidity are among the most significant risk factors for developing gapabentinoid abuse. A meta-analysis of case series found that GBP dependence was reported at 1.1% in the general population compared with 22% in drug addiction centers.[16]

It has been reported that GBPs are not fatal, even in overdose unless used in combination with opioids and sedatives.[13] The true addictive potential of GBPs is best reflected by the number of cases in individuals with no prior substance use experience who exhibit signs of behavioral addiction after GBP use, although such cases are rare.[13]

GBP overdose can be fatal, especially when used in combination with opioids and benzodiazepines, and can induce respiratory or cardiac failure.[13] In a study conducted at a French addiction center, 31 deaths related to gabapentinoid use were reported, the majority involving PGB (25 PGB, 6 GBP).[17] Side effects of coma, dyspnea, convulsions, and conduction disorders were observed in nearly all cases related to PGB use.[17] In terms of abuse, PGB rose from 15th place in 2017 to 1st place by 2019.[17] In the study by Grosshans et al.[18] PGB was detected in the urine of opioid-dependent individuals who had no medical indication for its use. Therefore, before prescribing GBP, patients should be carefully evaluated for a history of substance abuse.

Physical symptoms, such as the development of tolerance and withdrawal are more predictive of the recurrence or chronicity of addiction compared to behavioral symptoms like drug-seeking and loss of control.[13] Behavioral addiction symptoms related to GBPs are less frequent than those seen with PGB.[13]

The current high abuse rates of GBPs can be attributed to their broad indications, ease of prescription, rapid dose titration, initial lack of awareness among doctors regarding their abuse potential, the search for alternatives to opioid therapy, relatively low cost, and the ease of illegal acquisition. Most individuals abusing GBPs are men under the age of 40.[19]

the opioid risk tool is commonly used to assess risk during opioid use.[20] A score above 8 on this scale indicates a high risk of opioid addiction.[20] By using this scale on patients before using GBPs, a preliminary idea about their addiction potential can be obtained.

USE OF GABAPENTINOŞDS IN THE TREATMENT OF SUBSTANCE USE DISORDER

The treatment of SUDs involves medications, behavioral therapy, or a combination of both; however, success of the treatment remains limited. Thus, alternative options for withdrawal treatment are still being explored. Although GBPs have addictive potential, they are recommended off-label for the treatment of withdrawal.

GBPs affect the overactive glutamatergic system during withdrawal. It is believed that GBPs alleviate benzodiazepine

(BZD) withdrawal symptoms by reducing glutamate release from glutamatergic nerve terminals and decreasing glutamate binding to the AMPA receptor.[21] Side effects and abuse rates of GBPs are considerably lower than that of BZDs.[21] Although BZDs are an effective short-term treatment for alcohol withdrawal, discontinuing the treatment can lead to life-threatening withdrawal symptoms, and tolerance and addiction can develop even at therapeutic doses.[21] In double-blind, placebo-controlled studies, it has been shown that PGB significantly reduces anxiety scores in patients undergoing BZD withdrawal who were previously treated for generalized anxiety disorder.[22] Although GBPs are recommended off-label for addiction treatment, more randomized controlled trials are needed to substantiate their efficacy.[21]

GABAPENTINOID TOXICITY AND TREATMENT

Even when taken in high doses, these drugs are considered relatively safe when used alone. However, their interaction with other CNS depressants increases the risk of respiratory depression.[14] When taken by themselves, GBPs do not cause significant toxicity.[19] While symptoms like tremors, dizziness, tachycardia, bradycardia, ataxia, and hypotension are generally manageable in outpatient settings, more severe cases may rarely develop mental status changes, coma, or respiratory depression requiring intubation.[19,23]

Cases of PGB toxicity and abuse are increasing day by day, associated with an increase in overall consumption.[19] In PGB toxicity, most patients are also using other substances, especially BZDs, which can intensify clinical symptoms.[19] Isolated GBPs toxicity typically does not present a life-threatening risk.[19]

PGB abuse-related toxicity is more common in men, whereas suicide-related toxicity is more frequent in women.[19]

In cases of GBPs toxicity with tachycardia or hypotension, intravenous hydration should be initiated. Isolated GBPs toxicity shows no benefit from activated charcoal treatment. In cases of respiratory depression, the administration of naloxone is recommended if opioids have been taken concurrently. If myoclonus develops because of GBPs toxicity, it resolves upon discontinuation of the drug. If myoclonus occurs alongside renal failure, hemodialysis should be performed. In renal failure, extracorporeal treatment is suggested along with supportive care. A pharmacokinetic study found that 17%–51% of GBP and >50% of PGB were cleared with 3–4 hours of dialysis.

GABAPENTINOID WITHDRAWAL SYNDROME

Symptoms of GBPs withdrawal syndrome can emerge 12 hours–7 days after discontinuation of the drug, often developing within 24–48 hours.[16] Withdrawal symptoms associated with GBPs include sweating, tachycardia, gastrointestinal symptoms, anxiety, agitation, confusion, catatonia, and epileptic seizures.[16] In a study involving inmates, 85% of those using PGB exhibited withdrawal symptoms, with dissatisfaction and aggression being the most common clinical manifestations.[24]

In the same study, 93% of inmates using PGB were taking it in doses exceeding the recommended maximum dose of 600 mg/day, often in combination with other addictive agents.[24] Gradual reduction of GBPs may alleviate withdrawal syndrome symptoms.[16]

GABAPENTINOIDS AND MORTALITY

GBPs can be prescribed together with opioids for pain management.[25] Because of the stringent controls placed on opioids over the years, off-label medications, including GBPs, have also been prescribed for pain management.[26] The risk of opioid-related mortality increases when used in conjunction with GBPs.[25] While mortality due to overuse of both opioids and GBPs was higher in women until 2020, this difference has since diminished.[26] Opioids slow gastrointestinal motility, which prolongs the retention time of GBPs in the upper small intestine; thus, increasing their absorption and bioavailability.[25] In Australia, between 2000 and 2020, 81.3% of GBPs-related deaths were classified as accidental poisoning, whereas 18.8% were attributed to intentional drug overdose.[14] In GBPs-related deaths, there is a 99.8% prevalence of the use of other non-GBPs medications, frequently including opioids, hypnotics, and antidepressants.[14] Co-contributory diseases in GBPs-related deaths have most commonly been identified as cardiovascular system diseases.[14]

CONSIDERATIONS WHEN PRESCRIBING GABAPENTINOIDS

GBPs are considered a potential safer alternative to opioids, which is why GBPs prescription for chronic pain management is on the rise while the rates of opioid prescriptions are decreasing.[27] However, the potential for side effects increases when GBPs are prescribed alongside opioids.[27]

The most common side effects associated with GBPs are CNS-related symptoms, such as somnolence, dizziness, and walking and balance disorders. However, GABA receptors are not only found in the CNS; they are also present in the gastrointestinal, hematopoietic, and immune systems as well as in the ovaries, bladder, pancreas, lungs, and spleen. Although stroke and malignancy have been reported in users of GBPs, there is insufficient data to associate these with the medication.[27]

CONCLUSION

Given the increased usage in recent years, applying opioid risk tools to each patient before starting treatment can provide preliminary insights into the potential for addiction prior to prescribing GBPs. Moreover, avoiding the drug's prescription to those scoring 8 or above on the scale may help prevent the development of GBPs-related addiction.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Chan AYL, Yuen ASC, Tsai DHT, et al. Gabapentinoid consumption in 65 countries and regions from 2008 to 2018: a longitudinal trend study. *Nat Commun*. 2023;14(1):5005. doi:10.1038/s41467-023-40637-8
2. Gulec G, Kosger F, Essizoglu A. Alcohol and substance use disorders in DSM-5. Psikiyatride Guncel Yaklasimlar - Current Approaches in Psychiatry. Published online 2015. doi:10.5455/cap.20150325081809
3. Maldonado R, Calvé P, García-Blanco A, Domingo-Rodriguez L, Senabre E, Martín-García E. Vulnerability to addiction. *Neuropharmacology*. 2021;186:108466. doi:10.1016/j.neuropharm.2021.108466
4. Reed B, Kreek MJ. Genetic vulnerability to opioid addiction. *Cold Spring Harb Perspect Med*. 2021;11(6):a039735. doi:10.1101/cshperspect.a039735
5. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403-426. doi:10.1007/s40265-017-0700-x
6. Athavale A, Murnion B. Gabapentinoids: a therapeutic review. *Aust Prescr*. 2023;46(4):80-85. doi:10.18773/austprescr.2023.025
7. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. *Br J Pain*. 2020;14(2):104-114. doi:10.1177/2049463720912496
8. McAnally H, Bonnet U, Kaye AD. Gabapentinoid benefit and risk stratification: mechanisms over myth. *Pain Ther*. 2020;9(2):441-452. doi:10.1007/s40122-020-00189-x
9. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? *CNS Drugs*. 2014;28(6):491-496. doi:10.1007/s40263-014-0164-4
10. Althobaiti YS, Almalki A, Alsaab H, et al. Pregabalin: potential for addiction and a possible glutamatergic mechanism. *Sci Rep*. 2019;9(1):15136. doi:10.1038/s41598-019-51556-4
11. Stannard C. Misuse of gabapentin and pregabalin: a marker for a more serious malaise? *Addiction (Abingdon, England)*. 2016;111(10):1699-1700. doi:10.1111/add.13408
12. Schjerning O, Rosenzweig M, Pottegård A, Damkier P, Nielsen J. Abuse potential of pregabalin: a systematic review. *CNS Drugs*. 2016;30(1):9-25. doi:10.1007/s40263-015-0303-6
13. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol*. 2017;27(12):1185-1215. doi:10.1016/j.euroneuro.2017.08.430
14. Darke S, Duflou J, Peacock A, Farrell M, Lappin J. Characteristics of fatal gabapentinoid-related poisoning in Australia, 2000–2020. *Clin Toxicol*. 2022;60(3):304-310. doi:10.1080/15563650.2021.1965159
15. Erden Y, Kaya SS, Okçu M. Pregabalin and gabapentin use disorders. *Fiziksel Tıp ve Rehabilitasyon Bilimleri Dergisi*. 2019;22(3):126-133. doi:10.31609/jpmrs.2019-66052
16. Mersfelder TL, Nichols WH. Gabapentin: abuse, dependence, and withdrawal. *Ann Pharmacother*. 2016;50(3):229-233. doi:10.1177/1060028015620800
17. Tambon M, Ponté C, Jouanjus E, Fouilhé N, Micallef J, Lapeyre-Mestre M. Gabapentinoid abuse in France: evidence on health consequences and new points of vigilance. *Front Psychiatry*. 2021;12:639780. doi:10.3389/fpsyt.2021.639780
18. Grosshans M, Lemenager T, Vollmert C, et al. Pregabalin abuse among opiate addicted patients. *Eur J Clin Pharmacol*. 2013;69(12):2021-2025. doi:10.1007/s00228-013-1578-5
19. Antunovic M, Vucinic S, Kotur-Stevuljevic J, et al. Rise of pregabalin poisoning and abuse cases in Serbia: a ten-year retrospective study. *Int J Gen Med*. 2023;16:1239-1250. doi:10.2147/IJGM.S405616
20. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med*. 2005;6(6):432-442. doi:10.1111/j.1526-4637.2005.00072.x
21. Warlick H, Leon L, Patel R, et al. Application of gabapentinoids and novel compounds for the treatment of benzodiazepine dependence: the glutamatergic model. *Mol Biol Rep*. 2023;50(2):1765-1784. doi:10.1007/s11033-022-08110-9
22. Hadley SJ, Mandel FS, Schweizer E. Switching from long-term benzodiazepine therapy to pregabalin in patients with generalized anxiety disorder: a double-blind, placebo-controlled trial. *J Psychopharmacol*. 2012;26(4):461-470. doi:10.1177/0269881111405360
23. Wills B, Reynolds P, Chu E, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. *J Med Toxicol*. 2014;10(3):254-260. doi:10.1007/s13181-014-0384-5
24. Novotny M, Bulla J, Hubl D, et al. Pregabalin use in forensic hospitals and prisons in German speaking countries—a survey study of physicians. *Front Public Health*. 2024;11:1309654. doi:10.3389/fpubh.2023.1309654
25. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case–control study. *PLoS Med*. 2017;14(10):e1002396. doi:10.1371/journal.pmed.1002396
26. Powell D, Shetty KD, Peet ED. Trends in overdose deaths involving gabapentinoids and Z-drugs in the United States. *Drug Alcohol Depend*. 2023;249:109952. doi:10.1016/j.drugalcdep.2023.109952
27. Kuo YF, Polychronopoulou E, Raji MA. Signal detection of adverse events associated with gabapentinoid use for chronic pain. *Pharmacoepidemiol Drug Saf*. 2024;33(1):e5685. doi:10.1002/pds.5685

Academic Journal of Neurology & Neurosurgery

Case Report

DOI: 10.51271/AJNN-0024

Cardio-cerebral infarction following syncope

Şeyda Gedikaslan, Tahir Şahin, Ahmet Burak Erdem

Department of Emergency Medicine, Ankara Etlik City Hospital, Ankara, Turkiye

Received: 31/10/2024 • Accepted: 27/01/2025 • Published: 21/03/2025

Cite this article: Gedikaslan Ş, Şahin T, Erdem AB. Cardio-cerebral infarction following syncope. *Acad J Neurol Neurosurg.* 2025;2(1):13-15.

Corresponding Author: Şeyda Gedikaslan, gedikaslanseyda@gmail.com

ABSTRACT

Cardio-cerebral infarction (CCI) initially introduced by Omar et al. in 2010, pertains to the concurrent manifestation of acute ischemic stroke (AIS) and acute myocardial infarction (AMI). In this study, we presented a 50-year-old man who arrived at the emergency department with syncope 6 hours prior. Neurological examination revealed left nasolabial fold flattening and left hemiparesis. Computed tomography brain scan showed no intracranial hemorrhage, while diffusion brain magnetic resonance imaging displayed restricted diffusion of the right centrum ovale in the periventricular space. Electrocardiogram indicated subacute ST-segment elevation in V2-V4, which resulted in the diagnosis of CCI. Due to ST-elevated myocardial infarction, he received aspirin, ticagrelor, and heparin before undergoing emergent coronary angiography. After multidisciplinary discussion, the patient was planned for coronary artery bypass graft surgery. His AIS was medically managed with antiplatelet and anticoagulant therapy. CCI is a rare and high-mortality disease arising from the simultaneous occurrence of AIS and AMI. Due to its rarity, there's no consensus on its treatment. The treatment process for AIS is limited to the patient's suitability for thrombolytic and thrombectomy therapy. We advise using a hybrid angiography laboratory for AIS patients.

Keywords: Cardio-cerebral infarction, acute myocardial infarction, acute ischaemic stroke, syncope

INTRODUCTION

Cardio-cerebral infarction (CCI), first defined in 2010 by Omar et al., refers to the simultaneous occurrence of acute ischemic stroke (AIS) and acute myocardial infarction (AMI).[1] Its incidence rate has been documented at 0.009%.[2] CCI can result from aortic dissection, hypotension, AMI, atrial fibrillation, and embolus originating from prosthetic valves.[3] Due to the limited number of cases, there is no consensus on the treatment management of CCI patients. The objective of this case presentation is to illustrate a patient with CCI who presented to the emergency department (ED) following a syncopal episode, with a detailed outline of our treatment approach, following the acquisition of informed consent.

CASE

A 50-year-old man was admitted to the ED with syncope 6 hours before arrival. His medical history was significant for type 2 diabetes mellitus (DM) and chronic tobacco use. He was on metformin 500 mg twice a day (2×1) orally and was not taking any antiplatelet or anticoagulant therapy. He reported mild diaphoresis. His vital signs were normal. Glucose level was 125 mg/dl. Glasgow Coma Scale score was 15. Neurologic examination revealed flattening of the left nasolabial fold and left hemiparesis. His National Institutes of Health Stroke Scale (NIHSS) score was 2. Magnetic resonance imaging (MRI) showed acute cytotoxic edema compatible with restricted diffusion of the right centrum ovale in periventricular space (Figure 1). Computed tomography (CT) angiography of the aorta didn't show aortic dissection (Figure 2). Electrocardiogram (ECG) showed subacute ST-segment elevation in V2-V4 (Figure 3). hs-TroponinT was 754 ng/L. Echocardiography showed a left ventricular ejection fraction (LVEF) of 40% associated with hypokinetic apex. He was loaded with 300 mg aspirin, 180 mg ticagrelor and 5000 IU heparin, then taken for emergent coronary angiography (CAG). CAG revealed a filling defect in the left coronary artery but distal flow was adequate. Because he was hemodynamically stable and distal Thrombolysis in Myocardial Infarction (TIMI) grade flow was 3 (complete perfusion), percutaneous coronary intervention (PCI) was not performed. The patient planned for coronary artery bypass graft (CABG) surgery. His AIS was managed medically with antiplatelet and anticoagulant therapy. The patient was discharged on the 7th postoperative day with a modified Rankin score of 1, and was prescribed aspirin 100 mg once daily and enoxaparin 40 mg subcutaneously once daily for ten days. At the one-week follow-up, the patient was started on dual antiplatelet therapy with lifelong aspirin 100 mg daily and clopidogrel 75 mg daily.

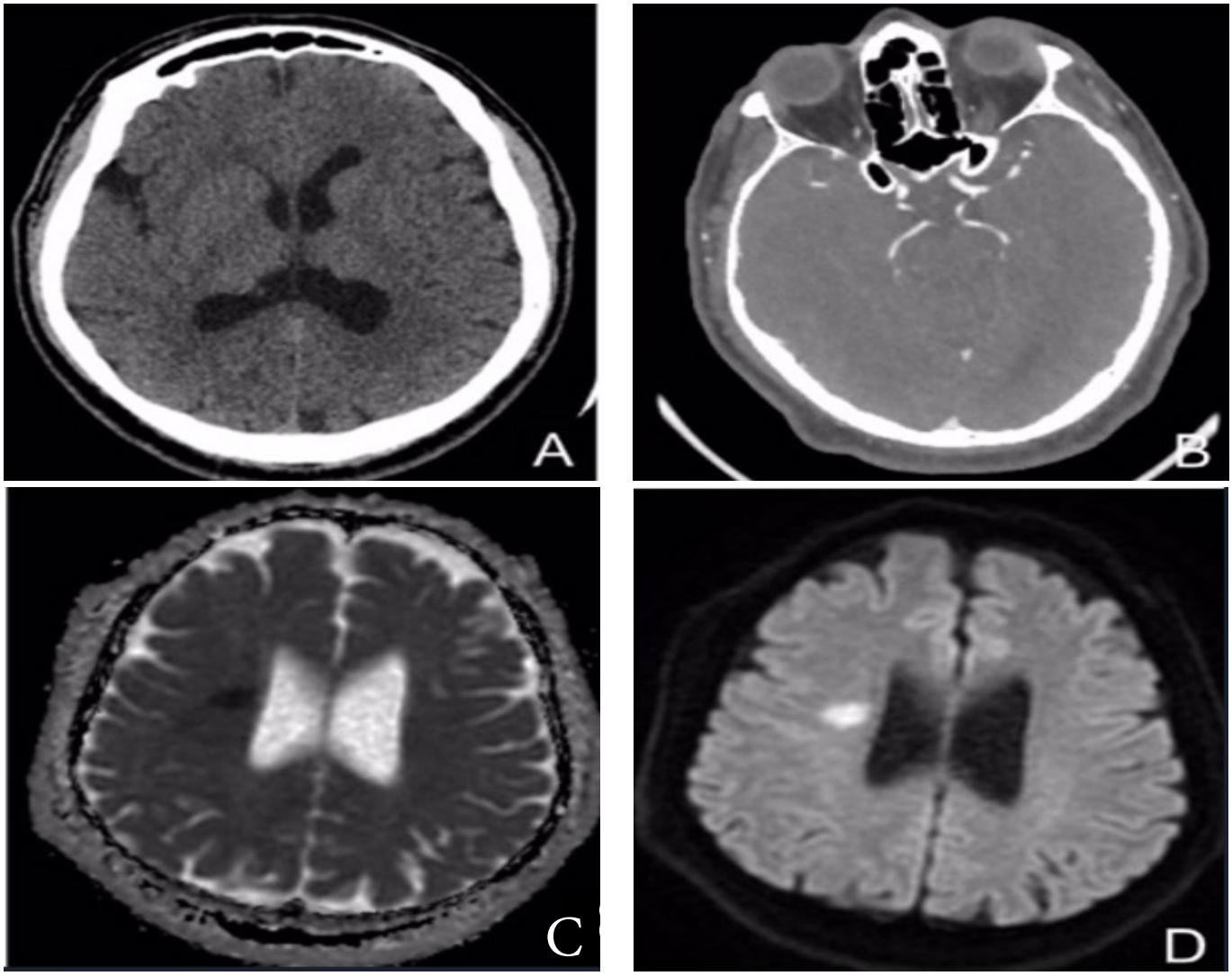


Figure 1. **A**) The brain computed tomography scan did not reveal any signs of intracranial bleeding. **B**) There was no major vessel occlusion in the cerebral angiography. **C**) Acute diffusion restriction detected in the centrum ovale on apparent diffusion coefficient (ADC) magnetic resonance imaging sequence. **D**) The hyperintensity observed in the diffusion-weighted imaging (DWI) scan is consistent with acute ischemic stroke

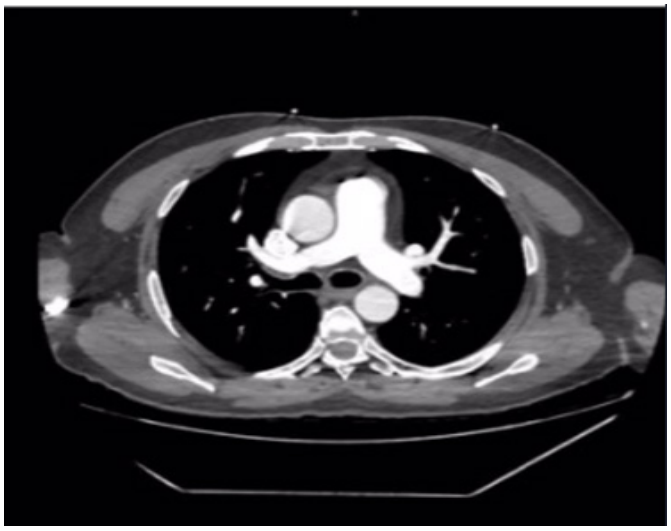


Figure 2. Aortic dissection is not present in the computed tomography angiography

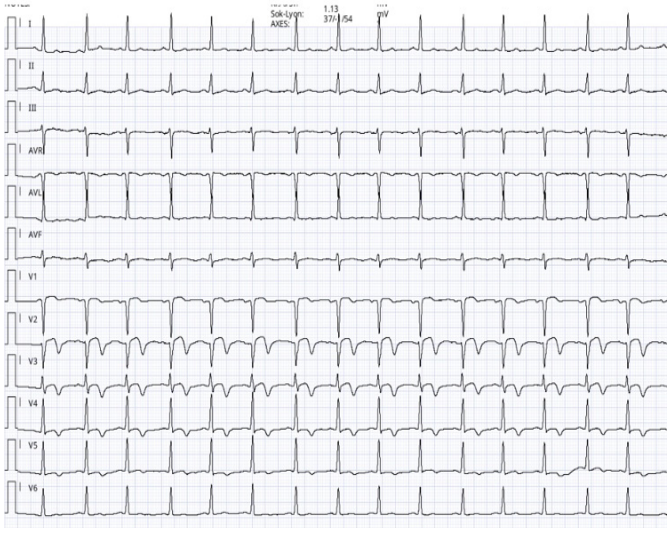


Figure 3. The electrocardiogram reveals signs consistent with anterior myocardial infarction

DISCUSSION

CCI is a condition characterized by the simultaneous occurrence of AIS and AMI, resulting in high mortality rates.[4] CCI can be categorized into two groups based on the timing of component occurrences. Synchronized CCI refers to the simultaneous infarction of coronary and cerebral vessels, while metachronous CCI involves sequential infarctions of coronary and cerebral vessels.[2,4] It has been reported that 66% of cases are synchronized, and 33% are metachronous. Men are found to be more susceptible than women, and the average age is commonly in the fifth decade of life. The most prevalent comorbidities are smoking, DM, and hyperlipidemia.[1] In our presented case, we observed a metachronous CCI in a 50-year-old male with a history of smoking and DM. Thus, our case is consistent with the demographic characteristics reported in the literature.

Left ventricular dysfunction arising from AMI increases the risk of left ventricular thrombus formation and embolism.[5,6] In the presented case, echocardiography revealed an LVEF of 40% and apical hypokinesis. Therefore, we believe that CCI may stem from central hypoperfusion due to reduced cardiac output or cardiac microthrombi. A similar case in the literature describes a 71-year-old patient who presented to the ED with speech impairment following syncope. Diffusion MRI revealed acute diffusion restriction in the left parietal cortex. CAG was performed on the patient with a De Winter pattern on the ECG. Subsequently PCI was performed on the circumflex artery (CX). In this CCI case, the development of cerebral infarction was attributed to hypoperfusion. The patient was discharged seven days later with antiplatelet and anticoagulant therapy without any neurological impairment.[7]

Due to the rarity of CCI, there is no consensus on its treatment. Personalized treatment modalities include PCI and cerebral thrombectomy, only 0.9 mg/kg (cerebral dose) intravenous (IV) thrombolytic, 0.9 mg/kg IV thrombolytic and PCI, dual antiplatelet therapy and anticoagulant treatment were applied according to the patient.[3] In this case, the patient exceeded the therapeutic window and had a low NIHSS score, so thrombectomy and IV thrombolytic therapy were not administered. For AMI, the patient underwent CAG revealing an 80% stenosis before the diagonal branch of the left anterior descending artery (LAD), an 80% stenosis at the ostium of first diagonal artery (D1), and a 98% stenosis after D1, leading to CABG surgery.

CONCLUSION

The medical history of patients arriving at the ED with acute neurological symptoms should be taken comprehensively, followed by a performed ECG. In the treatment process, if simultaneous intervention is required for stroke and AMI, intervention can be performed in the hybrid angio laboratory. If thrombolysis and thrombectomy are not suitable for stroke, AMI treatment should be done first.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Desai R, Mondal A, Prasad A, et al. Concurrent cardio-cerebral infarctions in COVID-19: a systematic review of published case reports/series. *Curr Probl Cardiol*. 2023;48(10):18. doi:10.1016/j.cpcardiol.2023.101814
2. Yeo LL, Andersson T, Yee KW, et al. Synchronous cardiocerebral infarction in the era of endovascular therapy: which to treat first? *J Thromb Thrombolysis*. 2017;44(1):104-111. doi:10.1007/s11239-017-1484-2
3. Chong CZ, Tan BY, Sia CH, et al. Simultaneous cardiocerebral infarctions: a five-year retrospective case series reviewing natural history. *Singapore Med J*. 2022;63(11):686-690. doi:10.11622/smedj.2021043
4. Omar HR, Fathy A, Rashad R, Helal E. Concomitant acute right ventricular infarction and ischemic cerebrovascular stroke; possible explanations. *Int Arch Med*. 2010;26(1):3-25. doi:10.1186/1755-7682-3-25
5. Kijpaisalratana N, Chutinet A, Suwanwela NC. Hyperacute simultaneous cardiocerebral infarction: rescuing the brain or the heart first? *Front Neurol*. 2017;8(1):664. doi:10.3389/fneur.2017.00664
6. Gianstefani S, Douiri A, Delithanasis I, et al. Incidence and predictors of early left ventricular thrombus after ST-elevation myocardial infarction in the contemporary era of primary percutaneous coronary intervention. *Am J Cardiol*. 2014;113(7):1111-1116. doi:10.1016/j.amjcard.2013.12.015
7. Erdem AB, Tumer M. De Winter wave with ST segment elevation equivalent with speech disorder; a case report. *J Emerg Med Case Rep*. 2022;13(1):19-21. doi:10.33706/jemcr.991552

Academic Journal of Neurology & Neurosurgery

Case Report

DOI: 10.51271/AJNN-0025

Multiple cranial nerves involvement as initial presentation of Guillain-Barré syndrome

Wai Hou Khuan[1], Dhayalen Krishnan[1], Raja Ahmad Reza Raja Lope Ahmad[1], Hairuddin Achmad Sankala[2]

[1]Department of Neurology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[2]Department of Radiology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Received: 10/12/2024 • **Accepted**: 16/01/2025 • **Published**: 21/03/2025

Cite this article: Khuan WH, Krishnan D, Ahmad RARRL, Sankala HA. Multiple cranial nerves involvement as initial presentation of Guillain-Barré syndrome. *Acad J Neurol Neurosurg.* 2025;2(1):16-19.

Corresponding Author: Wai Hou Khuan, khuanwei2@gmail.com

ABSTRACT

Guillain-Barré syndrome (GBS) is an immune-mediated peripheral nerve disease with classical symptoms of progressive ascending bilateral upper and lower limb weakness. Cranial nerves involvement can be part of manifestation of GBS. Case reports on early involvement of multiple cranial nerves in this disease are limited. We hereby describe a 49 year old man who was diagnosed as GBS presenting unusually with facial diplegia and bulbar palsy that preceded lower limbs weakness and paresthesia. The diagnosis was supported with rare neuroimaging findings of bilateral facial nerves enhancement. He recovered well with supportive management.

Keywords: Guillain-Barré syndrome, facial diplegia, bulbar palsy, cranial nerves

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute inflammatory peripheral nerve disease which classically presented with rapidly progressive ascending flaccid paralysis. Multiple cranial nerves involvement are rare and usually occurs after the weakness of limbs. The importance of early recognition is to anticipate the progression of disease. Moreover, cranial nerve enhancement by magnetic resonance imaging (MRI) in GBS is rare. High index of suspicion by an attending doctor is required when encountering these unusual presentations in order to get proper diagnosis.

CASE

A 49 year old man with underlying hypertension, ischemic heart disease, heart failure and diabetes mellitus experienced sudden loss of facial expression and dribbling from his mouth while drinking. His speech also became slurred. His gait became unsteady subsequently. Otherwise, there was no history of recent infection and trauma.

His vital signs were within normal limits. Examination showed lower motor neuron type of facial diplegia (Figure A and B) and nasal speech. Gag reflex was absent. He was ataxic on his feet although power of bilateral lower limbs was Medical Research Council (MRC) Scale of 5. The power of bilateral lower limbs was reduced from MRC scale of 5 to 4 on day 4 of illness with paresthesia. All deep tendon reflexes were absent. Pain sensation and proprioception were intact.

Patient refused lumbar puncture. Nerve conduction studies showed prolonged left median nerve sensory peak latency while reduced sensory nerve action potential of bilateral ulnar and median nerves (Table 1); prolonged distal motor latencies of right medial, left ulnar and bilateral peroneal nerves (Table 2). F wave latencies were within normal range (Table 3). There were absence of response from bilateral trigeminal and facial nerves. Anti-ganglioside antibody panel was negative. MRI of the brain and spine showed enhancement of the distal intracanalicular, geniculate ganglion (Figure C) and tympanic (Figure D) segments of facial nerves bilaterally as well as the cauda equina on post-contrast T1 weighted sequences.

His GBS disability scale was 4. IVIg was not prescribed in view of thrombotic risk because of his background of coronary artery disease. He received supportive care such as physiotherapy and speech therapy. He was discharged in the second week of illness with the ability to swallow safely and no worsening of other symptoms. Upon follow up at the fourth month of illness, his symptoms much improved with being able to ambulate without any aids.

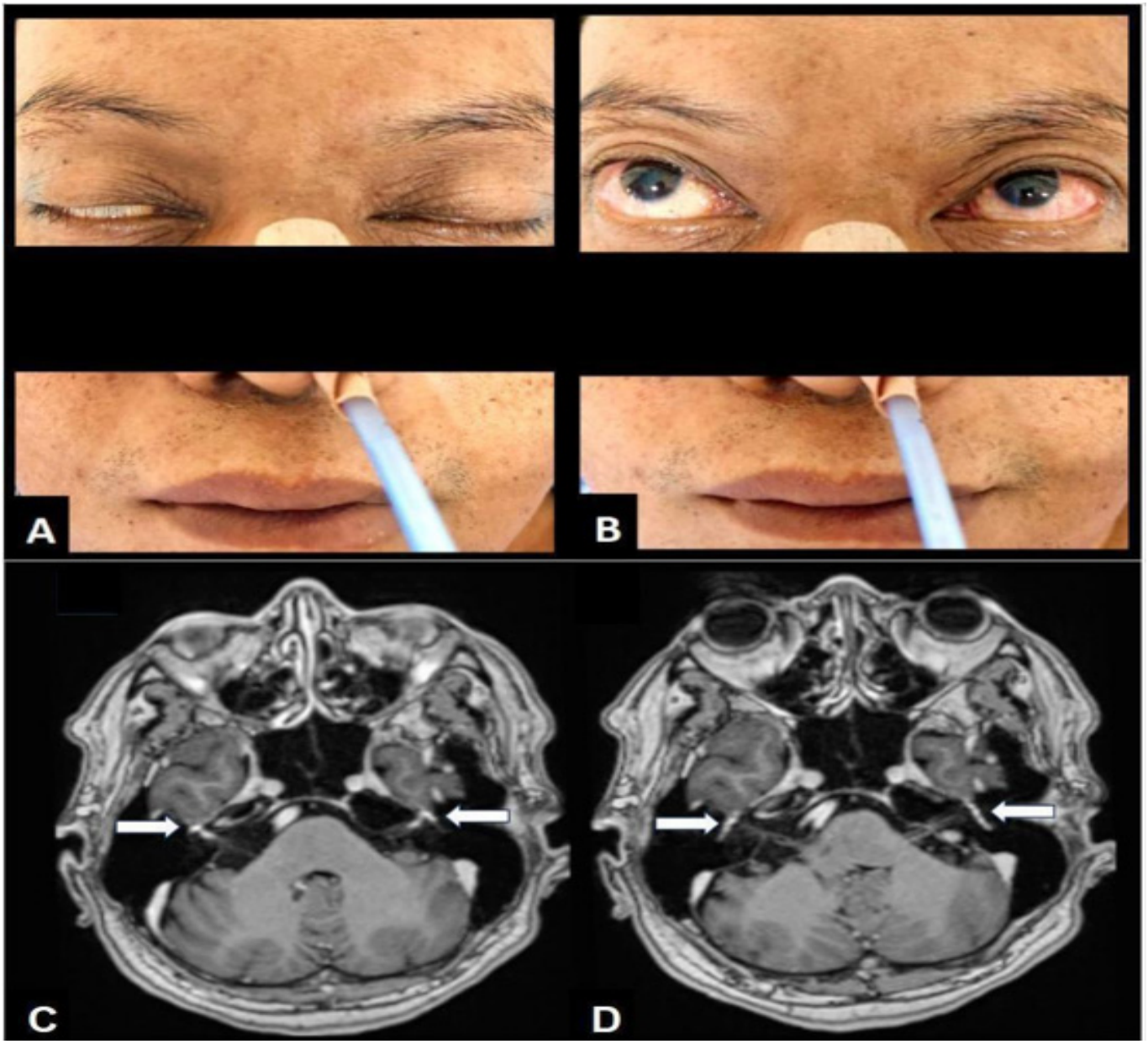


Figure. Bilateral lagophthalmos with loss of nasolabial folds and ryle tube was inserted for bulbar palsy (**A**); Weakness of bilateral frontalis muscles (**B**). Post-contrast T1MPRAGE images of the brain on axial show enhancement (arrows) of the distal intracanalicular and geniculate ganglion (**C**) and tympanic (**D**) segment of bilateral facial nerves

Table 1. Sensory nerve conduction studies

Nerve/sites	Receptor site	Onset latency (ms)	Peak latency (ms)	NP Amp (μV)	PP Amp (μV)	Segments	Distance (cm)	Velocity (m/s)
Right median-digit II (antidromic)								
Wrist	Index finger	2.71	3.60	13.8	13.3	Wrist-index	15	55
Left median-digit II (antidromic)								
Wrist	Index finger	3.08	4.29	9.8	10.8	Wrist-index	15	49
Right ulnar-digit V (antidromic)								
Wrist	Little finger	2.38	3.29	6.2	10.4	Wrist-little finger	13	55
Left ulnar-digit V (antidromic)								
Wrist	Little finger	2.29	3.25	10.4	10.5	Wrist-little finger	13	57
Left sural (antidromic)								
Calf	Ankle	2.60	3.54	16.1	21.0	Calf-ankle	14	54
Right sural (antidromic)								
Calf	Ankle	2.71	3.65	19.0	21.8	Calf-ankle	14	52
Left superficial peroneal - ankle								
Lateral leg	Ankle	1.94	2.75	11.2	15.0	Lateral leg-ankle	11	57
Right superficial peroneal - ankle								
Lateral leg	Ankle	2.19	2.98	8.3	8.7	Lateral leg-ankle	13	59

Table 2. Motor nerve conduction studies

Nerve/sites	Muscle	Latency (ms)	Amplitude (mV)	Area (mVms)	Duration (ms)	Relative amptitude (%)	Segments	Distance (cm)	Latency difference (ms)	Velocity (m/s)	Relative velocity (%)
Right median- abductor pollicis brevis (APB)											
Wrist	APB	5.1	6.9	28.7	10.33		Wrist-APB	8			
Elbow	APB	9.31	5.7	27.0	10.46	83	Elbow-wrist	25	4.21	59	100
Right ulnar-adductor digiti minimi (ADM)											
Wrist	ADM	2.88	4.4	14.6	7.77	100	Wrist-ADM	8			
Below elbow	ADM	6.81	3.5	9.9	6.81	80.8	Below elbow-wrist	26	3.94	66	100
Above elbow	ADM	11.23	2.6	7.7	5.69	75.1	Albow-below elbow	13	4.42	29	44.6
Left ulnar- adductor digiti minimi (ADM)											
Wrist	ADM	4.19	6.1	19.5	6.52	100	Wrist-ADM	8			
Below elbow	ADM	8.69	5.0	16.7	6.83	82.6	Below elbow-wrist	26	4.50	58	100
Above elbow	ADM	11.98	3.4	13.6	7.17	67.1	Albow-below elbow	15	3.29	46	
Left peroneal- extensor digitorum brevis (EDB)											
Ankle	EDB	6.79	2.0	9.2	7.6	100	Ankle-EDB	8			
Below fibula head	EDB	14.29	1.7	8.1	7.6	85.8	Below fibula head-ankle	32	7.50	43	100
Above fibula head	EDB	15.67	1.8	8.9	8.0	105	Above-below fibula head	10	1.37	73	
Right peroneal-extensor digitorum brevis (EDB)											
Ankle	EDB	4.81	4.3	18.7	8.19	100	Ankle-EDB	8			
Below fibula head	EDB	15.65	3.2	16.3	9.27	75.7	Below Fibula head-ankle	36	8.83	41	100
Above fibula head	EDB	15.27	4.2	20.9	9.19	130	Above-below fibula head	10	1.62	62	
Left tibial-anterior tibialis (AH)											
Ankle	AH	5.33	13.9	50.4	8.29	100	Ankle-AH	8			
Knee	AH	15.58	11.1	46.9	9.06	80	Knee-ankle	40	10.25	39	100
Right tibial-anterior tibialis (AH)											
Ankle	AH	4.73	8.9	37.3	9.21	100	Ankle-AH	8			
Knee	AH	15.85	7.1	34.5	8.96	79.9	Knee-ankle	40	11.13	36	100

Table 3. F wave

F wave	Minimum F latency (ms)	Maximum F latency (ms)	Mean F latency (ms)
Right ulnar-ADM	25.5	38.0	30.1
Right median-APB	32.6	34.2	33.2
Left ulnar-ADM	29.4	30.2	29.8
Left peroneal-EDB	42.2	44.3	43.4
Left tibial-AH	30.9	39.6	35.2
Right peroneal-EDB	41.8	66.8	47.9
Right tibial-AH	40.0	45.9	42.9

ADM: Adductor digiti minimi, APB: Abductor pollicis brevis, EDB: Extensor digitorum brevis, AH: Anterior tibialis

DISCUSSION

GBS typically manifests as ascending limb weakness. Cranial nerve involvement is seen in 50% of patients with GBS and it usually follows limb involvement.[1] However, facial diplegia and bulbar palsy as initial manifestation of GBS followed by lower limb weakness is a rare occurrence.[1-3] Recognition of early cranial nerve involvement as part of the GBS spectrum is important to anticipate the typical disease progression.[4-6] These prominent symptoms could be features of GBS variants such as sensory ataxic variant, facial diplegia with paresthesia and acute bulbar palsy plus.

GBS is diagnosed clinically and supported with various investigations such as cerebrospinal fluid analysis, nerve conduction studies, neuroimaging or serum anti-ganglioside

antibodies. MRI could be a supplementary diagnostic modality to exclude infectious, vascular or neoplastic causes. Rare findings of bilateral facial nerves enhancement in this patient provide supportive evidence for nerve inflammation in GBS.[7,8]

Decision of prescribing IVIg was weighed between risk of thrombosis and progression of symptoms. There is lack of clinical evidence to support the safe use of IVIg in patients with severe cardiovascular disease. There are cases of myocardial infarction after use of IVIg.[9] Thus, this patient did not receive IVIg in view of his symptoms which did not further progress with risk consideration of his comorbidities. There is also limited evidence for IVIg in milder forms and variants of GBS.[10]

CONCLUSION

Initial cranial nerve involvement is the unusual presentation of GBS which should not be missed in the clinical practice. Future study is required to explore the safety of IVIg use in patients with ischemic heart disease and its benefits in milder or variant forms of GBS.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Aravind SM, Karri VPVR, Suganya K, Tumbanatham A. Facial diplegia as an initial presentation of Guillain-Barré syndrome. *J Clin Diagn Res*. 2023;17(4):OD04-6. doi:10.7860/JCDR/2023/60781.17720
2. Susuk K, Koga M, Hirata K, Isogai E, Yuki N. A Guillain-Barré syndrome variant with prominent facial diplegia. *J Neurol*. 2009;256:1899-1905. doi:10.1007/s00415-009-5254-8
3. Michael TA, Joyce LO, Kelly M, Rashida YW. Guillain-Barré syndrome clinical presentation: history, physical examination. Medscape. https://emedicine.medscape.com/article/315632-clinical#:~:text=Cranial%20nerve%20involvement%20is%20observed,droop%20(may%20mimic%20Bell%20palsy). Updated July 29, 2024. Accessed December 11, 2024.
4. Bhargava A, Banakar BF, Pujar GS, Khichar S. A study of Guillain-Barré syndrome with reference to cranial neuropathy and its prognostic implication. *J Neurosci Rural Pract*. 2014;5(Suppl 1):S43-47. doi:10.4103/0976-3147.145200
5. Rodríguez-Méndez AA, Briseño-Ramírez J, Rivas-Ruvalcaba FJ, et al. Clinical predictors for mechanical ventilation assistance in Guillain-Barré syndrome. *Front Neurol*. 2024;15:1385945. doi:10.3389/fneur.2024.1385945
6. Maskin LP, Wilken M, Lucci FR, et al. Risk factors for respiratory failure among hospitalized patients with Guillain-Barré syndrome. *Neurologia (Engl Ed)*. 2024;39(1):36-42. doi:10.1016/j.nrleng.2023.12.004
7. Yardimci N, Avci AY, Kayhan E, Benli S. Bilateral facial nerve enhancement demonstrated by magnetic resonance imaging in Guillain-Barré syndrome. *Neurol Sci*. 2009;30(5):431-433. doi: 10.1007/s10072-009-0120-0
8. Fulbright RK, Erdum E, Sze G, Byrne T. Cranial nerve enhancement in the Guillain-Barré syndrome. *AJNR Am J Neuroradiol*. 1995;16(4 Suppl):923-925.
9. Barsheshet A, Marai I, Appel S, Zimlichman E. Acute ST elevation myocardial infarction during intravenous immunoglobulin infusion. *Ann N Y Acad Sci*. 2007;1110:315-318. doi:10.1196/annals.1423.033.
10. Verboon C, van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry*. 2017;88(4):346-52. doi: 10.1136/jnnp-2016-31486