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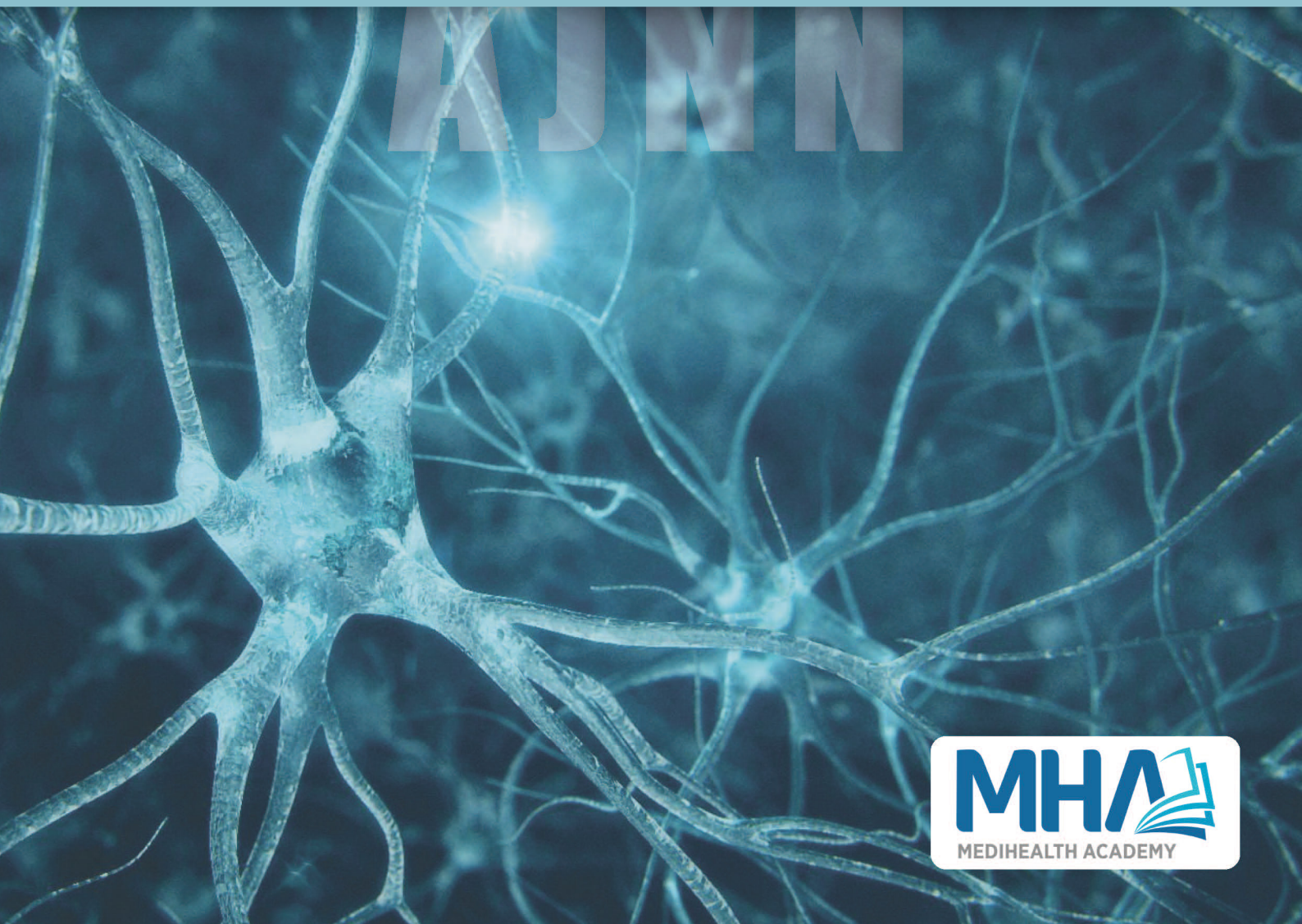

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Original Article

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The impact of high dose corticosteroid treatment affect on cardiac abnormalities in patients with multiple sclerosis

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ABSTRACT

Aims: High-dose corticosteroids to control acute relapses of Multiple sclerosis, leveraging their anti-inflammatory effects. However, these treatments can lead to cardiovascular side effects. Understanding the pathophysiology of corticosteroid induced bradycardia is paramount for healthcare providers. Our aim in this study are to identify risk factors for cardiac side effects and assess the timing of cardiac complications relative to treatment.

Methods: Patients who met the McDonald's criteria for definite MS and patients requiring admission for pulse steroid treatment with an acute recurrence were included. Individuals taking cardiac medications, or with a heart illness were excluded. Patients were given 1 g IV methylprednisolone in 2 hours for five to seven days in order to treat acute relapses.

Results: We studied with 23 patients (6 males and 17 females, 26.1/73.9% respectively). The mean±SD age of the patients was 34.6±9.9 (18-43) years and the mean±SD duration of disease was 5.5±4.9 years. Most of the patients were relapsing–remitting MS in 73.9%, primary progressive in 4.4% and secondary progressive in 21.7%.The most common cardiac arhythmia during corticosteroid pulse therapy was sinus bradycradia(n=6).

Conclusion: The combination of direct effects on cardiac myocytes, electrolyte disturbances, autonomic dysfunction, and individual genetic factors can contribute to the development of bradycardia in MS patients treated with high-dose methylprednisolone. Close monitoring and prompt intervention are crucial to manage this adverse effect and optimize patient safety.

Keywords: Multiple sclerosis, pulse corticosteroid, bradicardia

INTRODUCTION

High dose corticosteroid therapy has long been established as a treatment modality for various immune related conditions.[1] It is also a cornerstone in the management of multiple sclerosis (MS) exacerbations, serving to alleviate symptoms and hasten recovery.[2] MS exacerbations represent acute inflammatory demyelinating events in the central nervous system, characterized by patient-reported or objectively observed symptoms lasting at least 24 hours, as defined by the revised McDonald criteria.[3] Typically, involving intravenous administration of doses exceeding 1 gram per day for a duration of 5 to 7 doses, these regimens have proven efficacy in managing acute exacerbations.[4]

However, the use of high dose corticosteroids in MS exacerbations is not without its risks, particularly concerning cardiovascular adverse events.[5] Beyond acute exacerbations, glucocorticoid use has been associated with various cardiovascular risks, including myocardial infarction, stroke, heart failure, and a notable twofold increase in the risk of atrial fibrillation or flutter, as demonstrated in population based case control studies.[6] Moreover, sinus bradycardia following high dose methylprednisolone therapy is considered an uncommon side effect.[7] More details regarding the frequency of this adverse event.

Despite its rarity, the occurrence of sinus bradycardia underscores the importance of vigilance regarding cardiovascular complications associated with corticosteroid therapy in MS exacerbations. Understanding the pathophysiology and clinical implications of corticosteroid induced bradycardia is paramount for healthcare providers involved in optimizing patient safety during treatment.[8]

METHODS

From April 2023 to March 2024, 23 consecutive patients who met the McDonald's criteria for definite MS and patients requiring admission for pulse steroid treatment with an acute recurrence to the Neurology Department at Alanya Alaaddin Keykubat University Hospital were enrolled retrospectively. The study was approved by the Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.10.2022, Decision No: 10-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Any worsening of symptoms that lasted more than 24 hours was considered as a relapse. Individuals taking beta blockers or antiarrhythmic medications, or those with a history of heart illness, were not allowed to participate. Patients were given 1 g IV methylprednisolone (diluted in 500 cc of 5% dextrose water) in 2 hours for five to seven days in order to treat acute relapses. For those who experienced symptoms such as vertigo, dizziness, or chest pain, cardiac monitoring was done. Disturbances in cardiac rhythm were identified by a specialist. Patients who have a history of cardiac pathology likes arrhythmia, thyroid disease, hyperlipidemia, diabetes, and autonomic dysfunction were excluded.

RESULTS

We studied with 23 consecutive patients retrospectively (6 males and 17 females, 26.1/73.9%) with acute MS relapse who underwent treatment with corticosteroid pulse therapy at Alanya Alaaddin Keykubat University Hospital. The mean±SD age of the patients was 33.6±8.9 (18-43) years and the mean±SD duration of disease was 3.5±1.9 years. Most of the patients were relapsing–remitting MS in 73.9%, primary progressive in 4.4% and secondary progressive in 21.7%. The most common cardiac arrhythmia during corticosteroid pulse therapy was sinus bradycardia that was detected in 6 patients (shown in Figure 1). The electrocardiogram (ECG) findings had no acute abnormalities. Prior to during and following the bradycardia induced dose reduction of the pulse steroid treatment were shown in Figure 2.

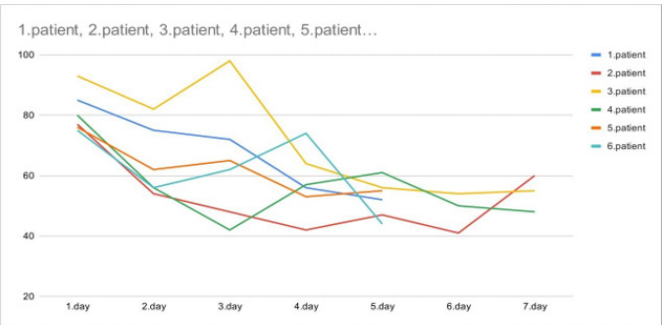


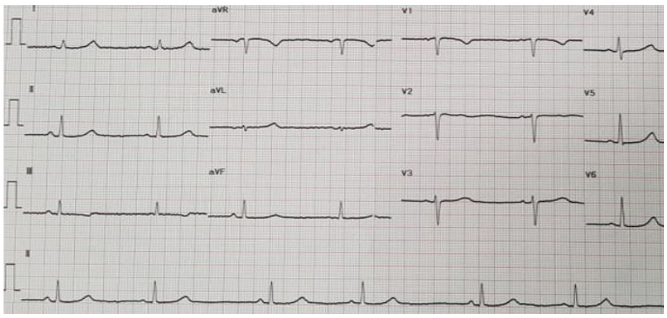
Figure 1. Heart rate changes during pulse steroid treatment

Case 1

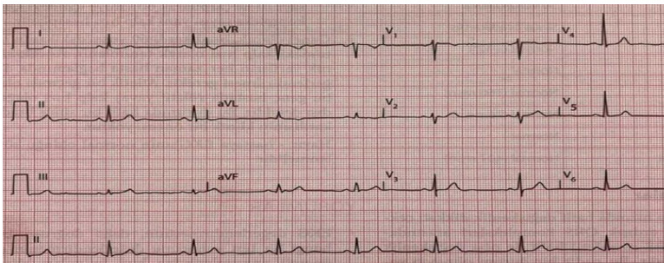
A 29 years old woman had a persistent numbness on the right half of her face for a week. She underwent a thorough neurological examination at emergency which revealed hypoesthesia limited to the right side of her face. Routine blood tests showed no abnormalities. Contrast-enhanced MRI scans were revealing: demyelinating plaques were observed in various regions of her brain, indicative of MS exacerbations.

Over a period of 5 days, she received 1000 mg of methylprednisolone daily. While initially, her vital signs

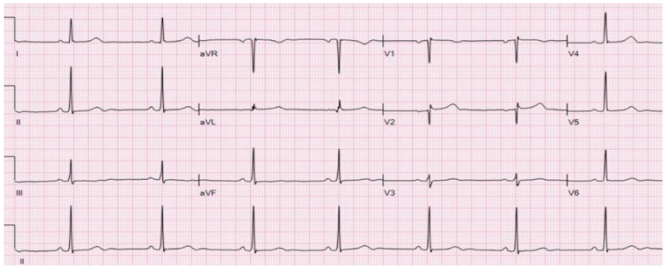
A (Patient 1)



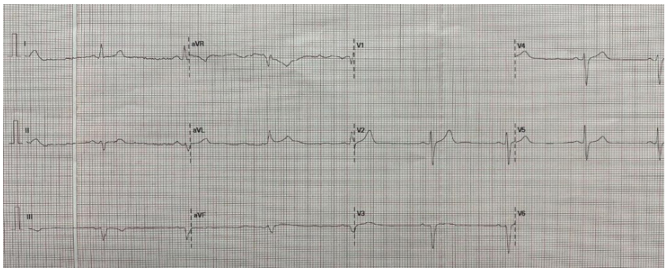
B (Patient 2)



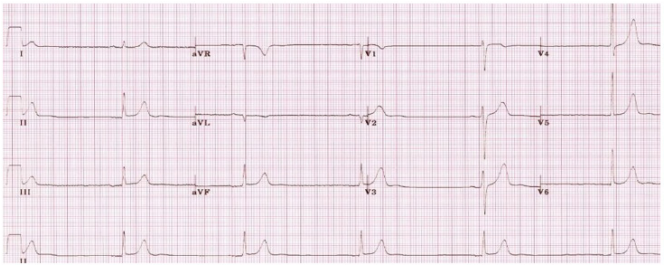
C (Patient 3)



D (Patient 4)



E (Patient 5)



F (Patient 6)

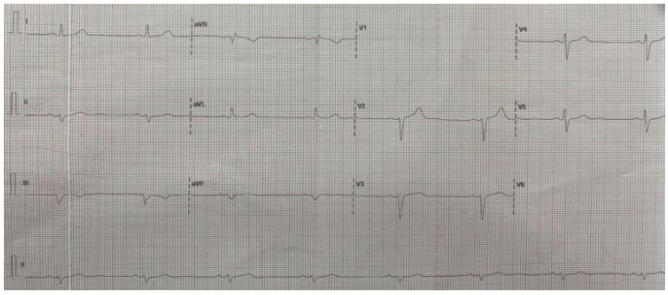


Figure 2. Electrocardiography findings while giving pulse steroid treatment

remained stable, about eight hours after receiving the treatment, her pulse rate dropped to 50 beats per minute, indicating a case of sinus bradycardia. However, she remained asymptomatic, and closely monitoring her condition. Fortunately, as the steroid treatment progressed, her pulse rate gradually normalized, and significant improvement in her symptoms was observed. Following the completion of her 5 day treatment course, her pulse rate returned to its pre-treatment levels, and she was discharged from the hospital with appropriate follow-up plan.

Case 2

A 25 years old woman diagnosed with MS in 2016, presented to the neurology outpatient clinic with complaints of blurred vision in her right eye and weakness in both lower extremities. Contrast-enhanced brain MRI revealed multiple hyperintense lesions within the cerebral white matter, periventricular area, some extending perpendicularly to the callososeptal interface. Peripheral dominant contrast enhancement was observed in lesions located in specific brain regions, indicating active demyelinating plaque formations.

Based on these findings, 7 day course of methylprednisolone treatment was planned. Throughout the treatment period, her vital signs were closely monitored. Similar to other patients, she experienced a temporary decrease in heart rate following steroid administration, which normalized post treatment. After completing the steroid treatment, her symptoms were significantly diminished and her pulse rate returned to baseline levels.

Case 3

A 41 years old man with a five year history of diagnosed MS, presented to the emergency department with complaints of numbness in his legs that had been progressively worsening over the past month. Neurological examination revealed asymmetric motor weakness and hypoesthesia in his lower extremities, prompting further investigations. Imaging studies, including contrast-enhanced brain and spinal MRI scans, confirmed the presence of MS plaques in bilateral periventricular cerebral white matter, the corpus callosum, and the cervical and thoracic spinal cord. Despite the absence of contrast enhancement suggestive of active lesions in some areas, initiating a 7 day course of methylprednisolone treatment to manage his symptoms and potentially prevent further disease progression.

During the course of his steroid treatment, he experienced a sinus bradycardia, which resolved post-treatment. With close monitoring and management, he was discharged from the hospital with plans for ongoing follow-up care.

Case 4

A 33 years old woman with no known prior illnesses, presented to the neurology outpatient clinic with complaints of numbness in her right arm. Contrast-enhanced MRI scans of the brain, cervical, thoracic, and lumbar regions were performed, revealing no significant lesions suggestive of MS.

However, given the clinical suspicion and the possibility of early or subtle disease manifestations, over the course of a 5 day treatment regimen, She received methylprednisolone, closely monitored for any adverse effects. She experienced a temporary decrease in heart rate following steroid administration, which resolved post-treatment. With continued monitoring and management, she was discharged from the hospital with plans for ongoing follow-up care.

Case 5

A 25 years old woman with no known comorbidities, presented to the neurology outpatient clinic with intermittent numbness in her left arm and legs, as well as episodic blurred vision over the past three years. Concerned about the possibility of MS, contrast-enhanced MRI scans of the brain, cervical, and thoracic regions revealed notable appearances of MS plaques, particularly in the cerebral white matter and juxtacortical fibers. Despite the absence of contrast-enhancing lesions, suggestive of active disease, she was initiated a 5-day course of methylprednisolone treatment to manage her symptoms and potentially prevent disease progression.

During the course of her steroid treatment, she experienced a brief episode of bradycardia, which resolved post-treatment. With close monitoring and management, her symptoms were dissappearad ,and she was discharged from the hospital with plans for ongoing follow-up care to monitor her condition and adjust treatment as needed.

Case 6

A 32 years old man with no known comorbidities, presented with a complaint of vision impairment in his right eye for the past three days. Concerned about the possibility of optic neuritis, a comprehensive evaluation, including ophthalmological examination, visual evoked potential (VEP) test, lumbar puncture, and MRI imaging.

VEP testing indicated prolonged p100 wave latency in the right eye, suggestive of optic neuritis. However, MRI scans did not reveal any abnormalities, raising questions about the underlying cause of his symptoms. Despite the absence of definitive imaging findings, he was taken a 5 day course of methylprednisolone treatment to manage his symptoms and potentially prevent further vision loss.

Throughout the course of his steroid treatment, he experienced a sinus bradycardia, which resolved post-treatment. He was discharged from the hospital with plans for ongoing follow-up care to monitor his condition and adjust treatment as needed.

DISCUSSION

In our present study, we observed that methylprednisolone, a commonly used corticosteroid in the management of multiple sclerosis (MS) exacerbations, exhibited the adverse effect of sinus bradycardia. Compared to previous literature, our present findings are consistent with the known cardiovascular side effects of high-dose corticosteroid therapy, which include arrhythmias and sudden death.[9,10]

The common feature of our MS patients showing this adverse effect was the use of intravenous pulse therapy with methylprednisolone. Corticosteroids have been utilized to treat inflammatory illnesses; however, because of differences in dosage, duration, and mode of administration, not all possible side effects have been well understood. The side effects of intravenous pulse therapy that are most frequently reported are infections, behavioral abnormalities, hyperglycemia, hypokalemia, and hypertension. Arrhythmias and sudden death have been documented in the literature as the most severe side effects.[11]

Methylprednisolone, a potent corticosteroid commonly used in the management of MS exacerbations, has been associated

with various cardiovascular adverse effects, including sinus bradycardia. Understanding this phenomenon is crucial for clinicians managing MS patients undergoing corticosteroid therapy Symptomatic bradycardia, characterized by symptoms such as dizziness, chest pain or dyspnea, requires prompt evaluation and intervention to prevent adverse outcomes.[12] Close monitoring of vital signs, including heart rate and telemetry may be warranted during corticosteroid therapy, especially in high-risk patients. Management of methylprednisolone induced bradycardia typically involves conservative measures such as dose reduction or discontinuation of corticosteroid therapy, electrolyte correction if indicated, and supportive care.

The etiology of methylprednisolone induced symptomatic sinus bradycardia in MS patients is multifactorial and not fully elucidated. However, several mechanisms have been proposed to explain the occurrence of bradycardia following corticosteroid therapy. Animal studies suggest that high-dose methylprednisolone can affect cardiac myocytes, altering cardiovascular sensitivity to catecholamines and potentially leading to bradycardia. Changes in the responsiveness of cardiac cells to catecholamines could lead to a decrease in heart rate, manifesting as sinus bradycardia.[13,14]

Additionally, corticosteroids may induce electrolyte imbalances, disrupt normal cardiac rhythm, and contribute to bradycardia. Sudden shifts in electrolyte concentrations, particularly potassium, can disrupt the normal electrical conduction system of the heart, potentially leading to cardiac arrhythmias such as bradycardia. This mechanism is particularly relevant in patients with MS, as they may already have alterations in autonomic function, which can further predispose them to electrolyte imbalances.[15] Corticosteroids may induce physiological changes in sodium and water balance. This can result in the expansion of plasma volume and activation of low-pressure baroreceptors. Baroreceptors are sensors located in blood vessels and the heart that regulate blood pressure and heart rate. Activation of these receptors may lead to reflex bradycardia as a compensatory mechanism to maintain blood pressure homeostasis.[16]

Also some MS patients may have underlying cardiac abnormalities or autonomic dysfunction, which predisposes them to develop bradycardia in response to corticosteroid therapy. Additionally, genetic factors or variations in drug metabolism pathways may influence an individual's susceptibility to cardiac side effects of methylprednisolone.

CONCLUSION

Methylprednisolone induced sinus bradycardia represents a rare but clinically significant complication in MS patients undergoing corticosteroid therapy. Clinicians should maintain a high index of suspicion for this adverse effect, closely monitor patients, and promptly intervene when necessary to ensure optimal outcomes. Further research is warranted to elucidate the underlying mechanisms and refine strategies for managing corticosteroid induced bradycardia in MS patients. While bradycardia associated with corticosteroid therapy is usually transient and resolves spontaneously following end of the treatment, it is essential for clinicians to assess and mitigate potential risks in MS patients, optimizing both therapeutic efficacy and patient safety.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Researches Ethics Committee (Date:19.10.2022, Decision No: 10-04).

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.

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Original Article

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Evaluation of the relationship between thrombophilia gene mutations and demographic data, imaging findings and stroke subtypes in young patients followed up with a diagnosis of stroke

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ABSTRACT

Aims: A stroke is defined as a focal or generalized neurological deficit that develops suddenly, lasts for more than 24 hours, or ends in death within this period, with a cause other than a vascular cause. Stroke is among the leading causes of morbidity and mortality in the general population. In our study, we examined the prevalence of all prothrombotic gene mutations observed in patients with and without predisposing risk factors for young patients with stroke and discussed their roles in stroke formation in the context of existing literature.

Methods: In the present study, we conducted a retrospective review of the medical records of 300 patients aged 18 to 49 years who were hospitalized in the neurology clinic of our hospital between June 2023 and June 2024 and diagnosed with acute arterial ischemic stroke based on anamnesis, neurological examination, and radiological imaging (CT and MRI) results. The study cohort comprised 47 patients (23 males, 24 females) aged between 18 and 49 years with a diagnosis of ischemic stroke. In our study, we examined ischemic stroke-related gene polymorphisms in patients with early-onset ischemic stroke (before the age of 50 years). This study aims to investigate the prevalence of factor V-Leiden, prothrombin-G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, MTHFR A1298C, SERPIN 1, and Factor II polymorphisms in young patients with ischemic stroke.

Results: A total of 47 patients, comprising 23 males and 24 females, were included in the study. The mean age of the patients was 40.34±6.37 years. According to the TOAST classification system, 17 patients (36.2%) were diagnosed with large artery atherothrombosis, one patient (2.1%) had a cardioembolic infarction, and 29 patients (61.7%) had a small artery occlusion. In our study, when evaluating the thrombophilia mutation subtypes in young ischemic stroke patients, 23.4% (n=11) of the patients were found to be heterozygous for the FVL mutation, while 76.6% (n=36) had no mutation. Concerning the SERPIN 1 mutation, 40.4% (n=19) of the patients were heterozygous, 23.4% (n=11) were homozygous, and 36.2% (n=17) exhibited no mutation. The distribution of patients according to MTHFR C677T mutation revealed that 57.4% (n=27) were heterozygous, 19.1% (n=9) were homozygous, and 23.4% (n=11) had no mutation. Considering the distribution of patients according to the MTHFR A1298C gene mutation, a total of 38.3% (n=18) of the patients were heterozygous, 14.9% (n=7) were homozygous, and 46.9% (n=22) had no mutation. Upon analysis of the distribution of patients according to factor XIII mutation, it was identified that 19.1% (n=9) were heterozygous, 2.1% (n=1) were homozygous, and 78.7% (n=37) of the patients exhibited no mutation. Upon analysis of the distribution of patients according to prothrombin (Factor II) mutation, it was identified that 8.5% (n=4) were heterozygous, while 91.5% (n=43) exhibited no mutation.

Conclusion: Although stroke is less prevalent in young adults, the underlying etiology is highly varied. Further research, including the investigation of genetic and prothrombotic mutations, is vital for the prevention of recurrent strokes in young adults.

Keywords: Stroke, protrombotic mutation, young patient

INTRODUCTION

A stroke is defined as a focal or generalized neurological deficit that develops suddenly, lasts for more than 24 hours, or ends in death within this period, with a cause other than a vascular cause. Stroke is among the leading causes of morbidity and mortality in the general population.[1,2] Stroke is the second leading cause of mortality and the third leading cause of disability worldwide. Annually, more than 11 million individuals worldwide experience an ischemic stroke. Although it is well known that the prevalence of ischemic stroke increases with age, it is notable that 10-15% of cases occur in young individuals between the ages of 18 and 50.[3] The incidence of stroke in the young population is variable, with rates ranging from 2.5-40/100,000 individuals,[4,5] with a notable increase in incidence with advancing age, with a higher prevalence observed in females between the ages of 18-44 compared to males.[2] Among the etiologic causes, age, gender, race, and family history are non-modifiable risk factors, while hypertension, diabetes mellitus, heart disease, hypercholesterolemia, smoking, and carotid stenosis are definitively modifiable factors. However, despite comprehensive investigations, a definitive cause cannot be identified in 23-25% of cases.[6]

The etiologic evaluation of young patients with stroke involves a different set of investigations than those employed in elderly patients. While classical atherosclerotic risk factors become apparent after the age of 35 years, cardioembolism, dissection, non-atherosclerotic vasculopathy, and prothrombotic conditions have been reported to be important in patients aged 18-35 years.[7] The prevalence of hypercoagulability in young patients with stroke is between 6-15%.[8] Evaluation of Factor V Leiden (FVL), prothrombin G20210A gene, methylenetetrahydrofolate reductase (MTHFR) genes, protein C (PC), protein S (PS), antithrombin 3 (ATIII), fibrin, activated protein C resistance (APCR), homocysteine antinuclear antibody (ANA), and anticardiolipin antibody (ACA) tests in qualified laboratories, as well as their availability in all centers for young patients with stroke, present a significant challenge in clinical practice. However, these tests offer a comprehensive perspective.

In our study, we examined the prevalence of all prothrombotic gene mutations observed in patients with and without predisposing risk factors for young patients with stroke and discussed their roles in stroke formation in the context of existing literature.

METHODS

The study was approved by the Sakarya University Faculty of Medicine Clinical Researches Ethics Committee (Date: 02.05.2023 Decision No: 108). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the present study, we conducted a retrospective review of the medical records of 300 patients aged 18 to 49 years who were hospitalized in the neurology clinic of our hospital between June 2023 and June 2024 and diagnosed with acute arterial ischemic stroke based on anamnesis, neurological examination, and radiological imaging (CT and MRI) results. The study cohort comprised 47 patients (23 males, 24 females) aged between 18 and 49 years with a diagnosis of ischemic stroke. Patients with sinus venous thrombosis, intracranial hemorrhage, and subarachnoid hemorrhage were excluded from the study. The medical history of patients was reviewed to identify potential risk factors for stroke, including hypertension, diabetes mellitus, coronary heart disease, history of stroke, atrial fibrillation, smoking, hyperlipidemia, heart valve replacement, hyperthyroidism/hypothyroidism, vasculitic disease, hematologic disease, chronic alcohol consumption, and oral contraceptive (OCS) drug use.

The etiology of patients' stroke was determined according to the TOAST and BAMFORD classification systems.[9] The results of the analysis of genetic polymorphisms associated with thrombophilia, as recorded in the patient files, were also documented.

In our study, we examined ischemic stroke-related gene polymorphisms in patients with early-onset ischemic stroke (before the age of 50 years). This study aims to investigate the prevalence of FVL, prothrombin-G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, MTHFR A1298C, SERPIN 1, and Factor II polymorphisms in young patients with ischemic stroke.

RESULTS

A total of 47 patients, comprising 23 males and 24 females, were included in the study. The mean age of the patients was 40.34±6.37 years. The age range was from 24 to 49 years. The number of female patients was 24 (51.1%), and the number of male patients was 23 (48.9%). Six patients (12.8%) had accompanying hypertension, five (10.6%) had diabetes mellitus, four (8.5%) had coronary artery disease, eight (17%) had hyperlipidemia, and two (4.3%) had atrial fibrillation. Twenty-eight of the patients (59.6%) were identified as current smokers.

The demographic data of the patients are presented in Table 1.

Table 1. Demographic data

	Min-Max	Mean±SD
Age	24-49	40.34±6.37
	n (%)	
Male gender	23 (48.9)	
Hypertension	6 (12.8)	
Diabetes mellitus	5 (10.6)	
Smoking	28 (59.6)	
Coronary artery disease	4 (8.5)	
Hyperlipidemia	8 (17)	
Atrial fibrillation	2 (4.3)	

Min: Minimum, max: maximum, SD: Standart deviation

Doppler ultrasonography of the carotid vertebral arteries revealed that 42 patients (89.3%) exhibited normal vasculature, 2 patients (4.3%) demonstrated symptomatic ICA stenosis exceeding 50%, and 3 patients (6.4%) exhibited vertebrobasilar insufficiency. Upon evaluation of the transthoracic echocardiograms performed on admission, it was determined that 45 patients (95.7%) showed normal echocardiographic findings, while segmental hypokinesia was identified in two patients (4.3%) (Table 2).

Table 2. Doppler and echocardiography findings

		n (%)
Doppler	Normal	42 (89.3)
	ICA stenosis below 50%	0 (0.0)
	ICA stenosis over 50%	2 (4.3)
	Vertebrobasilar insufficiency	3 (6.4)
Echocardiography	Normal	45 (95.7)
	Valve disease	0 (0.0)
	Segmentary hypokinesia	2 (4.3)

According to the TOAST classification system, 17 patients (36.2%) were diagnosed with large artery atherothrombosis, one patient (2.1%) had a cardioembolic infarction, and 29 patients (61.7%) had a small artery occlusion. Following the BAMFORD classification, 40 (85.1%) of the patients included in the study exhibited anterior circulation strokes, while 7 (14.9%) demonstrated posterior circulation strokes.

Table 3 presents the ischemic stroke subtypes according to the TOAST and BAMFORD classifications.

In our study, when evaluating the thrombophilia mutation subtypes in young ischemic stroke patients, 23.4% (n=11) of the patients were found to be heterozygous for the FVL mutation, while 76.6% (n=36) had no mutation. Concerning the SERPIN 1 mutation, 40.4% (n=19) of the patients were heterozygous, 23.4% (n=11) were homozygous, and 36.2% (n=17) exhibited no mutation. The distribution of patients according to MTHFR C677T mutation revealed that 57.4% (n=27) were heterozygous, 19.1% (n=9) were homozygous, and 23.4% (n=11) had no mutation. Considering the distribution of patients according to the MTHFR A1298C gene mutation, a total of 38.3% (n=18) of the patients were heterozygous, 14.9% (n=7) were homozygous, and 46.9% (n=22) had no mutation. Upon analysis of the distribution of patients according to factor XIII mutation, it was identified that 19.1% (n=9) were heterozygous, 2.1% (n=1) were homozygous, and 78.7% (n=37) of the patients exhibited no mutation. Upon analysis of the distribution of patients according to prothrombin (Factor II) mutation, it was identified that 8.5% (n=4) were heterozygous, while 91.5% (n=43) exhibited no mutation.

Table 3. Prevalence rates of stroke subtypes according to TOAST and BAMFORD classification

TOAST		**n (%)**
	Large vessel disease	17 (36.2)
	Cardioembolic	1 (2.1)
	Lacunar infarction	29 (61.7)
	Due to other causes	0 (0.0)
	Unspecified cause	0 (0.0)
BAMFORD		
	Anterior circulation stroke	40 (85.1)
	Posterior circulation stroke	7 (14.9)

Table 4 and Table 5 present the incidence of prothrombotic gene polymorphisms and the distribution of gene polymorphisms in subgroups according to the TOAST classification.

Table 4. Frequency of prothrombotic gene polymorphisms

	Normal n (%)	Heterozygous n (%)	Homozygous n (%)
mthfrC667T	11 (23.4)	27 (57.4)	9 (19.1)
SERPIN1	17 (36.2)	19 (40.4)	11 (23.4)
mthfrA1298C	22 (46.8)	18 (38.3)	7 (14.9)
Factor XIII	37 (78.7)	9 (19.1)	1 (2.1)
Factor II	43 (91.5)	4 (8.5)	0 (0.0)
Factor V Leiden	36 (76.6)	11 (23.4)	0 (0.0)

Table 5. Rates of genetic polymorphisms in stroke subgroups according to TOAST classification

		Large vessel disease	Cardioembolic stroke	Lacunar infarct
		n (%)	n (%)	n (%)
MTHFRC667T	Normal	4 (8.5)	0 (0.0)	7 (14.9)
	Heterozygous	9 (19.1)	1 (2.1)	17 (36.2)
	Homozygous	4 (8.5)	0 (0.0)	5 (10.6)
SERPIN1	Normal	4 (8.5)	0 (0.0)	13 (27.7)
	Heterozygous	9 (19.1)	0 (0.0)	10 (21.3)
	Homozygous	4 (8.5)	1 (2.1)	6 (12.8)
MTHFRA1298C	Normal	8 (17.0)	1 (2.1)	13 (27.7)
	Heterozygous	6 (12.8)	0 (0.0)	12 (25.5)
	Homozygous	3 (6.4)	0 (0.0)	4 (8.5)
Factor XIII	Normal	12 (25.5)	1 (2.1)	24 (51.1)
	Heterozygous	4 (8.5)	0 (0.0)	5 (10.6)
	Homozygous	1 (2.1)	0 (0.0)	0 (0.0)
Factor II	Normal	13 (27.7)	1 (2.1)	29 (61.7)
	Heterozygous	4 (8.5)	0 (0.0)	0 (0.0)
	Homozygous	0 (0.0)	0 (0.0)	0 (0.0)
Factor V Leiden	Normal	16 (34.0)	1 (2.1)	19 (40.4)
	Heterozygous	1 (2.1)	0 (0.0)	10 (21.3)
	Homozygous	0 (0.0)	0 (0.0)	0 (0.0)

DISCUSSION

Thrombophilia can be defined as a disturbance in the equilibrium of the coagulation system, which predisposes the individual to the formation of thrombi. This tendency can be caused by acquired factors or genetic variations that affect clotting. Hereditary thrombophilia is a condition in which these genetic variations affect the amount or function of a protein in the coagulation system, thereby creating a tendency to clot.[9] The two most common causes of hereditary thrombophilia worldwide are FVL and prothrombin G20210A gene variations.

Ischemic stroke is a complex multifactorial disorder in which genetic and environmental factors play a role in its etiopathogenesis. Since strokes cause severe health and socio-economic losses, it is crucial to identify stroke risk factors in detail and implement precautions.[10] Some studies have demonstrated that prothrombotic gene mutations are a risk factor in the etiopathogenesis of ischemic stroke.

Although ischemic stroke is less prevalent in young adults than in the elderly, it is diverse with respect to its underlying pathogenesis and risk factors. Approximately 10-15% of all strokes occur between the ages of 18 and 50.[11-13]

Some types of hereditary thrombophilia are clearly considered as a risk factor for ischemic stroke.[14]

The protein 5,10-methylene tetrahydrofolate reductase, encoded MTHFR, is a folate-dependent enzyme that catalyzes the rate-limiting step in the methylation of homocysteine to methionine. The C677T polymorphism in MTHFR results in the conversion of alanine to valine at amino acid 222, and is associated with elevated circulating homocysteine levels.[10,15] Elevated homocysteine levels have been identified as a risk factor for atherosclerosis and atherothrombosis, due to induced endothelial dysfunction. The C677T transition has been linked to an increased risk of ischemic stroke. These polymorphisms have also been observed in healthy individuals.[16]

A meta-analysis of 24 studies with a total of 900 patients that investigated the effect of MTHFR C677T mutations on ischaemic stroke showed that stroke patients had elevated homocysteine levels compared with controls.[17] A study by Alkanlı[18] and colleagues investigating genetic risk factors for ischaemic stroke in 82 patients with ischemic stroke and 92 controls reported that the MTHFR A1298C gene polymorphism is a genetic risk factor for ischemic stroke in the Thrace region, while the MTHFR C677T gene polymorphism is a risk factor for the unspecified subtype. In our study, the MTHFR C677T mutation was identified in 76.5% of patients with stroke. Of these, 57.4% were heterozygous and 19% were homozygous.

The role of the FVL mutation in the etiology of arterial thrombosis and ischemic stroke remains unidentified. The FVL mutation may modestly increase the risk of arterial thrombotic events relative to venous thromboembolism, with a more pronounced effect observed in individuals younger than 55 years and females.[19] The increased prevalence of the FVL mutation in ischemic stroke patients suggests its potential role in the pathogenesis of ischemic stroke, but it does not increase the risk in the presence of other risk factors.

In a study conducted in the Turkish population, the prevalence of the FVL mutation was reported to be 10%. It accounts for 25% of all hereditary thrombophilia cases.[20] While the presence of a heterozygous FVL mutation has been shown to increase the risk of thrombosis by a factor of 5-10, the presence of a homozygous mutation increases the risk by a factor of 50-100.[21] In a study by Grossmann et al.[22] 93 patients with a history of ischemic stroke under the age of 50 were compared with 186 healthy individuals. The FVL mutation was identified in 13 patients in the control group and 15 patients in the patient group (6.9% in the control group and 16.1% in the patient group). These findings led to the conclusion that Factor V Leiden mutation is a significant risk factor for stroke in young adults.[22]

Slooter et al.[23] performed a comparative analysis of 193 female patients aged 20-49 years with ischemic stroke and 767 healthy individuals. This study found that women who use contraceptive pills and carry the FVL mutation have an increased risk of ischemic stroke. In our study, the heterozygous FVL mutation was identified in 23.4% of patients with stroke, while no homozygous mutation was observed. The prothrombin G20210A mutation has been shown to increase the amount of plasma prothrombin by affecting the synthesis of prothrombin at the mRNA and protein levels. The prothrombin G20210A mutation has been shown to result in serum prothrombin levels that are 30% higher than those observed in normal controls.[24] In a study of 72 patients who had suffered an ischemic stroke before the age of 50 and had no other risk factors, the risk of stroke was found to be 4-5 times higher in individuals with the prothrombin G20210A mutation.[25] The results of this study suggest that the prothrombin G20210A mutation contributes to the increased risk of cerebral ischemia. The prevalence of the heterozygous form of the prothrombin mutation in the general population is 1-2%. In our study, the heterozygous prothrombin G20210A mutation was identified in 8.5% of young patients with ischemic stroke, and no homozygous mutation was detected.

PAI-1 (SERPIN 1) functions to inhibit the activity of tissue plasminogen activator and uricinase, which act as activators in the conversion of plasminogen to plasmin. Serum levels of PAI-1 are associated with genetic factors, and elevated serum levels contribute to the development of a hypofibrinolytic state by increasing the risk of thrombosis.[26] The prevalence of PAI-1 heterozygosity was 44.0%, while homozygosity was observed in 24.0%.[27] The presence of the PAI-1 4G allele is associated with elevated PAI-1 levels. Several studies have investigated the association between the PAI-1 4 guanosine/5 guanosine (4G/5G) polymorphism and the development of VTE. The results of these studies have been inconsistent. In our study, we identified a SERPIN 1 mutation in 63.8% of patients with stroke. Of these mutations, 40.4% were heterozygous and 23.4% were homozygous.

Factor XIII is a transglutaminase enzyme that plays a critical role in the final step of the coagulation system. The Factor XIII Valine34Losine (FXIII V34L) mutation is the result of leucine to valine substitution at position 34 of the Factor XIII gene, resulting in a change in the region three amino acids from the thrombin cleavage site. Recent reports suggest that the FXIII V34L mutation paradoxically may have a mild protective effect against arterial and venous thrombosis. The presence of the FXIII V34L mutation has been observed to provide some protection against cerebral infarction, but at the same time increase the risk of hemorrhagic stroke.[28] Thrombophilia, also known as a coagulation disorder, can lead to thromboembolic processes, contributing to the development of stroke. Therefore; the thrombophilia panel is studied to elucidate this etiology, especially in patients with stroke at a young age. The thrombophilia tests evaluated in our study included Factor II prothrombin G20210A, FVL, MTHFR C677T, MTHFR A1298C, and Factor XIII, PAI mutations. In light of these data; the etiology of young ischemic stroke is multifactorial, and prothrombotic gene mutations may increase the occurrence of ischemic stroke only in combination with risk factors such as hypertension, diabetes, smoking, and alcohol consumption.

CONCLUSION

Although stroke is less prevalent in young adults, the underlying etiology is highly varied. Further research, including the investigation of genetic and prothrombotic mutations, is vital for the prevention of recurrent strokes in young adults.

The present study is limited by the absence of a control group, the relatively small sample size, and inadequate data on biochemical parameters (homocysteine and fibrinogen).

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Sakarya University Faculty of Medicine Clinical Researches Ethics Committee (Date: 02.05.2023 Decision No: 108).

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.

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Case Report

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Third cranial nerve palsy with confirmed HHV-6 positivity

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ABSTRACT

We present a rare case of a 38-year-old man diagnosed with third cranial nerve paralysis, where no abnormalities were detected on magnetic resonance imaging (MRI). Human herpes virus-6 (HHV-6) infection affecting the central nervous system and associated with cranial nerve paralysis is an unusual occurrence. This report underscores the importance of considering HHV-6 as a differential diagnosis in patients presenting with cranial nerve palsy and suggests the use of cerebrospinal fluid (CSF) HHV-6 polymerase chain reaction (PCR) testing for confirmation.

Keywords: HHV-6, cranial nerve palsy, human herpes virus, oculomotor nerve palsy

INTRODUCTION

The third cranial nerve is responsible for innervating several extraocular muscles, including the superior, inferior, and medial rectus, the inferior oblique, and the levator palpebrae superioris muscles. Oculomotor paralysis can arise due to a variety of causes, extending from lesions in the mesencephalon to pathology in the orbital segment.[1]

Human herpes virus-6 (HHV-6) is primarily recognized for causing roseola infantum, also known as exanthema subitum, predominantly affecting children under two years of age. This virus is commonly associated with symptoms like febrile seizures and encephalitis, though asymptomatic infection is present in 90-95% of healthy adults.[2]

Here, we examine a case of third nerve palsy in an immunocompetent 38-year-old male, where HHV-6 DNA was detected in the cerebrospinal fluid.

CASE

A 38-year-old male presented with sudden onset of diplopia, which had persisted for a week, and right-sided eyelid drooping, which had developed over the past three days. He reported a throbbing headache on the right side, ongoing for three months, without associated nausea or vomiting. Neurological examination showed right eyelid ptosis and restricted movement in all directions except lateral gaze (Figure 1). Bilateral light reflexes were intact. Also, hypoesthesia was detected in the right V1, V2, and V3 sensory branches of the trigeminal nerve.

Extensive imaging, including brain magnetic resonance imaging (MRI), computed tomography (CT) angiography, orbital MRI, and venography, showed no abnormalities. However, cerebrospinal fluid (CSF) analysis revealed the presence of HHV-6 DNA, detected through PCR. CSF pressure, cell count, and protein levels were within normal limits, and no growth was observed in the CSF culture (CSF pressure: 15 mmHg, glucose: 68 mg/dl, simultaneous blood glucose: 100 mg/dl, protein: 40 mg/dl). Following the detection of HHV-6 positivity, the patient was started on 2x350 mg ganciclovir by the department of ınfectious diseases and clinical microbiology.

Additionally, petechial rashes were noted on the patient's limbs, which were diagnosed as cutaneous candidiasis. A comprehensive immunological workup revealed normal CD4, CD2, CD3, and CD8 lymphocyte counts, as well as adequate immunoglobulin levels and immune function. Tests for other infectious agents, including HIV, HBV, HCV, EBV, Treponema pallidum, and Leishmania, were all negative.

The patient's neurological examination remained stable on the 8th day of treatment. He was referred back to the infectious disease specialists for a review of the treatment plan, and it was recommended to extend the antiviral therapy for another 14 days. On the 14th day, with no significant change in symptoms, oral steroids at a dose of 1 mg/kg were initiated, and a follow-up visit was scheduled for ten days later. At this follow-up, the right eyelid ptosis had improved, though restrictions in inward and upward gaze persisted (Figure 2). Continued oral methylprednisolone treatment was recommended, with another clinic review planned in two weeks.

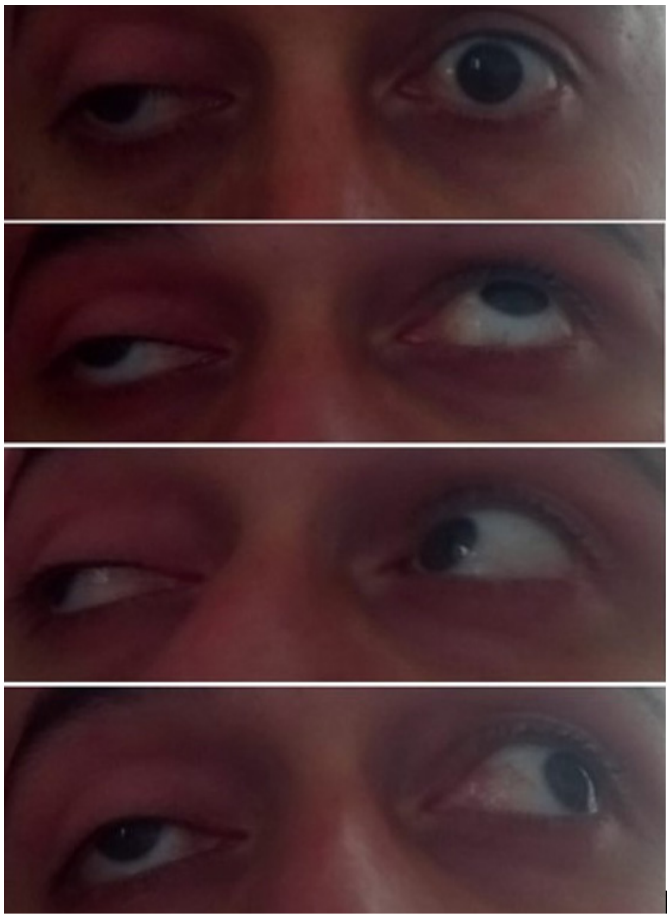

Figure 1. A. Exotropia and ptosis in the right eye in the primary position **B**. Limitation of upward gaze in the right eye **C**. Introspection limitation in the right eye **D**. Lateral gaze is preserved in the right eye

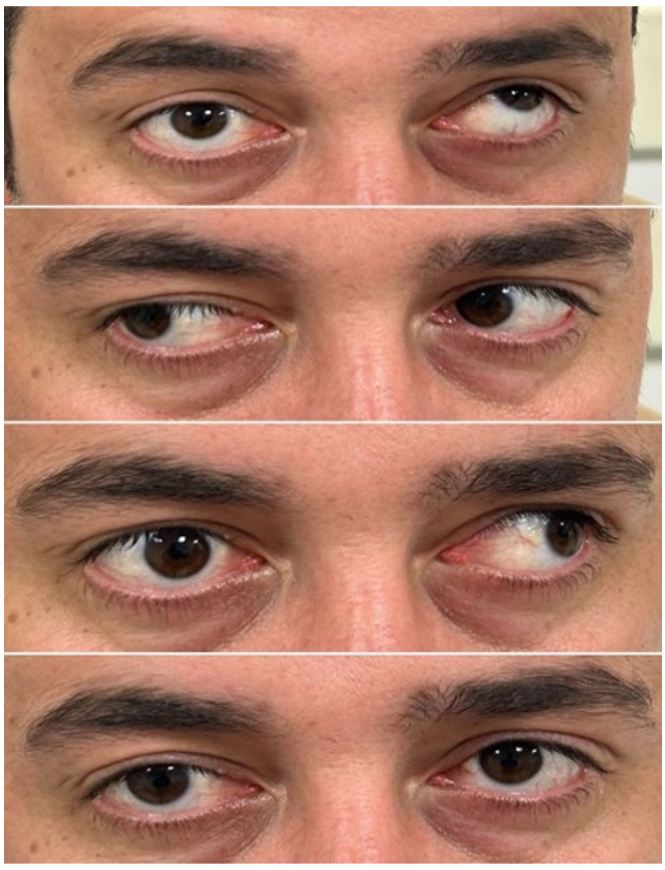

Figure 2. Eye movements of the patient after treatment **A**. A regression was observed in the limitation of upward gaze. **B**. Lateral gaze is preserved in the right eye. **C**. A regression in introspection limitation was observed in the right eye. **D**. In the primary position, regression of exotropia and ptosis was observed in the right eye.

DISCUSSION

Though HHV-6 is primarily known for causing febrile illness in children, it has also been implicated in neurological disorders such as multiple sclerosis, encephalitis, and epilepsy.[1] The mechanism through which the virus invades the central nervous system is not fully understood. However, though it has been hypothesized that viral reactivation within brainstem nuclei could contribute to cranial nerve palsies.[10]

In this case, although MRI showed no inflammatory changes, the presence of HHV-6 DNA in the CSF suggests a viral involvement in the patient's third nerve paralysis. Previous studies report on the molecular mechanisms of inoculation, dissemination, persistence, latency and reactivation of HHV-6 in inflammatory processes in the ocular tissue. After inoculation of the cornea, viral antigen was found in ocular nerves.[12] Although our patient's MRI did not show an inflammation in the orbital and brainstem MRI, 3rd. cranial nerve paralyses may be caused by due to a molecular mechanism.

A post-mortem study showed that herpesviruses can establish latency in cranial ganglia, with HHV-6 being the most commonly detected virus in autopsy studies of trigeminal and facial ganglia in latently infecting 64% of cases.[11] Cranial nerves are not only the pathways along which viruses are transported from one tissue to another, but are also sites of pathological changes resulting in their dysfunction.[3,5,10] The patient also exhibited hypoesthesia in the V1, V2, and V3 branches of the trigeminal nerve. It has been previously demonstrated that herpesviruses, including HHV-6, can randomly infect cranial nerve nuclei.[8-10] A case report presented fourth cranial nerve palsy following HHV 6 infection of the central nervous system.[6]

Though typically benign, HHV-6 has been associated with more severe central nerve system (CNS)-manifestations, even in immunocompetent individuals.[1,13] It can rarely occur as a complication of roseola or as a primary manifestation of HHV-6 infection in immunocompetent individuals. In our case, the patient demonstrated normal immune function.

As suggested in case reports, possible treatment options include ganciclovir, foscarnet, cidofovir, and brincidofovir.[7] The department of ınfectious diseases initiated a 14-day course of ganciclovir therapy for the patient, who exhibited a mild clinical response to the antiviral treatment. Corticosteroids are commonly used to address inflammation, and pulse steroid therapy within the first 24 hours of symptom onset has been linked to reduced rates of complications in HHV-6/HHV-7-related neurological manifestations.[4] After reviewing the immunologic panel, we initiated oral steroid treatment. Although the exact mechanisms of viral damage to cranial nerve cells are not fully understood, several case reports support the link between cranial nerve injury and herpetic infections, with appropriate antiviral therapy often leading to improvement or full complet recovery of cranial nerve function

CONCLUSION

To the best of our knowledge, 3rd cranial nerve palsy is association with HHV6 infection has been reportedly very rare. This report highlights that HHV-6 should be taken into consideration as a possible cause and might be included in the panel of diagnostic analyses even in immunocompetent adults.

ETHICAL DECLARATIONS

Informed Consent

All patients signed the 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.

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Case Report

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A rare cause of low back pain: lumbar lateral meningocele

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ABSTRACT

Lumbar meningocele is the herniation of the arachnoid mater enlarged neural foramen to the thecal sac. A 55-year-old female patient applied with low back pain. Physical examination there were multiple cutaneous neurofibromas. The strength of lower extremity muscles was normal bilaterally. Babinski sign was negative bilaterally with normoactive deep tendon reflexes. Lumbarmagnetic resonance imaging images show ectasia. The diagnosis was lateral meningocele associated with neurofibromatosis. Lumbar meningocele is a benign pathology that can be seen in a wide range from asymptomatic to paraparesis, which does not require surgical treatment, unless it is symptomatic, which is frequently associated with neurofibromatosis type 1 (NF1).

Keywords: Lateral meningocele, neurofibromatosis type 1, low back pain

INTRODUCTION

Meningocele is the herniation of the arachnoid mater and neural elements from the enlarged neural foramen to the thecal sac.[1] Lateral meningocele is rare and usually associated with neurofibromatosis type 1 (NF1) and Marfan syndrome.[2] Although lateral meningocele is mostly asymptomatic, it may cause paraparesis in case of spinal cord involvement.[3] Since lateral meningocele is mostly asymptomatic, it is diagnosed with magnetic resonance imaging (MRI) incidentally.[4] The MRI is superior to other imaging methods for evaluating the subarachnoid distance and pressure of the meningocele on the spinal cord.[5]

To the best of our knowledge, there are a few case reports and studies about lateral meningocele in the literature. In this article, we presented a patient with chronic low back pain with lateral meningocele, which may be interesting for clinicians.

CASE

A 55-year-old female patient admitted to physical medicine and rehabilitation (PMR) outpatient clinic with a complaint of low back pain for two years. She had mechanical low back pain spreading to both legs. She stated that she received nonsteroidal anti-inflammatory drugs, physical agents, and therapeutic exercises before, and she did not benefit from these treatments. She had a history of asthma and NF1 with multiple cutaneous neurofibromas. She had no history of trauma or fall.

On physical examination there were multiple cutaneous neurofibromas located on her face, arms, legs, abdomen, and back. She was ambulated independently. The strength of lower extremity muscles was normal (5/5) bilaterally. There was a decreased sensation in the L4-L5 dermatomes of the lower right extremity. Babinski sign was negative bilaterally with normoactive deep tendon reflexes. Furthermore, neurological examination of the upper limps was normal.

Laboratory tests including comple blood count (CBC) liver function tests, renal function tests, C-Reactive Protein (CRP), and erythrocyte sedimentation rate (ESR) were in normal range. A lumbar spine MRI was performed to determine the etiology of the chronic low back pain. The MRI showed that there was ectasia and right paravertebral bulging of the dural sac at the level of L5. Scalloping of the corpus was also present in the L5 vertebrae. In addition, subcutaneous neurofibromas in varying sizes were detected. The diagnosis was lateral meningocele associated with neurofibromatosis (Figure 1 A, B).

The patient referred to the neurosurgery department for lateral meningocele. Surgical intervention was not recommended by the neurosurgeon, because the patient did not have any motor deficit. Moreover, regular follow-up was recommended. Individual based-exercises and analgesic medical treatment were given to the patient. She was informed about emergencies

and was advised to follow up regularly in the PMR and neurosurgery departments. Written informed consent was obtained from the patient.

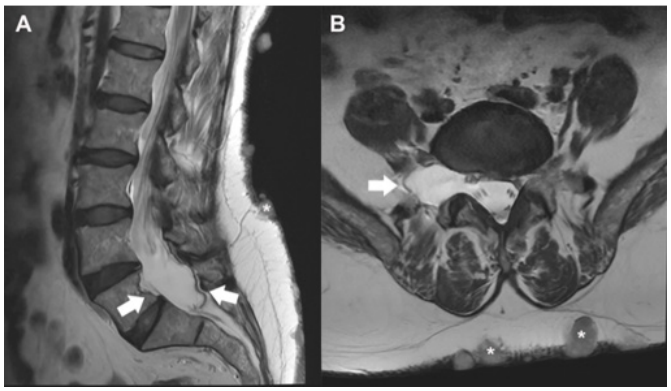

Figure 1 A, B. Sagittal (A) and axial (B) T2 weighted MRI images show ectasia and right paravertebral bulging of the dural sac at the level of L5 (arrows in A and B). Scalloping of the corpus was also present in the L5 vertebrae. The diagnosis was lateral meningocele associated with neurofibromatosis. Note the presence of subcutaneous neurofibromas in varying sizes (asterisks)

DISCUSSION

NF1 is a neurocutaneous disease, which is inherited in an autosomal dominant manner with an incidence of 1 in 3500 births.[6] NF1 is mostly characterized with brown skin spots called café-au-lait (milk coffee), Lisch nodules in the iris, acoustic neurinomas, neurofibromas and skeletal abnormalities such as kyphoscoliosis.[7]

Spinal meningoceles are the herniation of the dura and arachnoid mater into the thecal sac through a canal or foramen of the spine and are mostly seen in the thoracolumbar region.[1] So et al.[2] conducted MRI and computed tomography (CT) in patients with neurofibromatosis. They reported that meningocele in the cervical, thoracic, and lumbar regions were rare and generally associated with NF1 and Marfan syndromes.[2] Previous studies showed that clinical presentation of lateral meningocele may be in a wide range between asymptomatic and paraparesis.[3] Our patient had a complaint of low back pain with no motor deficit. However, hypoestesia was found at the right L4-5 dermatomes.

In the literature, spinal MRI findings of the NF1 patients have been reported as dural ectasia and lateral meningocele, which are consistent with the MRI findings of our patient.[8] In a study conducted by Leeds et al.[9] 28 patients with NF1 were evaluated in terms of spinal pathologies. They reported that only three of them had dural ectasia. The MRI findings of the lateral meningocele include lesion, which is hypointense in T1-weighted images and hyperintense in T2-weighted images. Li et al.[10] reported that the signal intensity in T1-weighted images might be similar to or slightly less than the cord, and the signal intensity in T2-weighted images will be more than the cord.

Complications of thoracic meningocele reported as hemothorax, hydrothorax and spontaneous rupture and surgical treatment was not recommended unless it's symptomatic. Consist with the literature, surgery was not recommended to our patient by the neurosurgeon and regular follow-up was adviced. Conservative treatment including analgesic medication and individual based exercise program were recommended. Also, she was informed about the complications of the lateral meningocele, and regular follow-up recommended.

CONCLUSION

In conclusion, lumbar lateral meningocele is a benign pathology that can be seen in a wide range from asymptomatic to paraparesis, which does not require surgical treatment, unless it is symptomatic, which is frequently associated with NF1. Clinicians should consider lateral meningosele in patients with NF1 having low back pain. An multidisiplinary follow up may be beneficial including neurosurgery, neurology, and PMR in these patients follow up and arrangement of the treatment. In addition, patients with lateral meningosele should be closely followed up in terms of developing neurological deficits or their progressions for early treatment and preventing neurological deficits.

ETHICAL DECLARATIONS

Informed Consent

All patients signed the 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

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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.

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Case Report

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A case of consecutive four-level lumbar spondylolysis and spondylolisthesis

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ABSTRACT

This rare and unusual case is about a 54-year-old female, who has pars fractures involving consecutive four-level bilateral spondylolysis and spondylolisthesis. Due to the increasing intensity with lumbar instability, the patient had severe low back pain. For diagnosis, dynamic X-Ray, magnetic resonance, 3D tomography were performed, and bilateral L2-3-4-5 pars fracture and L3-4 spondylolisthesis were observed. This case was treated surgically byspinal canal decompression at L3-4, L4-5 and L5-S1, posterior lumbar interbody fusion at L4–5 and L5–S1, and pedicle screw fixation at L2–S1. The lower back pain disappeared after the surgery.

Keywords: Spondylolysis, spondylolisthesis, low back pain

INTRODUCTION

The estimated incidence of lumbar spondylolysis is 3%–10% among the general population and the incidence of isthmic spondylolisthesis is circa 2.6%–4.4%.[1] The ratio of spondylolysis occured at the fourth and fifth lumbar vertebrae is approximately more than 95% of the total cases of spondylolysis. Multiple-level lumbar spondylolysis (MLLS) is commonly seen at the three-fourth and fifth lumbar vertebrae. However, spondylolysis involving more than three levels is quite rare.

We report here on a rare case of bilateral four level lumbar spondylolysis.

CASE

Fifty-four years-old female patient had been suffering from lumbago, bilateral leg pain and numbness for 2 years. The pain had been caused by lifting heavy objects and walking the road. After 3 months of conservative treatment including physical therapy, and non-steroidal antiinflammatory drugs, the patient was admitted for surgery because of worsening back pain and leg numbness. Visual Analog Scores (VAS) for low-back pain was evaluated preoperatively. Radiographs, CT scans, and MR images showed bilateral spondylolytic defects at L2, L3, L4, and L5, associated with spondylolisthesis (anterolisthesis at L3-4) and spinal canal stenosis at L4-5 and L5-S1 (Figure 1). The patient underwent spinal canal decompression at L3-4, L4-5 and L5-S1, posterior lumbar interbody fusion at L4–5 and L5–S1, and pedicle screw fixation at L2–S1 (Figure 2). VAS for low-back pain was assessed postoperative 3rd month.

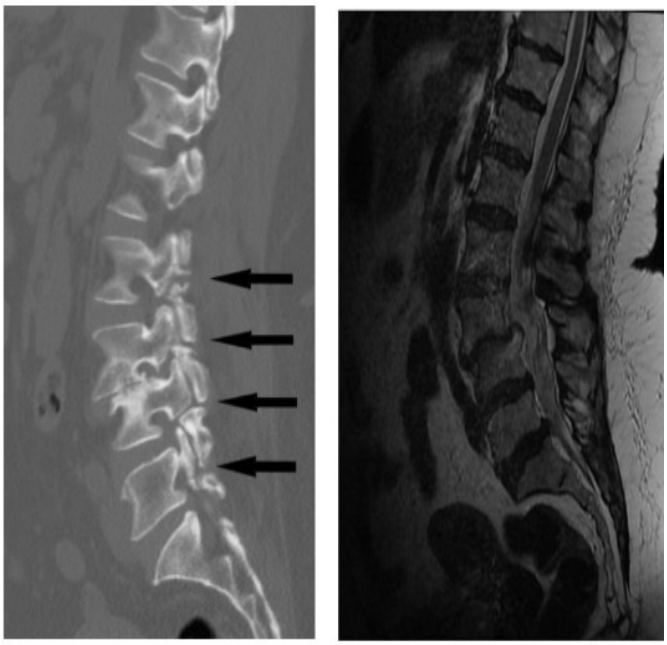

Figure 1. Preop sagittal CT- preop sagittal T2 MRI image. L2-3/L3-4/L4-5/L5-S1 pars fracture, L3-4 listhesis and stenosis are observed.

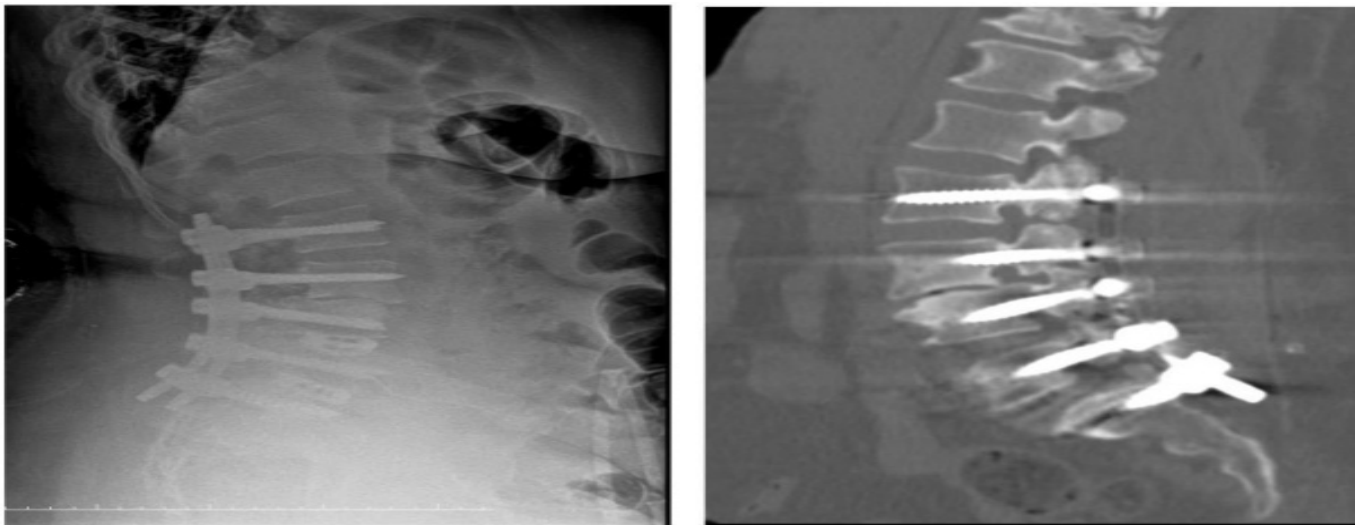

Figure 2. Postoperative lateral x-ray and sagittal CT image. L2-S1 posterior stabilization and fusion with L4-5 and L5-S1 anterior interbody are observed.

DISCUSSION

In the literature, there are very few cases on MLLS and there are no reports about bilateral 4 level spondylolysis. In our case, bilateral spondylolysis at levels L2-3-4-5 and spondylolisthesis at L3-4 are reported.

There are many etiology for single level spondylolysis (SLS) and MLLS.[3] MLLS and spondylolisthesis can be associated with consecutive trauma, heavy labour and contact sports . Since these conditions are generally encountered by men, multiple spondylolysis is more common among men.[3–6] Our patient is female and an agricultural labour, so her complaints increase while she works.

L4 and L5 vertebraes are most common affected levels in lumbar spondylosis. In the upper lumbar vertebrae the spondylolysis has been reported by various authors to be between 0.2% and 1.5%.[7] It has been suggested that two important factors play a role in the pathogenesis of spondylolysis: the genetic factor and the mechanical factor of the lumbar spine. Familial cases of spondylolysis has been signified by Friberg and Willis and Wiltse , and it braces that a genetic factor can be involved with this malady, even so the specific gene that affects spondylolysis isn't named.[8–10]

As our acknowledge, 2 level spondylolysis is more common than 3 or 4 level spondylolysis. Multiple-level lumbar spondylolysis most commonly occurs at L3-5.[1–5] According to literature, sequential bilateral 4-level spondylolysis has not been described. The occurence of 4 level bilateral spondylolysis with L3-4 spondylolisthesis in our female patient is an unique presentation.

X-Ray, 3D computed tomography (CT) and magnetic resonance imaging (MRI) are usefull tool for identification of spondylolysis. X-ray radiograph is diagnostic for pars lesions; however, it cannot differentiate acute lesions from chronic.[3,11] Dynamic flexion/extension radiograph should be used to evaluate spinal instability in symptomatic patients. 3D CT is more reliable and more valuable because it shows the bone anatomy and distinguishes whether the fracture is complete or incomplete.[12] MRI is not very sensitive for evaluation of pars fracture. We use MRI mostly to evaluate foraminal stenosis if spinal stenosis and spondylolisthesis accompany these cases.

In our case, we confirmed the levels of lumbar spondylolysis using three-dimensional CT. We believe that three-dimensional CT is an excellent and convenient tool for diagnosing multiple spondylolysis and for determining the appropriate levels for fusion.

In our case the patient was suffering from lower back pain, bilateral leg pain and numbness for a long time. Surgical or conservative treatments may be considered in MLLS. The standard treatment for spondylolysis and spondylolisthesis is conservative management in cases where the Meyerding grade is less than III.[4] Restrictive sporting activity, lumbosacral orthosis and physiotherapy exercise are recommended during 3 months as conservative treatment. Single level spondylolysis usually responds to conservative treatment. On the contrary, MLLS usually responds poorly to conservative traetment and often requires surgery.[3,13] For pars interarticularis defects seen at multiple-level lumbar spondylolysis without spondylolisthesis, can be directly restored by using segmental wire fixation and bone grafting or using pedicle screw fixation, a laminar hook, and bone grafting.[5,6] Even so, these methods cannot accomplish adequate segmental stability for multiple-level lumbar spondylolysis with spondylolisthesis.

We applied posterior pedicle screw and posterior lumbar interbody fusion to our patient. Following the procedure, spinal instability was significantly improved and the patient experienced a notable reduction in lower back and bilateral leg pain. We present this well-managed case of multiple spondylolysis as the first documented instance in the literature of a four-level bilateral pars fracture.

CONCLUSION

Although multiple-level lumbar spondylolysis is a rare we presented a case of four-level spondylolysis in a female patienti marking the first case in the literature.

ETHICAL DECLARATIONS

Informed Consent

All patients signed the 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

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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.

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