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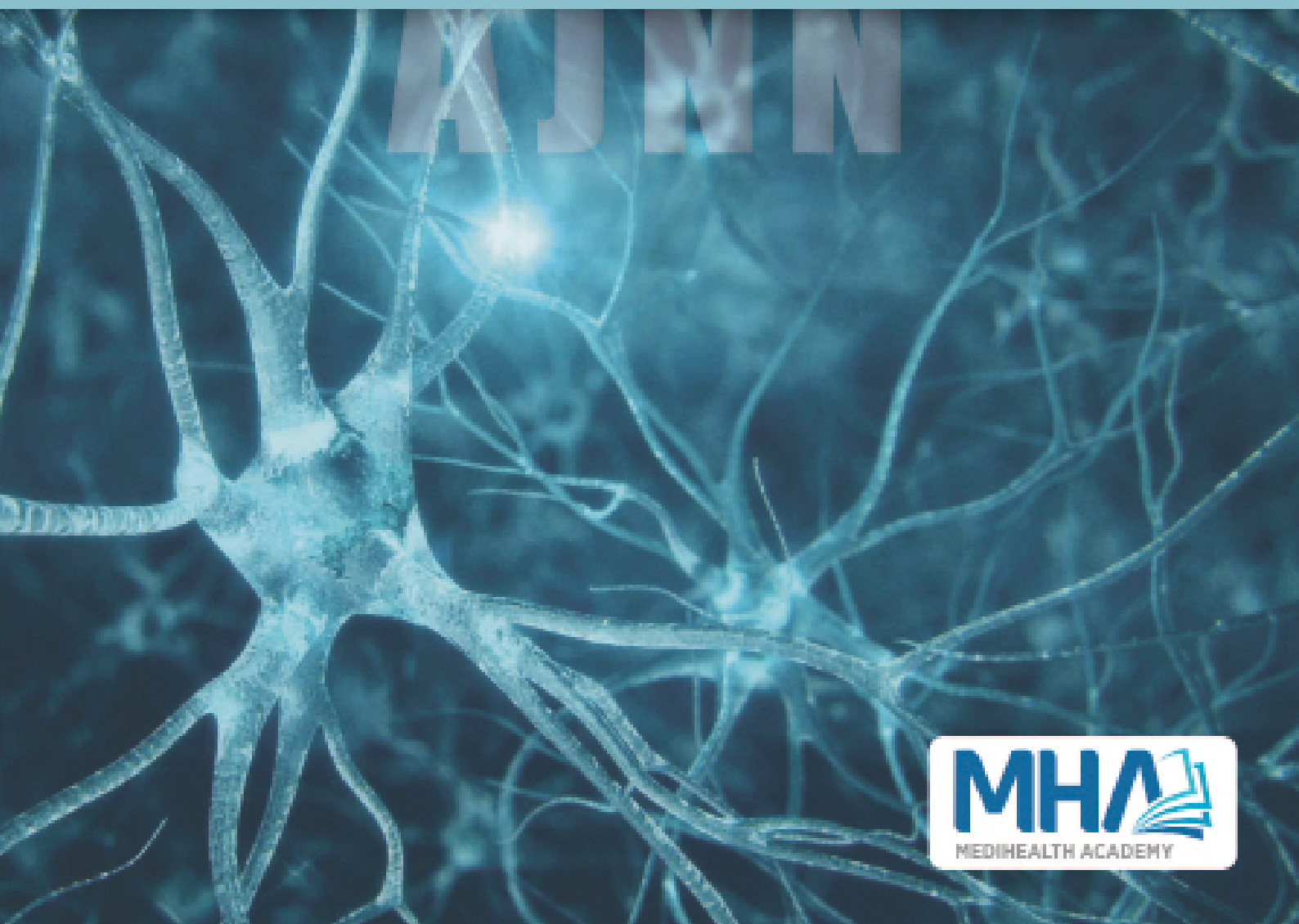

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Original Article

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Bone biopsy results of patients who underwent percutaneous vertebroplasty: clinical study

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ABSTRACT

Aims: Vertebral corpus fractures (VCF) can occur after trauma, osteoporosis, benign or malignant tumors, metastases, or infections. In this study, biopsy results of patients undergoing percutaneous vertebroplasty were discussed.

Methods: Digital hospital records were retrospectively reviewed and age, gender, hemoglobin, leukocyte, neutrophil, lymphocyte, basophil, eosinophil, platelet, C-reactive protein, biopsy pathology result, and hospitalization day of patients who underwent vertebroplasty for VCF were recorded. In addition, preoperative and postoperative radiologic images were examined.

Results: Fifty-one patients (17 males, and 34 females) were included in the study. When the patients were grouped as under and over 65 years of age, infection was found in two patients under 65 years of age, and malignant tumor was found in patients over 65 years of age. When the patients were grouped according to gender, 4 male patients had cancer or infection. The diagnoses made in the biopsy materials had already been clinically established in all patients. Although ROC-Curve analysis revealed that gender, leukocyte, and neutrophil counts could be used as predictive markers for diagnosing "pathologic fracture" in patients with VCF, regression analysis showed that none of these parameters could be used as the "best predictive marker".

Conclusion: This study showed that because up to 8% of patients undergoing vertebroplasty might have abnormal biopsy results, it is necessary to obtain a biopsy from these patients, especially male patients, before cementing the fractured vertebra

Keywords: Vertebroplasty, biopsy, pathology, metastasis, infection

INTRODUCTION

Osteoporotic vertebral corpus fracture (VCF) is usually seen in elderly patients with decreased bone mineral density (BMD). Fractures can occur as a result of minor trauma or without any history of trauma. Worldwide, 1.416.000 osteoporotic VCFs occur, and approximately 40% of women experience at least one osteoporotic VCF in their lifetime.[1] On the other hand, 5-30% of cancer patients may develop spinal metastases during their disease. Especially prostate, breast, blood, and lung malignancies may cause vertebral metastasis in addition to primary organ pathology. Metastatic vertebral involvement may cause erosion of the vertebrae, resulting in vertebral corpus fracture and subsequent pain and spinal instability.[2] In addition, pyogenic vertebral osteomyelitis may be confused with osteoporotic vertebral fractures in radiologic imaging studies.[3]

When VCF is encountered, many clinicians may assume that the cause is isolated trauma. However, the clinician should be careful when diagnosing VCF, whether it is spontaneous or secondary to cancer metastasis or osteomyelitis.[4] Computed tomography (CT) may not provide accurate information about whether VCF is acute or chronic and its etiology, and magnetic resonance (MR) imaging is more effective in diagnosing acute VCF. Especially in MR images with the "Short Tau Inversion Recovery" (STIR) sequence, the development of edema-induced hyperintensity in the vertebra supports the diagnosis of acute VCF, and contrast-enhanced MR should be performed if spinal metastasis or osteomyelitis is suspected.[5] However, in some patients, a definitive diagnosis could not be made despite all these tests and MR imaging cannot always differentiate osteoporotic VCFs from metastatic fractures or infection-related fractures.

Percutaneous vertebroplasty (PVP) and kyphoplasty (KP) are the treatment options for these patients preventing macroscopic collapse and providing stability within the fractured vertebral body.[6] On the other hand, the incidence of the incidental detection of spinal metastases in biopsy materials obtained during PVP/ KP has been reported to be between 1% and 3%.[7,8] Therefore, pathologic examination is still advocated as the gold standard method for differential diagnosis of VCF.[4,9] In addition, failure to perform a biopsy during PVP /KP may pose a medical-legal problem and malpractice lawsuits against physicians.[10,11]

This study aimed to examine the biopsy pathological examination results of patients who underwent PVP. Additionally, this study aimed to investigate whether patients' blood biochemistry results could predict pathological VCF. Additionally, it was planned to evaluate the complications of the PVP procedure applied to the study group.

METHODS

The study was carried out with the permission of Ethical Committe of Faculty of the Kırıkkale University Faculty of Medicine (Date: 22.05.2024, Decision No: 2024.05.18).

Patients

In this study, hospital digital patient records were retrospectively reviewed and data of patients who underwent PVP for VCF between January 2021 and January 2024 were recorded.Patients were divided into two groups according to their age as follows and the results were compared:

- <65-year-old group (n: 13)
- >65-year-old (n: 38)

In addition, the patients were divided into two groups according to gender as follows and the results were compared:

- Female group (n: 34)
- Male group (n: 17).

In addition, the patients were divided into groups according to the presence or absence of cement leakage as follows and the results were compared:

- Leakage (-) (Patients without cement leakage, n: 31)
- Leakage (+) (Patients with cement leakage, n: 17).

Pediatric patients, patients who underwent kyphoplasty, and patients with vertebral burst fractures were excluded from the study.

Age and gender, biopsy pathology results, and duration of hospitalization were recorded. Hemoglobin (reference range 10-18 g/dl), leukocyte (reference range 4400-11300 /ul), neutrophil (reference range 1,100-9600 /uL), lymphocyte (reference range 500-6000 /ul), basophil (reference range 0-300 /ul), and platelet (reference range 150000-500000 /ul) counts and C-reactive protein (CRP) levels (normal range 0-5 mg/L) were also recorded. In addition, preoperative and postoperative X-ray, CT, and MR images were analyzed to determine the fractured vertebra performed PVP, cement leakage, and the location of cement leakage.

Statistical Analysis

Power analysis was applied to the study results using G-Power 3.1 software and it was concluded that the number of individuals included in the study constituted an adequate sample (effect size d=9.60, power=0.96, critical t=4.303, power=0.95, minimum total sample size=4). Independent Samples t-test was used to evaluate the differences between groups regarding parametric data ($p<0.05$). *Mann-whitney U* test was used to compare nonparametric data between groups ($p<0.05$). *Pearson chi-square* test was used to evaluate the differences between groups regarding categorical data ($p<0.05$). *Sp*earman's rho Correlation test was used to determine the correlations between the parameters ($p<0.05$). ROC-curve test, and linear *regression* test were applied to determine the predictive study parameter(s) for decision-making of the pathological vertebral fracture ($p<0.05$).

RESULTS

Fifty-one patients (17 males, and 34 females) were included in the study. When the patients were grouped according to age, no statistical difference was found between the groups regarding the study parameters (Table 1). However, osteomyelitis in two male patients under 65 years of age (one with "*Brucella melitensis*" in T7 vertebrae (Figure 1) and one with "*Mycobacterium tuberculosis*" in L1 vertebrae (Figure 2) and malignant tumor infiltration in two male patients over 65 years of age (one with "multiple myeloma" in T8 vertebrae (Figure 3) and one with "poorly differentiated upper gastrointestinal tumor" in T10 vertebrae) (Figure 4) were detected in the biopsy materials (X2=1.187, p=0.034). In all patients, these diagnoses had already been made clinically before.

Platelet count values (t=2.141, p=0.037) and biopsy results (X2=7.957, p=0.019) were statistically different between genders (Table 2).

When the patients were grouped according to the presence of cement leakage, information about cement leakage could not be obtained because the postoperative imaging of 3 patients was not available. On the other hand, it was found that 14 patients had 1-level cement leakage and 3 patients had 2-level cement leakage (13 to the disc space and 4 to the spinal canal). However, foraminal cement leakage was not detected in any patient. In addition, CRP values were found to be higher in patients without leakage compared to normal laboratory values (Z=-2.253, p=0.024)(Table 3).

At the end of the correlation analysis, it was hypothesized that males would be more likely to diagnose infection or tumor in biopsy material (r=0.407, p=0.004), and the CRP values would be higher in patients without leakage (r=0.340, p=0.022). *ROC-Curve* analysis revealed that gender (AUC=0.854, p=0.021, male gender, 100% sensitivity, 71%

Table 1. Distribution table of the study parameters of the patients according to age

Variable		<65-year-old Mean±SD/ Median (min-max)/ N (%)	>65-year-old Mean±SD/ Median (min-max)/ N (%)	t/ Z/ X2	p
Gender	Female	9 (17.6%)	25 (49.0%)	0.052‡	0.820
	Male	4 (7.8%)	13 (25.5%)		
Hemoglobin		13.30 (10-14.90)	13 (6.90-16.80)	-0.054†	0.957
Leukocyte		8688±3022.80	7891±3026.80	0.819*	0.416
Neutrophil		5610 (3490-11260)	4475 (1530-14760)	-1.037†	0.300
Lymphocyte		1660±684.12	1720±686.12	-0.276*	0.784
Basophil		30 (10-60)	30 (10-140)	-0.166†	0.868
Eosinophil		160 (10-310)	100 (10-460)	-0.141†	0.888
Platelet		273230±6352.41	246789±8090.07	1.069*	0.291
C-reactive protein		12.80 (0.6-69.20)	4.50 (0.20-106.80)	-0.685	0.494
Segment	1	8 (15.7%)	26 (51.0%)	0.690‡	0.708
	2	5 (9.8%)	11 (21.6%)		
	3	0 (0.0%)	1 (2.0%)		
Area	Thoracic	8 (15.7%)	15 (29.4%)	2.266‡	0.322
	Lumbar	5 (9.8%)	21 (41.2%)		
	Thoracolumbar	0 (0.0%)	2 (3.9%)		
Fractured vertebrae	T4	0 (0.0%)	1 (2.0%)	7.612‡	0.868
	T5	0 (0.0%)	1 (2.0%)		
	T6	1 (2.0%)	3 (5.9%)		
	T7	2 (3.9%)	1 (2.0%)		
	T8	0 (0.0%)	2 (3.9%)		
	T9	1 (2.0%)	1 (2.0%)		
	T10	0 (0.0%)	1 (2.0%)		
	T11	1 (2.0%)	1 (2.0%)		
	T12	1 (2.0%)	6 (11.8%)		
	L1	2 (3.9%)	10 (19.6%)		
	L2	2 (3.9%)	4 (7.8%)		
	L3	1 (2.0%)	4 (7.8%)		
	L4	1 (2.0%)	2 (3.9%)		
	L5	1 (2.0%)	1 (2.0%)		
Biopsy result	Bone material	10 (20.8%)	34 (70.8%)	6.788‡	0.034
	Tumor	0 (0.0%)	2 (4.2%)		
	Infection	2 (4.2%)	0 (0.0%)		
Cement leakage	No	10 (20.8%)	21 (43.8%)	1.187‡	0.276
	Yes	3 (6.2%)	14 (29.2%)		
Leakage segment	No	10 (20.8%)	21 (43.8%)	1.641‡	0.440
	1 level	2 (4.2%)	12 (25.0%)		
	2 level	1 (2.1%)	2 (4.2%)		
Leakage to intervertebral disk area	No	11 (22.9%)	24 (50.0%)	1.236‡	0.266
	yes	2 (4.2%)	11 (22.9%)		
Leakage to spinal canal	No	12 (25.0%)	32 (66.7%)	0.010‡	0.922
	Yes	1 (2.1%)	3 (6.2%)		
Leakage to other side	No	12 (25.0%)	34 (70.8%)	0.555‡	0.456
	Yes	1 (2.1%)	1 (2.1%)		
Hospitalization time (day)		2 (1-14)	1 (1-9)	-1.430†	0.153

(*) t value, Independent Samples t-test; (†) Z value, Mann-Whitney U test; (‡) X2value, Pearson Chi-square test, p<0.05
(min: minimum, max: maximum, SD: standard deviation, N: patient number)

specificity), leukocyte counts (AUC=0.134, p=0.017, cut-off value <5445 uL, 75% sensitivity, 95% specificity), and neutrophil counts (AUC=0.186, p=0.040, cut-off value <3710 uL, 75% sensitivity, 74% specificity) could be used as predictive markers for the diagnosis of "pathologic fracture" in vertebral fractures. (Table 4, Figure 5). However, *linear logistic regression* analysis revealed that none of these parameters could be used as the "best predictive marker".

Table 2. Distribution table of the study parameters of the patients according to gender

Variable		Female Mean±SD/ Median (min-max)/ N (%)	Male Mean±SD/ Median (min-max)/ N (%)	t/ Z/ X2	p
Age (year)		71.65±11.92	70.88±10.79	0.223*	0.825
Hemoglobin		12.80 (9-16.80)	14 (6.90-15.40)	-0.054†	0.957
Leukocyte		8353±2750.10	7578±3520.13	0.863*	0.392
Neutrophil		5355 (2450-11260)	4130 (1530-14760)	-1.037†	0.300
Lymphocyte		1745±684.12	1622±683.91	0.602*	0.550
Basophil		30 (10-140)	30 (10-60)	-0.166†	0.868
Eosinophil		105 (10-360)	110 (10-460)	-0.141†	0.888
Platelet		269323±72584.63	221941±78296.29	2.141*	0.037
C-reactive protein		3.95 (0.3-106.80)	11.60 (0.20-61.80)	-0.685†	0.494
Segment	1	24 (47.1%)	10 (19.6%)	2.360‡	0.307
	2	10 (19.6%)	6 (11.8%)		
	3	0 (0.0%)	1 (2.0%)		
Area	Thoracic	15 (29.4%)	8 (15.7%)	0.349‡	0.840
	Lumbar	18 (35.3%)	8 (15.7%)		
	Thoracolumbar	1 (2.0%)	1 (2.0%)		
Fractured vertebrae	T4	1 (2.0%)	0 (0.0%)	10.971‡	0.613
	T5	0 (0.0%)	1 (2.0%)		
	T6	3 (5.9%)	1 (2.0%)		
	T7	1 (2.0%)	2 (3.9%)		
	T8	1 (2.0%)	1 (2.0%)		
	T9	1 (2.0%)	1 (2.0%)		
	T10	0 (0.0%)	1 (2.0%)		
	T11	1 (2.0%)	1 (2.0%)		
	T12	5 (9.8%)	2 (3.9%)		
	L1	9 (17.6%)	3 (5.9%)		
	L2	5 (9.8%)	1 (2.0%)		
	L3	4 (7.8%)	1 (2.0%)		
	L4	1 (2.0%)	2 (3.9%)		
	L5	2 (3.9%)	0 (0.0%)		
Biopsy result	Bone material	31 (64.6%)	13 (27.1%)	7.957‡	0.019
	Tumor	0 (0.0%)	2 (4.2%)		
	Infection	0 (0.0%)	2 (4.2%)		
Cement leakage	No	20 (41.7%)	11 (22.9%)	0.000‡	0.990
	Yes	11 (22.9%)	6 (12.5%)		
Leakage segment	No	20 (41.7%)	11 (22.9%)	0.006‡	0.997
	1 level	9 (18.8%)	5 (10.4%)		
	2 level	2 (4.2%)	1 (2.1%)		
Leakage to intervertebral disk area	No	22 (45.8%)	13 (27.1%)	0.168‡	0.682
	yes	9 (18.8%)	4 (8.3%)		
Leakage to spinal canal	No	29 (60.4%)	15 (31.2%)	0.406‡	0.524
	Yes	2 (4.2%)	2 (4.2%)		
Leakage to other side	No	29 (60.4%)	17 (35.4%)	1.144‡	0.285
	Yes	2 (4.2%)	0 (0.0%)		
Hospitalization time (day)		1.5 (1-14)	2 (1-9)	-1.430†	0.153

(*) t value, Independent Samples t-test; (†) Z value, Mann-Whitney U test; (‡) X2value, Pearson Chi-square test, p<0.05
(min: minimum, max: maximum, SD: standard deviation, N: patient number)

Table 3. Distribution table of the study parameters of the patients according to the presence or absence of cement leakage

Variable		LEAKAGE (-) Mean ± SD/ Median (min-max)/ N (%)	LEAKAGE (+) Mean ± SD/ Median (min-max)/ N (%)	t/ Z/ X2	p
Age (year)		69.91±11.01	73.41±12.98	-0.973*	0.336
Gender	Female	20 (%41.7)	11 (%22.9)	0.000‡	0.990
	Male	11 (%22.9)	6 (%12.5)		
Hemoglobin		13.50 (6.90-16.80)	13 (9-15.40)	-0.561†	0.575
Leukocyte		8158±2822.77	8124±3479.99	0.037*	0.971
Neutrophil		4520 (2760-11260)	4820 (1530-14760)	-0.313†	0.755
Lymphocyte		1724±680.51	1734±720.33	-0.046*	0.964
Basophil		30 (10-140)	30 (10-80)	-0.166†	0.868
Eosinophil		120 (10-460)	90 (10-270)	-0.518†	0.604
Platelet		265451±80130.24	226352±68567.43	1.698*	0.096
C-reactive protein		11.80 (0.30-106.80)	2.15 (0.20-69.20)	-2.253†	0.024
Segment	1	21 (43.8%)	11 (22.9%)	1.867‡	0.393
	2	10 (20.8%)	5 (10.4%)		
	3	0 (0.0%)	1 (2.1%)		
Area	Thoracic	17 (35.4%)	6 (12.5%)	1.715‡	0.424
	Lumbar	13 (27.1%)	10 (20.8%)		
	Thoracolumbar	1 (2.1%)	1 (2.1%)		
Fractured vertebrae	T4	1 (2.1%)	0 (0.0%)	11.335‡	0.583
	T5	1 (2.1%)	0 (0.0%)		
	T6	3 (6.2%)	1 (2.1%)		
	T7	3 (6.2%)	0 (0.0%)		
	T8	0 (0.0%)	2 (4.2%)		
	T9	1 (2.1%)	1 (2.1%)		
	T10	1 (2.1%)	0 (0.0%)		
	T11	2 (4.2%)	0 (0.0%)		
	T12	4 (8.3%)	3 (6.2%)		
	L1	7 (14.6%)	2 (4.2%)		
	L2	3 (6.2%)	3 (6.2%)		
	L3	3 (6.2%)	2 (4.2%)		
	L4	1 (2.1%)	2 (4.2%)		
	L5	1 (2.1%)	1 (2.1%)		
Biopsy result	Bone material	26 (57.8%)	15 (33.3%)	1.305‡	0.521
	Tumor	1 (2.2%)	1 (2.2%)		
	Infection	2 (4.4%)	0 (0.0%)		
Cement leakage	No	31 (64.6%)	0 (0.0%)	48.000‡	<0.001
	Yes	0 (0.0%)	14 (29.2%)		
Leakage segment	1 level	31 (64.6%)	4 (8.3%)	32.511‡	<0.001
	2 level	0 (0.0%)	13 (27.1%)		
Leakage to intervertebral disk area	No	31 (64.6%)	13 (27.1%)	7.957‡	0.005
	Yes	0 (0.0%)	4 (8.3%)		
Leakage to spinal canal	No	31 (64.6%)	15 (31.2%)	3.806‡	0.051
	Yes	0 (0.0%)	2 (4.2%)		
Leakage to other side	No	31 (64.6%)	15 (31.2%)	3.806‡	0.051
	Yes	0 (0.0%)	2 (4.2%)		
Hospitalization time (day)		2 (1-9)	1 (1-14)	-0.535†	0.593

(*) t value, Independent Samples t-test; (†) Z value, Mann-Whitney U test; (‡) X2value, Pearson Chi-square test, p<0.05
(min: minimum, max: maximum, SD: standard deviation, N: patient number)

Table 4. Results of ROC-Curve analysis for parameters that can predict pathological fracture

Variable	AUC	p	Cut-off value	Sensitivity	Specificity	95% Confidence Interval Lower	Upper
Gender	0.854	0.021	Male	%100	%71	0.731	0.976
Leukocyte	0.134	0.017	<5445 ul	%75	%95	0.000	0.299
Neutrophil	0.186	0.040	<3710 ul	%75	%74	0.039	0.333

(AUC: area under the curve)

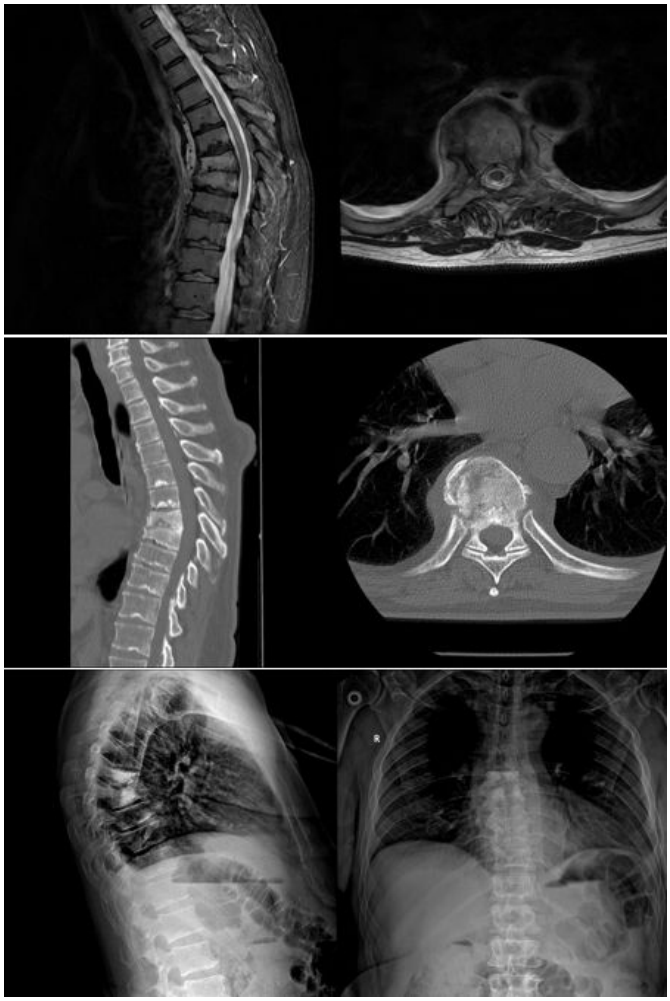

Figure 1. Preoperative and postoperative radiologic images of the patient whose bone biopsy was reported as "Brucella osteomyelitis" on pathologic examination.

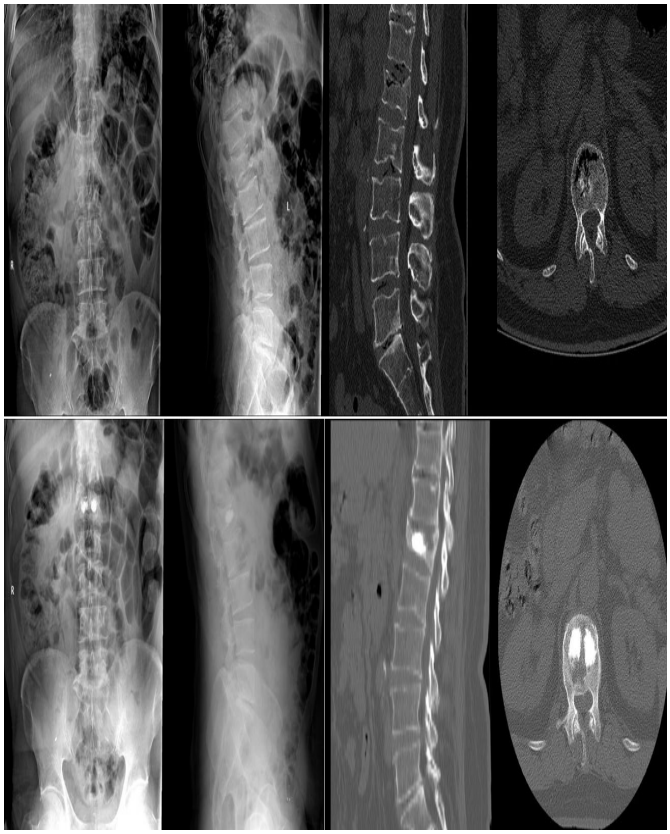

Figure 2. The pictures show the preoperative and postoperative radiologic images of the patient whose bone biopsy was reported as "tuberculosis osteomyelitis" on pathologic examination.

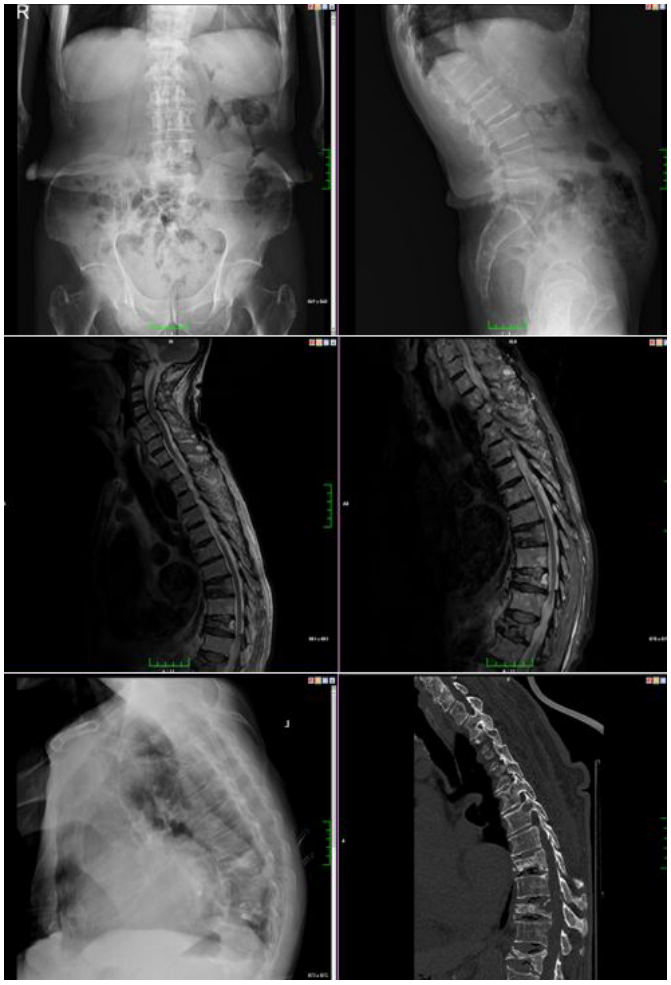

Figure 3. The pictures show the preoperative and postoperative radiologic images of the patient whose bone biopsy was reported as "multiple myeloma" on pathologic examination.

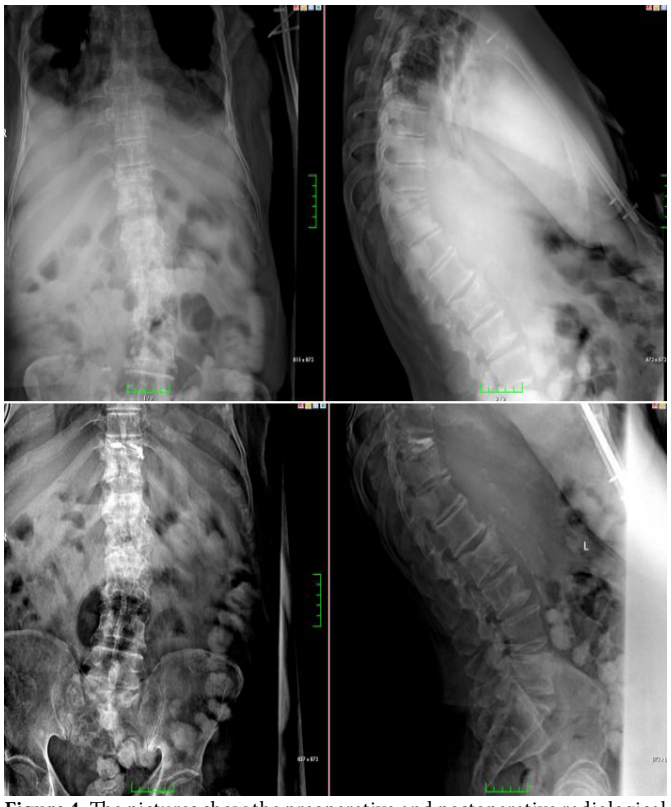

Figure 4. The pictures show the preoperative and postoperative radiological images of the patient whose bone biopsy was reported as a "malignant tumor of the gastrointestinal system" on pathological examination.

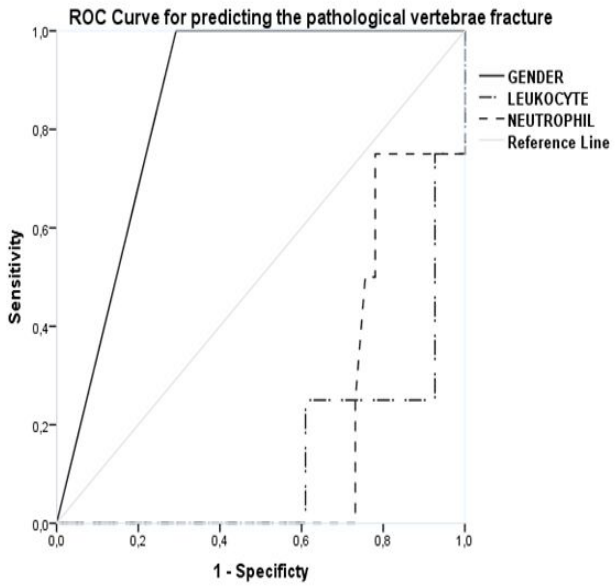

Figure 5. ROC-Curve graph for parameters that can predict pathologic fracture

DISCUSSION

Although imaging modalities such as MR, CT, and positron emission tomography are frequently used to diagnose benign and malignant spinal diseases, sometimes they cannot distinguish osteoporotic fractures from pathological fractures.[12,13] In this context, Zhihong et al.[15] showed that malignant processes can be successfully diagnosed with preoperative MR in almost 98% of patients with malignancy and several MR protocols (such as diffusion-weighted imaging, contrast-enhanced, and STIR sequences) can help differentiate benign and malignant VCF. Acute vertebral fractures show hypo intensity on T1-weighted MR images and hyperintensity on STIR-weighted MR images. Similarly, vertebral fractures due to osteomyelitis show hypo intensity on T1-weighted MR images and hyperintensity on T2-weighted MR and enhanced T1-weighted MR images. Therefore, tissue diagnosis is suggested for pathologic confirmation in such cases.[3,16,17]

The transpedicular biopsy in VCF is much more sensitive and specific (32.4%-89%) compared to most cancer screening methods. It can significantly reduce the likelihood of misdiagnosis and treatment costs and positively impact patients and their families by allowing for shorter treatment and earlier return to work.[18,19] In addition, the prevalence of pathologic findings on biopsy varies between 0.4% and 7.4% in the literature.14 In one study, a high incidence of malignancy of 4.9% was reported in the biopsy results of patients who underwent preoperative MR for VCF and were reported as osteoporotic VCF.[20] For this reason, taking bone biopsy during vertebral body augmentation procedures has become a routine practice in many centers.

In the present study, pathologic examination of biopsy material obtained during PVP was abnormal in 4 (8%) patients. All of these patients were male gender and in two middle-aged patients the pathological examination result

was reported in favor of osteomyelitis and in the remaining two elderly patients the pathological examination result was reported in favor of malignant metastasis. In light of these findings, it was argued that in patients with vertebral fractures who were planned to undergo PVP or KP, it would be appropriate to take a biopsy of bone tissue during the procedure.

In addition, when the patients were grouped according to age and gender, there was a statistical difference between the groups regarding bone biopsy pathologic examination results. With these results, it was thought that infection-related VCF may occur especially in male patients under 65 years of age and VCF secondary to tumor metastasis may occur in male patients over 65 years of age. As a result of the correlation analysis, it was concluded that a biopsy of the fractured bone tissue is necessary, especially in male patients. Furthermore, *ROC-curve* analysis revealed that male gender and decreased leukocyte and neutrophil counts may predict the possibility of pathologic vertebral corpus fracture. It is well known that in patients with osteomyelitis or malignant tumors, the inflammatory response may be reduced due to the existing chronic disease, and these patients may be immunocompromised. Therefore, these findings suggested that vertebral fractures occurring in men should be evaluated carefully, especially inflammatory cell counts should be taken into consideration. In conclusion, although *linear logistic regression* analysis suggested that these parameters could not be used as the "best predictive markers", it was argued that the results of these parameters should be evaluated more carefully in the decision-making of pathological vertebra fractures, especially in male patients.

Although cement leakage was common (27.4-41.7%), symptomatic complications only occurred in approximately 1% of cases. In the literature, the data indicate a significantly lower rate of cement leakage when performing KP compared to PVP. However, given the low incidence of symptomatic complications, this finding may not be clinically relevant. Studies involving osteoporotic fractures have found similar leakage rates between PVP and KP.[21] Cement leakage was detected in 17 (33.3%) patients in our study. Of these patients, 14 had 1-level and 3 had 2-level cement leakage (13 to the disc space and 4 to the spinal canal). However, foraminal cement leakage was not detected in any patient. In addition, none of the patients had any symptoms due to this cement leakage. All these findings were consistent with the literature. In addition, there was no statistical difference between patients with osteoporotic VCF and pathologic VCF regarding cement leakage. With these findings, it was concluded that PVP application can be used safely in both patient groups. On the other hand, CRP values were higher than the normal laboratory values in patients without cement leakage. In contrast, when the blood count results were analyzed, the leukocyte, neutrophil, lymphocyte, basophil, and eosinophil counts were not different between the two groups. Therefore, it was thought that the elevated CRP was not secondary to infection or an allergic reaction (such as a foreign body reaction).

Limitations

This study had some limitations. *First*, the study was retrospective and the study population was small. *Second*, the "Visual Analog Scale", "Oswestry Disability Index" and "Karnofsky Performance Scale" values were not included in this study because it was far from the purpose of the study. *Finally*, the study did not include the "Body Mass Index", bone mineral densitometry values, and serum parathormone, calcium, and phosphorus level values of the patients. Therefore, we could not provide information about the osteoporosis levels of patients with vertebral fractures.

CONCLUSION

The results of this study showed that it is necessary to take a biopsy from patients who will undergo PVP for VCF, especially from male patients, before cementing the fractured vertebra because abnormal biopsy results could be reported in up to 8%. There is no "conflict of interest" among the authors. Furthermore, through any of the products used in this research, no financial engagement has been established with any company that makes and/ or markets these products or with any corporation that produces and/or markets a competing product.

ETHICS COMMITTEE APPROVAL

Ethics Committee Approval

The study was carried out with the permission of Ethics Committe of the Kırıkkale University Faculty of Medicine (Date: 22.05.2024, Decision No: 2024.05.18).

Informed Consent

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

Referee Evaluation Process

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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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Factors affecting prognosis in patients undergoing acute thrombectomy: single center experience

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ABSTRACT

Aims: Our hospital is the only stroke center in the province and serves as a stroke center that welcomes patients from many districts and even surrounding provinces. We aimed to compare the results of endovascular treatment (EVT) applications performed in our hospital with the literature.

Methods: The data of 93 patients who received EVT treatment in the radiology angiography unit between 01.01.2022 and 30.06.2023 were examined. Statistical analyzes were applied on the data obtained.

Results: While a significant positive effect of the first pass recanalization of EVT on National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) was detected ($p<0.001$), the hemorrhagic transformation rate was also found to be significantly low ($p<0.001$). Exit NIHSS scores were significantly lower than entry NIHSS scores. A significant positive effect of short procedure time on exit NIHSS was detected. As the post-procedure complication rate increased, exit NIHSS and mRS values were also significantly higher. It was observed that the short procedure time significantly affected the exit NIHSS scores.

Conclusion: Although EVT is a treatment with proven effectiveness in acute stroke, conditions such as first pass recanalization, procedure complications and procedure duration affect the chance of success of the procedure. The success of EVT applied in our hospital gave similar results to the literature.

Keywords: Stroke, endovascular treatment, first pass recanalization, hemorrhage

INTRODUCTION

According to the World Health Organization definition, stroke is a clinical syndrome characterized by the rapid onset of signs and symptoms of focal cerebral function loss, without any apparent cause other than vascular causes. Stroke ranks first in both mortality and morbidity.[1] Approximately 80% of strokes are ischemic strokes.[2] In ischemic strokes, satisfactory results are obtained with early application and rapid intervention.[3] The effectiveness of intravenous tissue plasminogen activator (IVTPA) applied within the first 4.5 hours has been proven.[4] Endovascular treatment (EVT) also gives successful results when applied in the first 6 hours for anterior system strokes.[5] Various studies have demonstrated the success of EVT with appropriate patient selection in special cases such as strokes where thrombolytic treatment cannot be applied, wake-up strokes or strokes of unknown timing, and strokes presenting late.[6-9] Preliminary data from ongoing studies in this field also show that EVT is a successful treatment method even in strokes lasting up to 24 hours, when patients are selected with appropriate criteria.[7]

EVT success is also related to the duration of the stroke, procedure time, first pass recanalization, applied technique and procedure complications.[10] Previous publications have shown that the first pass recanalization significantly contributes to the risk of procedure success and morbidity. Additionally, it has been observed that the shortening of the processing time due to the first pass recanalization also has a positive effect.[11-12] It has been shown that the procedure has a positive contribution to long-term morbidity, as the combined technique used increases the first pass recanalization and shortens the procedure time. In addition, hemorrhagic transformation is lower in those with first pass recanalization.[12-13] It is expected that centers where EVT is applied will also meet these criteria in the long term.

It is inevitable that EVT applications will become a more widely and effectively applied treatment in the future with developing materials and techniques, and the fact that the applied centers meet certain criteria will have medical and economic consequences in both the acute and chronic periods.

METHODS

The study was carried out with the permission of Ethics Committe of Antalya Training and Research Hospital (Date:11.07.2024, Decision No: 10/17 All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of 93 patients who underwent EVT in the radiology angiography unit between 01.01.2022 and 30.06.2023 were examined. Since some patients had to be hospitalized in external intensive care units and non-hospital centers after the procedure, 3rd month mRS could not be obtained in all patients. Statistical analyzes were applied on the data obtained. Data on gender, age, laboratory data, involved artery area, TICI score, entry and exit NIHHS, 1st and 3rd month mRS, procedure duration, technique, and complications were collected.

Data were analyzed with IBM SPSS V23. Compliance with normal distribution was examined with Shapiro-Wilk and Kolmogorov-Smirnov tests. Chi-square test, Yates correction, Fisher's Exact test and Fisher-Freeman-Halton tests were used to compare categorical variables according to groups, and multiple comparisons of proportions were examined with the bonferroni-corrected Z test. One-way analysis of variance was used to compare normally distributed data according to three or more groups. The kruskal wallis test was used to compare non-normally distributed data according to three or more groups, and multiple comparisons were examined with the dunn test. Relationships between non-normally distributed quantitative data were examined with spearman's rho correlation coefficient. The relationships between continuous data and two-group categorical variables were examined with the Point-biserial correlation coefficient. Analysis results are mean±s for quantitative data. Categorical data were presented as deviation and median (minimum–maximum) and frequency (percentage). The significance level was taken as $p<0.050$.

RESULTS

There was no difference in terms of demographic data of the patients (Table 1). The average age of the patients participating in the study is 69.72±11.79 years and the age distribution is between 35.00 and 90.00 years. Considering the gender distribution, 48.4% of the 93 patients participating in the study were male and 51.6% were female. According to the results of occlusion location analysis, 10.8% had occlusion in the basilar region, 41.9% in the ICA region, 43% in the MCA M1 region and 4.3% in the MCA M2 region. According to TICI score evaluation, 21.5% of the patients had TICI score 0, 8.6% had TICI score 1, 9.7% had TICI score 2A, 16.1% had TICI score 2B, 4.3% had TICI score 2B. 39.8% were treated with TICI score 2C and 39.8% with TICI score 3. In the outcome evaluation,60.2% of the patients had good results, while 39.8% had poor results. According to hemorrhagic

Table 1. Demographical data

	Mean±s. deviation / Frequency (n)	Median (min. - max.) / percentage (%)
Age	69.72±11.79	70.00 (35.00 - 90.00)
Gender		
Male	45	48.4
Female	48	51.6
Location of the clot		
Basillary	10	10.8
ICA	39	41.9
MCA M1	40	43
MCA M2	4	4.3
TICI Score		
0.00	20	21.5
1.00	8	8.6
2A	9	9.7
2B	15	16.1
2C	4	4.3
3.00	37	39.8
TICI Result		
Good	56	60.2
Poor	37	39.8
Hemorrhagic transformation		
No	41	44.1
Yes	52	55.9
Hemorrhagic transformation scale		
HI1	27	51.9
HI2	8	15,4
PH1	13	25
PH2	4	7.7
Duration of the procedure (minute)	56.90±29.10	51.00 (16.00 - 151.00)
Type of the technique		
Aspiration	19	20.4
Combined	46	49.5
Stent	28	30.1
Number of EVT	1.62±1.22	2.00 (0.00 - 5.00)
First pass		
0	64	68.8
1	29	31.2
Complications related to the procedure		
No	80	86
Yes	13	14
Procedural complications		
CAS needed after EVT	2	15.4
CAS needed before EVT	2	15.4
Hemorrhage	1	7.7
Cateter problem	1	7.7
No access to the occlusion	3	23.1
Reocclusion	1	7.7
Vasospasm	3	23.1
Additional chronic diseases		
No	6	6.5
Yes	87	93.5
Hgb	12.31±2.23	12.60 (6.50 - 17.00)
Plt	228.60±72.70	212.00 (0.00 - 439.00)
Mpv	10.98±1.01	11.00 (9.30 - 13.70)
Wake-Up		
No	81	88
Yes	11	12
Duration of time from first symptom to the ER	4.48±3.97	3.00 (0.50 - 20.00)
IVTPA		
No	56	60.2
Yes	37	39.8
Initial NIHSS	14.50±5.05	15.00 (0.00 - 27.00)
Final NIHSS	11.56±6.55	11.00 (0.00 - 29.00)
The difference between NIHSS	3.19±5.95	3.00 (-14.00 - 20.00)
Postprocedural complications		
No	67	72
Yes	26	28
1.Month mRs	3.79±1.72	4.00 (0.00 - 6.00)
3.Month mRs	4.00±2.09	4.00 (0.00 - 6.00)

ICA: Internal carotid artery, MCA: Middle cerebral artery, TICI: The thrombolysis in cerebral infarction, HI: Hemorrhagic infarction, PH: Parenchymal hematoma, EVT: Endovascular treatment, Carotid artery stenting, Hgb: Hemoglobin, Plt: Platelet, Mpv: Mean platelet volüme ER: Emergency room, IVTPA: Intravenous tissue plasminogen activator, NIHSS: National institutes of health stroke scale, mRS: Modified rankin scale

transformation analysis, 44.1% of the patients did not experience hemorrhagic transformation, while 55.9% experienced hemorrhagic transformation. Looking at hemorrhagic transformation subgroups, 51.9% experienced HI1, 15.4% experienced HI2, 25% experienced PH1, and 7.7% experienced PH[2]. The average procedure time was 56.90±29.10 minutes and the range was 16.00 to 151.00 minutes.

The average number of mechanical thrombectomies was 1.62±1.22, with a range of 0.00 to 5.00. Of the patients who experienced complications during the procedure, 68.8% were treated in the first pass, while 31.2% were treated in the second pass. When procedure-related complications were examined, 86% experienced no complications, while 14% experienced various complications. While 6.5% of patients do not have additional chronic diseases, 93.5% have one or more chronic diseases. The average hemoglobin (Hbg) value is 12.31±2.23 g/dl and the range is between 6.50 and 17.00 g/dl. The average platelet (Plt) value is 228.60±72.70 /µl and the range is between 0.00 and 439.00/µl. Mean platelet volume (MPV) was 10.98±1.01 fl with a range of 9.30 to 13.70 fl. The mean entry NIHSS score was 14.50±5.05, the mean exit NIHSS score was 11.56±6.55, and the mean post-procedure NIHSS score difference mean was 3.19±5.95. Of the patients who experienced complications after the procedure, 72% did not experience complications, and 28% experienced various complications. According to the first month results, the average mRs (modified rankin score) value of the patients is 3.79±1.72 and the range is 0.00 to 6.00. According to the third month results, the average mRs value of the patients is 4.00±2.09 and the range is 0.00 to 6.00. Additionally, 88% of the patients did not experience a wake-up stroke, while 12% experienced a wake-up stroke. Lytic application was not applied in 60.2% of the patients and was applied in 39.8%. The average arrival time is 4.48±3.97 days and the range is between 0.50 and 20.00 days.

There is a difference between initial and final NIHSS medians (p<0.001) (Table 2). While the entry median was 15.00, the exit NIHSS median was 11.00. There is no difference between the distributions of TICI score according to IVTPA application (p=0.320). TICI results do not differ according to IVTPA application (p=0.924). Good results were obtained in 58.9% of the untreated group and 62.2% of the applied ones. The presence of hemorrhagic transformation and hemorrhagic transformations do not differ according to lytic application (p values 0.612, 0.816, respectively). Hemorrhagic transformation was observed in 58.9% of those who were not applied and 51.4% of those who were applied.

Table 2. The Comparison of the NIHSS

	Mean±s. deviation	Median (min. - max.)	Test statistic	p
Initial NIHSS	14.50±5.05	15.00 (0.00 - 27.00)	-4.958	<0.001
Final NIHSS	11.56±6.55	11.00 (0.00 - 29.00)		
Difference between NIHSS	s3.19±5.95	3.00 (-14.00 - 20.00)		

*Wilcoxon test
NIHSS: National institutes of health stroke scale, Min:Minumum; Max: Maksimum

A statistically significant, weakly positive relationship was obtained between Procedure Time (Minutes) and final NIHSS (r=0.274; p=0.008). No significant relationship was obtained between procedure time and initial NIHSS (p=0.275) (Table 3). No significant relationship was obtained between arrival time and initial and final NIHSS (p values 0.500, 0.227, respectively).

Table 3. Examining the relationship between processing time and arrival time and initial and final NIHSS values

	Duration of procedure (minute)		Application time	
	r	p	r	p
Initial NIHSS	0.116	0.275	0.073	0.500
Final NIHSS	0.274	0.008	0.129	0.227

r: Spearman's rho correlation coefficient
NIHSS: National institutes of health stroke scale

It shows that post-procedure complications have a significant relationship with the final NIHSS (National institutes of health stroke scale) score and the modified rankin score (mRs) at the end of the 1st month and 3rd month. The correlation coefficient (r) between the final NIHSS score and post-procedure complications was found to be 0.274, and the positive relationship between them was significant (p=0.008). It shows that a high final NIHSS score increases the risk of complications after the procedure. The correlation coefficient between post-procedure complications and mRs at the first month was calculated as 0.411, and there is a moderately significant relationship between them (p<0.001). A high 1-month mRs score may increase the risk of post-procedure complications. Finally, the relationship between mRs at 3 months and post-procedure complications is quite high. The correlation coefficient was calculated as 0.609 and this relationship is significant (p<0.001). This finding suggests that postprocedural complications can significantly affect long-term functional outcomes (Table 4). The connection between Wake-Up and TICI result was not statistically significant (p=0.518). Good results were obtained in 59.3% of those who did not wake up and in 72.7% of those who did.

Table 4. Examining the relationship between post-procedural complications final NIHSS and mRs scores

	Postprocedural complications	
	r	p
Final NIHSS	0.274	0.008
1. month mRs	0.411	<0.001
3. month mRs	0.609	<0.001

*Point-biserial correlation coefficient
mRS: Modified rankin scale

The correlation coefficient (r) between procedure time and hemorrhagic transformation was calculated as 0.171 and this relationship is not significant (p=0.102). On the other hand, when the relationship between transaction time and first pass recanalization is examined, the correlation coefficient is calculated as -0.352 and this relationship is statistically significant (p=0.001) (Table 5). It shows that as the transaction time decreases, the number of people opened with the first pass recanalization increases slightly.

Table 5. Examining the relationship between procedure time and Hemorrhagic transformation and first pass recanalization

	Duration of procedure (minute)	
	r	p
Hemorrhagic transformation	0.171	0.102
First pass effect	-0.352	0.001

*Point-biserial correlation coefficient

The presence of hemorrhagic transformation varies depending on the technique type (p=0.010). Hemorrhagic transformation occurred in 42.1% of the aspiration technique, 71.7% of the combined technique and 39.3% of the stent technique. This difference is between combination and stent. Hemorrhagic transformations differ depending on the technique type (p=0.040). Hemorrhagic transformation HI1 is present in 75% of the aspiration technique, 36.4% of the combined and 81.8% of the stent. This difference is between combination and stent. It varies between those opened with the first pass recanalization depending on the technique type (p=0.027). There are first pass recanalization in 52.6% of the aspiration technique, 19.6% of the combined technique and 35.7% of the stent technique. This difference is between combination and aspiration (Table 6). There are not any other significant findings for the other parameters.

DISCUSSION

Stroke is still one of the leading causes of mortality and morbidity in the world. Recently published data also supports this.[1] In studies based on AHA (American Heart Association) criteria, it was possible to draw a framework for the effectiveness, reliability and principles of thrombectomy treatments applied in acute stroke.[2] In ischemic stroke, many factors such as hospital admission time, risk factors leading to stroke, mRS, TOAST, and gender distribution contribute to the prognosis of the treatment.[3] Data supporting prehospital and emergency stroke care were reviewed, including the use of emergency medical service protocols to identify patients with stroke, intravenous thrombolysis in acute ischemic stroke, updates to recommended patient eligibility criteria and treatment time windows, and advanced imaging.[4] In fact, it is predicted that early intervention will increase with the widespread use of mobile stroke units.[5] The criteria for thrombectomy applications in acute stroke have expanded over time in terms of application time, and the number of patients who have been intervened and benefited from imaging techniques that enable the demonstration of salvageable penumbra tissue, apart from symptom time and admission time, has increased.[6,7]

Hemorrhagic complications related to thrombolytic treatments applied in acute stroke have been described in many studies and possible aggravating factors have been tried to be determined.[8] However, because the treatment range is narrow and its effectiveness in large vessel occlusions is controversial, compilations and analyzes have shown that thrombectomy alone gives similar results.[9]

Hemorrhagic complications could also cause late problems such as epilepsy after ischemic stroke. So it is also important to have less hemorrhagic complications.[10]Studies have shown that both the first pass recanalization and the success of the technique applied according to occlusion are important.[11-14] In our study, similar to the literature, it was concluded that patients with first pass recanalization had a better prognosis. Despite hemorrhagic transformation and recanalization, poor prognosis has been shown to be associated with high NIHSS, low ASPECT score and late presentation time.[13] In our study, it was observed that shorter procedure time in cases opened with first pass recanalization reduce complications and has a positive effect on mRS.

CONCLUSION

Increasing the number of stroke centers serving in the light of current literature and information will not only reduce mortality and morbidity, but will also benefit society socioeconomically.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committe of Antalya Training and Research Hospital (Date:11.07.2024, Decision No: 10/17).

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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Review

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Current approach to low back pain

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ABSTRACT

Low back pain is defined as pain in the area between the 12th rib and the inferior gluteal fold. Low back pain lasting 6 weeks is called acute, low back pain lasting 6-12 weeks is called subacute, and low back pain lasting more than 12 weeks is called chronic low back pain. Sedentary lifestyle, obesity, lack of fitness, smoking, working with vibrating tools, carrying heavy loads, sudden movements, depression, anxiety, pregnancy, traveling for a long time, low socioeconomic status, advanced age, anatomical disorders are risk factors for low back pain.

Keywords: Low back pain, mechanic pain, inflammatory pain

INTRODUCTION

Low back pain is defined as pain in the area between the 12th rib and the inferior gluteal fold. It may occur with or without leg pain. In developed countries, its prevalence ranks 2nd after headaches.[1] Low back pain lasting 6 weeks is called acute, low back pain lasting 6-12 weeks is called subacute, and low back pain lasting more than 12 weeks is called chronic low back pain.[2] The lifetime prevalence of low back pain has been found to be 59-80% in developed countries and 44- 79% in Turkiye.[3-5]

RISK FACTORS

Sedentary lifestyle, obesity, lack of fitness, smoking, working with vibrating tools, carrying heavy loads, sudden movements, depression, anxiety, pregnancy, traveling for a long time, low socioeconomic status, advanced age, anatomical disorders are risk factors for low back pain.

FUNCTIONAL ANATOMY

The spine consists of 33 vertebrae in total. There are 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal vertebrae in the human body. Consisting of 5 active vertebrae, the lumbar vertebrae account for 25% of the entire length of the spine. The lumbar spine is in close relationship with the sacrum. For this reason, both of these vertebrae are together referred to as the lumbosacral spine. The lumbar spine is subjected to greater loads than the cervical and thoracic vertebrae and is therefore larger. Intervertebral discs have shock absorbing properties. These discs make up 1/4 of the length of the spine in young people. This ratio decreases significantly with advanced age due to fluid loss. A facet joint is the joint between the upper articular process of one vertebra and the lower articular processes of the vertebra above it. Intervertebral foramen is the name given to the holes through which the spinal nerves leave the vertebral canal and exit. There are many muscles for the lumbosacral vertebrae to contract and move in harmony. The muscles of the extensor group are the erector spinae (iliocostalis, longissimus and spinalis) and the multifidus, interspinalis and quadratus lumborum muscles. Flexor group muscles are external and internal obliques, transversus and rectus abdominis, psoas major and iliacus muscles (Figure 1, 2, 3, 4, and 5).[1]

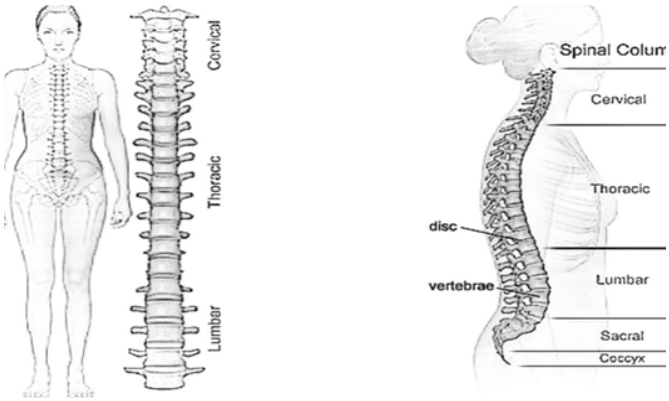

Figure 1. Anterior and lateral view of the spine, intervertebral discs and vertebrae

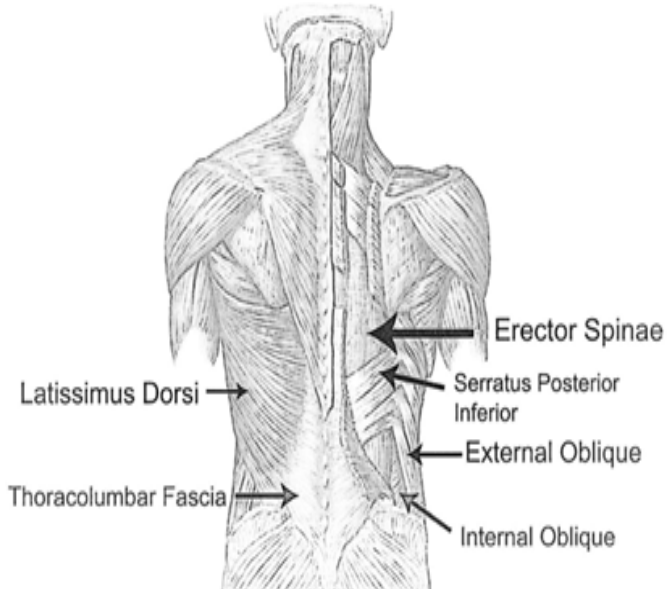

Figure 2. Muscles of the thoracolumbar region, posterior view

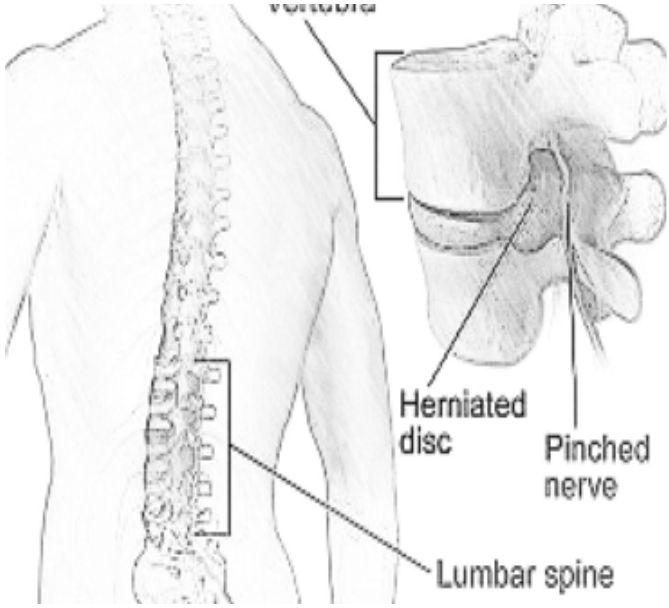

Figure 3. Nerve root compression due to lumbar disc herniation

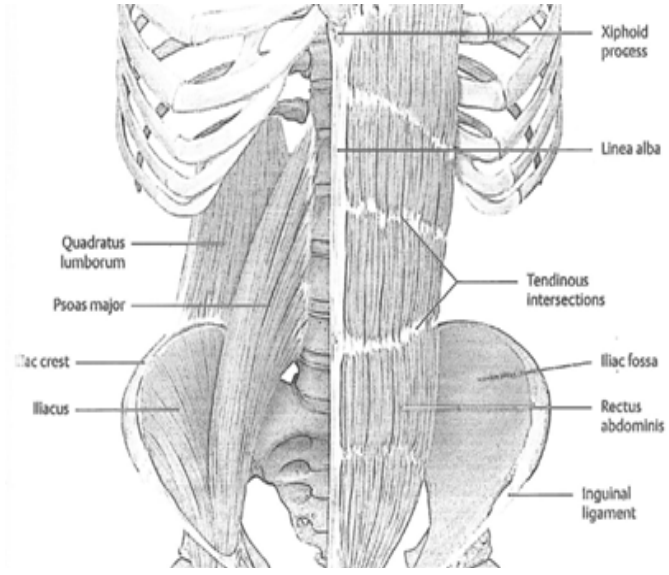

Figure 4. Some flexor and extensor muscle groups in the lumbosacral region

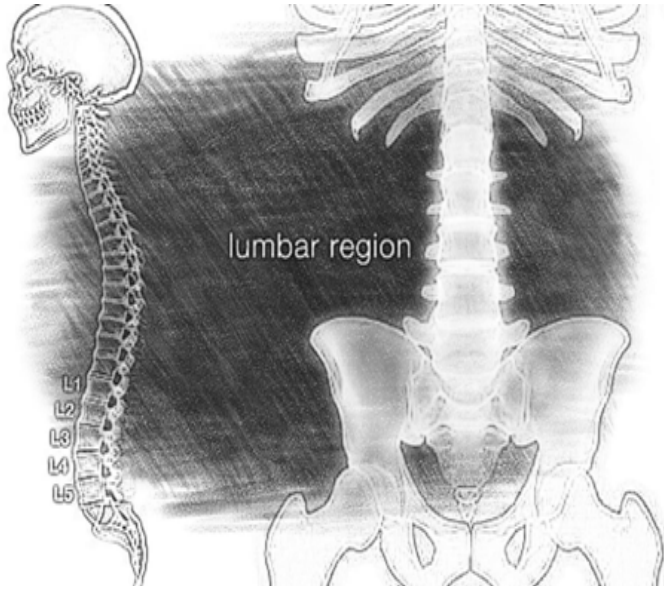

Figure 5. Lumbar vertebrae anatomy, this region constitutes 25% of the entire spine length.

CLINICAL EVALUATION

The causes of low back pain range from mild trauma and mechanical disorders to infectious and neoplastic diseases.[1] Lumbar spine disorders are mainly classified as mechanical or systemic. Mechanical causes account for 90% of low back pain. Mechanical pain is caused by overuse of normal anatomical structures, trauma or deformities in anatomical structures (discogenic pain, lumbar radiculopathy, spinal stenosis, facet syndrome, sacroiliac joint dysfunction, etc.).[6]

In clinical evaluation; firstly, it is determined whether the pain is specific or non-specific. Then, it is essential to identify red flags in low back pain in clinical diagnosis. If there are no red flags in low back pain, it is highly likely that the pain is non-specific. Over 50 years of age, unexplained fever, sweating, unexplained weight loss, severe trauma, nocturnal pain, saddle anesthesia, urinary and/or fecal incontinence, history or suspicion of cancer, history of osteoporosis, corticosteroid use, iv substance use, immunosuppression, progressive neurological disorders, lack of response to 6 weeks of conservative treatment, morning stiffness are among the red flags in low back pain.[1,7] Psychosocial factors that can influence low back pain are called 'yellow flags'. Yellow flags are psychosocial barriers that carry disability and labor risks. Yellow flags need to be treated to prevent low back pain from becoming chronic.[8]

When taking the patient's history, the patient's age, gender, occupation, when and how the low back pain started, whether it radiates to the thigh and leg, what causes the pain to increase or decrease, whether there is numbness, tingling, felting, whether there is urinary and/or fecal incontinence, night pain, morning stiffness should be questioned. The patient should be asked to show the painful area with his/her hand and draw its borders.[9]

CHARACTERISTICS OF PAIN

Pain is classified as superficial somatic, deep somatic, radicular, neurologic, reflected visceral and psychogenic pain.[6]

Superficial Somatic Pain

Originates in the skin, subcutaneous tissue. It is sharp and burning.

Deep Somatic Pains

Caused by muscle, fascia, periosteum, ligaments, joints, veins and dura. It is sharp, distressing and dull.

Radicular Pain

Caused by spinal nerves (disc herniation, spinal stenosis). It is radiating, shooting and tingling.

Neurological Pain

Caused by mixed motor and sensory nerves. It has a burning character.

Radiating visceral pain

Originating in the abdominal organs, pelvic organs, aorta, etc. It is distressing and colicky.

Psychogenic pain

It originates in the cerebral cortex and is variable in nature.

The cause of low back pain varies according to the age of the patients. Reiter's syndrome, endometriosis, osteid osteoma, lymphoma, pyogenic sacroileitis, aneurysmal bone cyst, ankylosing spondylitis start in the 20s. The age of onset of lumbar discopathies, isthmic spondylolisthesis, ochronosis, psoriatic spondylitis is 25-30. The age of onset of Paget's disease, osteoarthritis and metastatic bone cancers is usually 35-40 years. Polymyalgia rheumatica, osteoporosis, spinal stenosis and multiple myeloma are usually over 40. Parkinson's disease should be considered in sudden onset of stiffness and low back pain in the elderly.[10,11]

Duration of pain helps to diagnose low back pain. Mechanical low back pain is usually triggered by physical activity and lasts a short time, whereas specific low back pain starts more slowly and the initiating cause is usually not found. The cause usually becomes apparent after weeks or months.[1]

PHYSICAL EXAMINATION

Inspection

Before the examination, the patient's dorsal, lumbar and sacral areas should be completely stripped. The patient's gait, posture, color and shape changes in the lower back should be checked. In acute painful conditions, the lordosis is usually flattened and the paravertebral muscles are prominent. In disc herniations, antalgic scoliosis may be observed with flattening of the lordosis. Lipoma, increased hair growth, milky coffee and birthmarks on the skin often help the physician to identify an underlying neurologic or congenital bony pathology.[1]

Palpation

The line joining the upper points of the crista iliacae often passes through the L4-L5 interspinous interval. From this point, the spinous processes and interspinous intervals are palpated during the examination. If there is a step between the spinous processes, it suggests spondylolisthesis, and if the spinous process cannot be palpated and a depression is felt here, it suggests spina bifida. Palpation of peripheral pulses, especially a. dorsalis pedis and a. tibialis posterior, is helpful in differentiating whether leg pain is of vascular or neurogenic origin. Palpation is completed by palpating the gluteal muscles, ischial tuberosity, trochanter major and abdomen. Palpation of the abdomen can reveal causes of low back pain such as aortic aneurysm, renal colic and tumors.[1]

Range of Motion

The main movements of the lumbar vertebrae are flexion, extension, right left lateral flexion, right left rotation. Physiologic ROMs are flexion 40 degrees, extension 15 degrees, lateral flexions 30 degrees, rotations 40 degrees.[1]

Neurological Examination

The roots most commonly affected by lumbar spine pathologies are L4, L5 and S1. The cutaneous innervation area of L4 is the medial part of the lower leg. The quadriceps, the knee extensor, is examined for muscle strength. L5 has no specific reflex. Extensor hallucis longus is checked for muscle strength. S1 cutaneous innervation is the lateral aspect of the dorsum of the foot and the sole of the foot. Its reflex is achilles reflex. Muscle strength examination is done by looking at the plantar flexion strength of the thumb and foot. Neurologic examination is completed with superficial and pathologic reflexes, clonus and deep sensory examination.[1]

SPECIAL TESTS

Straight Leg Raise Test (SLRT)

This test is performed by grasping the heel and kneecap of the patient lying on the back and flexing the leg at the hip. The test is considered positive if there is pain between 30-70 degrees radiating to the lower back and/or the whole leg. Pain before 30 degrees or after 70 degrees is nonspecific. If there is pain only in the back of the thigh, Bragard's maneuver can be used for confirmation, as there may be stretching of the Hemstring muscles. SLRT test is sensitive but not specific for disc herniation. The SLRT test performed on the non-painful leg is called the contralateral SLRT test. When the non- painful leg is raised, we consider the test positive if movement is stopped on the painful side due to pain and this usually indicates a large central herniation.[12-14]

Femoral Nerve Stretch Test

With the patient in prone position, the leg is grasped below the knee and brought to extension. If there is pain in the leg, it means that there is L4 root compression.[1]

Double Leg Raise Test

The test is considered positive if a patient lying on his/her back feels pain in the lower back when raising the legs to 30 degrees without bending the knees, or if the test cannot be performed because of pain. This test indicates posterior element pathologies such as facet syndrome and spondylolisthesis. With the patient standing upright, 10 centimeters is marked from the S1 spinous process upwards. The patient then flexes as far as possible and the measurement is repeated. Normally, there should be a difference of at least 5 centimeters between the two measurements. If there is less than this, the test is positive and is a good indicator of lumbar flexibility.[1]

VISUALIZATION

In a patient presenting with low back pain, imaging is not indicated in the first 4-6 weeks unless there are neurologic findings, a systemic symptom, history of trauma, malignancy and/or suspicion, signs of infection, osteoporosis and old age.[15,16]

X-Ray Imaging

If there is no improvement in the patient's condition within the first 4-6 weeks, X- Ray imaging can be used to exclude malignancy, infection, fracture, instability, spondylolisthesis or spondyloarthropathies.[1]

Computed Tomography (CT)

Early and late degenerative changes in bone structures as well as traumatic changes can be seen.[17]

Magnetic ResonanceImaging (MRI)

Unlike X-Ray and CT images, it does not contain ionizing radiation. Three-dimensional images can be obtained. Another advantage is that it shows soft tissue pathologies that cannot be obtained with other imaging methods.[18]

Electrodiagnostic Tests

Although imaging modalities are now predominant in the management of low back pain, electrodiagnostic testing remains important. Electrodiagnosis is most commonly used to detect the presence of radiculopathy and to differentiate it from entrapment neuropathies.[19]

CAUSES OF LOW BACK PAIN

It is often difficult to determine the cause of pain in patients presenting to outpatient clinics with low back pain. In addition to physical examination, radiological examinations are also used for this purpose. The location and origin of the pain is quite complex. The most common factors that cause low back pain are listed below (Tables 1, 2, and 3).[1,3,6-10]

TREATMENT OF LUMBAR SPINE DISEASES

General Information

- Bed rest longer than 2 days is generally not recommended and may leave the patient weak. Patients should be encouraged to ambulate in the acute phase.
- Analgesics or NSAIDs are useful in pain control.
- Low-stress aerobic exercises can be started in the first 2 weeks of symptoms. Back-muscle exercises should be postponed until the end of the 2nd week.[6]

Conservative Approaches

The conservative approach includes patient education, controlled physical activity, bed rest, exercise and drug therapy with NSAIDs and muscle relaxants. The best outcome for patients with low back pain is associated with maintenance of normal activity as opposed to bed rest or extension exercises.[20,21]

Table 1. Mechanical causes of low back pain (97%)

i.	Congenital Anomalies
	Kyphosis, scoliosis
	Transitional Vertebra
	Facet joint asymmetry
	-Spina bifida occulta
ii.	Trauma
iii.	lumbar sprain and strain
iv.	Degenerative diseases of the lower back
	Spinal Stenosis
	Disc herniation
	Combined disc and facet degeneration
	Facet syndrome
	Discogenic pain
v.	Post operative disorders
vi.	Coccidine
vii.	Sacroiliac joint disorders
viii.	Myofascial pain syndromes
ix.	Thoracolumbar junction syndrome
x.	Compression fractures
xi.	Spondylolysis/ Spondylolisthesis

Table 2. Non-mechanical causes of low back pain (1%)

i.	Neoplasms
	Primary vertebral tumor
	Spinal neoplasms
	Multiple myeloma
ii.	Metastasis
iii.	Infections
	Vertebral osteomyelitis and discitis
	Epidural abscess
iv.	Seronegative spondyloarthropathies
v.	Scheuerman's disease
vi.	Metabolic bone diseases

Table 3. Nonspinal/visceral causes of low back pain (2%)[1]

i.	Pathologies originating from the gastrointestinal system (cholecystitis, pancreatitis, pepticulcer, etc.)
ii.	Pathologies originating from pelvic organs (prostatitis, endometriosis, pelvic inflammatory disease etc.)
iii.	Renal pathologies (nephrolithiasis, pyelonephritis, perinephritic abscess, etc.)
iv.	Psychological disorders

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS therapy is based on the gate-control theory of pain and regulates pain perception in the cerebral cortex bycounter-stimulation of the sensory system. TENS primarily stimulates low-threshold A alpha fibers. Stimulation of these fibers is thought to inhibit the nociceptive impulses of small nonmyelinated C fibers and A delta fibers.[6]

Medical Treatment

These agents include acetaminophen, non-steroidal anti-inflammatory drugs, myorelaxants, opiods, anti-depressants, anti-epileptics and systemic corticosteroids.[22] Surgical options should be considered in the absence of response to conservative treatment, development of cauda equina syndrome and progressive motor deficits.[23]

CONCLUSION

Regardless of the underlying cause, low back pain is a serious public health problem that is common in societies. History and physical examination are very important in diagnosing low back pain. Low back pain is divided into various classes according to their characteristics. Laboratory findings and radiological imaging options are very helpful to the clinician regarding low back pain. Recently, satisfactory alternatives have been discovered regarding treatment. Exercises and medical treatment are among the first preferred methods for PMR physicians in the treatment of low back pain. Surgical methods are used in cases that do not respond to treatment or in the development of progressive neurological deficits.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Review

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General approach to headache diagnosis and treatment management

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ABSTRACT

Headache is common worldwide and is one of the leading causes of disability. Given its high prevalence and high burden in terms of disability, it is important for clinicians to have general knowledge about the approach to the patient presenting with headache. Headache disorders are classified according to their etiology. The most important step in the approach to headache is to investigate the presence of a secondary cause of pain with a detailed history and physical examination. The presence of symptoms and signs considered as red flags requires further investigation in terms of secondary causes. Treatment of pain is also directed towards the etiology. Treatment of secondary headache disorders is directed towards the cause of the pain. In primary causes, there are some pharmacologic and non-pharmacologic treatment approaches for the diagnosis.

Keywords: Headache, red flags, SNNOOP10

INTRODUCTION

Headache is a common symptom affecting the majority of the population and has a wide range of etiologies. In order to treat headache effectively and successfully, an accurate diagnosis is essential. A systematic and multidisciplinary approach is important for making the correct diagnosis. In this review, we aimed to discuss the importance of systematic approach to the management of headache and current knowledge in the light of the existing literature.

EPIDEMIOLOGY

Although studies on the prevalence of headache have yielded different results, it is noteworthy that it is a complaint affecting the majority of the population. When prevalence studies are analyzed together, it is estimated that almost half of the global population has active headache complaints. Primary headache is more common than secondary headache. In addition, the prevalence of headache is higher in women.[1] According to WHO (World Healt Organization) it is estimated that half to three quarters of adults worldwide experience headaches. It is also stated that the vast majority of these headache sufferers do not consult health professionals due to headache and are not diagnosed by health professionals.[2]

Global Burden of Disease Study 2016, estimated that almost three billion people suffer from migraine or tension headache, and migraine is considered one of the leading causes of disability.[3]

ETIOLOGY AND CLASSIFICATION

Headache classification was first made by the International Headache Society in 1988 in order to facilitate the diagnosis of headaches with different etiology, duration, severity, frequency and accompanying findings and to use a common language. The latest version of the classification, ICHD-3, was published in 2018. This classification is guiding in terms of a systematic approach to headache. The headings in this classification are given in Table 1.[4]

Primary headache disorders are those in which there is no underlying cause of the headache and the disease manifests itself directly as headache. In secondary headache disorders,

headache is a manifestation of the underlying disease. In these cases, headache may be secondary to systemic or central nervous system pathology.[5]

Table 1. Classification of headache disorders

Primary Headaches
Migraine
Tension headache
Trigeminal autonomiccephalalgias
Other causes of primary headache
Secondary Headaches
Headache secondary to head or neck trauma/injury
Headaches due to cranial or cervical vascular disorders
Intracranial non-vascular headaches
Headache associated with substance (use) or withdrawal
Headache due to infection
Headache attributed to homeostasis disorder
Headache or facial pain associated with disorders of the cranium, neck, eyes, ears, sinuses, teeth, mouth or other facial or cranial structures
Headache associated with psychiatric disorders
Neuropathies, facial pain and other headaches
Painful lesions of the cranial nerves and other facial pains
Other headache disorders

Migraine, tension-type, trigeminal autonomic cephalalgias and other headaches that cannot be categorized constitute primary headaches. Cluster headache, paroxysmal hemicrania, unilateral neuralgiform short-term pain with conjunctival redness and lacrimation (SUNCT) and hemicrania continua are classified under trigeminal autonomic cephalalgias. Other primary causes of headache that have not yet been categorized include primary cough, exercise, cold stimuli, sexual activity, thunder and hypnic headache.[4]

Migraine is a common primary headache disorder that causes disability. Migraine is divided into two main types: with and without aura. Migraine without aura is a clinical syndrome defined by some specific features and associated symptoms. Migraine with aura usually progresses with transient focal neurological symptoms that precede or accompany the headache. Like migraine, tension-type headache is also common in the community. The mechanism of action of this type of headache is not yet fully known. This pain manifests itself as bilateral, compressive headache episodes6. Classification of primary headaches according to some common features is summarized in Table 2.

DIAGNOSIS

While laboratory and imaging tests help in the diagnosis of secondary headache disorders, the diagnosis of headache disorders is largely based on history.[7] It can be said that the patient's history is a more guiding step in the stages leading to the diagnosis of headache compared to many other neurological diseases.

Patients presenting to the outpatient clinic or emergency department with headache complaints usually have a primary headache disorder, most commonly migraine.[7,8] Nevertheless, in every patient presenting with headache, the priority should be to exclude secondary causes and a detailed and systematic approach should be adopted. This approach is important to avoid overlooking serious underlying causes that can be treated.[9,10]

In 2003, some symptoms, findings and features that are seen as red flags in headache were listed in order to suggest secondary causes that require further examination in patients presenting with headache, and the initials of these features were used to make an abbreviation called SNOOP. Some features were added to the list in 2019 and the name was updated as SNNOOP10 The red flags in the list are defined as findings or features that require further examination of the patient, while orange flags are defined as information that is of concern only when it occurs in combination with other orange or red flags.[11] The criteria in this abbreviation are listed in Table 3. Although there is no clear recommendation in the literature for the use of this list yet, SNNOOP10 has gained

Table 2. Classification according to common features in primary headaches

Headache	Character	Duration	Side	Location of pain	Concomitant finding	Frequency
Migraine	Throbbing	4-72 hours	Unilateral	Neck and forehead	Nausea, vomiting	Variable
Tension	Compactor	Half an hour - 7 days	Bilateral	Nape	Loss of appetite, nausea	Variable
Cluster	Reamer/driller	15-180 minutes	Unilateral	Orbital circumference	Autonomic symptoms	1-8/day
Cough	Stabbing, throbbing	1 second - 30 minutes	Bilateral	Back of the head	No	Associated with cough
Exercise	Blunt	5 minutes - 48 hours	Bilateral	Back of the head	No	Exercise-related
Hipnik	Compressive, throbbing	15-180 minutes	Bilateral	Widespread	No	More than 15 per month
Thunder	Explosive	1 hour-10 days	Bilateral	Nape or widespread	Nausea, vomiting	Does not recur regularly
SUNCT	Throbbing	5-240 seconds	Unilateral	Orbital circumference	Eye tearing	3-200/day
CPH	Burning, piercing	2-30 minutes	Unilateral	Orbital circumference	Autonomic symptoms	5>/day

Table 3. SNNOOP 10 Criteria	
Sign or symptom	Related Secondary Headaches
Systemic symptoms including fever	Headache attributed to infection or nonvascular intracranial disorders, carcinoid or pheochromocytoma
Neoplasm in history	Neoplasms of the brain; metastasis
Neurologic deficit or dysfunction (including decreased consciousness)	Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections
Onset of headache is sudden or abrupt	Subarachnoid hemorrhage and other headaches attributed to cranial or cervical vascular disorders
Older age (after 50 years)	Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders
Pattern change or recent onset of headache	Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders
Positional headache	Intracranial hypertension or hypotension
Precipitated by sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation
Papilledema	Neoplasms and other nonvascular intracranial disorders; intracranial hypertension
Progressive headache and atypical presentations	Neoplasms and other nonvascular intracranial disorders
Pregnancy or puerperium	Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (eg, preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes
Painful eye with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome; ophthalmic causes
Posttraumatic onset of headache	Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders
Pathology of the immune system such as HIV	Opportunistic infections
Painkiller overuse or new drug at onset of headache	Medication overuse headache; drug incompatibility

a widespread place in studies on headache and provides guidance in clinical practice. In some studies evaluating the efficacy and sensitivity of SNNOOP10, it has been concluded that its sensitivity is high in the detection of risky headaches requiring further investigation.[12,13]

While red flags are common in the approach to headache, some recent studies have suggested that it may be useful to designate a few symptoms as green flags. Green flags are designed to indicate that the pain of patients with these symptoms often points to a primary etiology. The symptoms and findings identified as green flags are compiled in Table 4.[14] It has been emphasized that green flags often indicate primary headache, but the priority is to question red flags when evaluating patients and more studies are needed in this regard for the widespread use of green flags.[14,15]

Table 4. Green flags in headache
Existing pain has persisted since childhood
The patient has days without headache
Family members have a headache similar to the patient's headache
Headache has a temporal relationship with the menstrual cycle
The headache has appeared or stopped a week ago

It is important to remember that the presence of a pre-existing primary headache does not exclude a secondary cause that may have developed in the patient's current condition.[9] Therefore, changes in the characteristics of headache must be questioned during history taking and a detailed examination must be performed in terms of new clinical symptoms.[16] Family history, age at onset, frequency and intensity of pain, localization of pain, other complaints accompanying pain, comorbidities, and conditions that trigger or increase pain should be questioned during anamnesis.

There are some conditions that require further investigation in the follow-up of patients with existing primary headache disorder. For example, patients with tension-type headache will need further investigation at the slightest sign of progression, as brain tumors and some secondary headaches can sometimes present with tension-type headache-like. Another scenario in which a patient with a primary headache should be investigated is if there is a change in pattern. When a patient with a chronic migraine has an acute sinus infection, chronic meningitis or an intracranial lesion, the patient may not be investigated because the headache is thought to be due to migraine. Therefore, any additional features or changes in the headache pattern or incurability should always be investigated in a patient with chronic primary headache.[17]

Questioning the period of onset of headache is an important step in the diagnosis. Headaches that begin at older ages, during pregnancy and in the postpartum period require the exclusion of secondary causes. New onset headache in the elderly is more likely to have a serious underlying cause compared to young adults.18 In this age group, intracranial space-occupying lesions (tumor, bleeding), temporal arteritis and drug-related headaches should be excluded. If secondary causes are excluded and primary headache is considered in the etiology, hemicrania continua, hypnic headache, primary cough headache, trigeminal neuralgia should be considered. Migraine and tension headache should be kept in mind in the differential diagnosis, although they occur less frequently in the older age group.[19]

Table 5. Secondary headache causes, symptoms and signs

Condition, signs and symptoms	Secondary headache cause
Periorbital, facial pain, especially in diabetic patients	Mucormycosis and other opportunistic infections
New-onset pain in immunosuppressed patients	Meningitis, intracranial infections, brain abscess, intracranial space-occupying lesion
Pain in the temporal region, presence of systemic symptoms, elevated sedimentation in a patient over 50 years of age	Temporal arteritis
Pain during pregnancy	Eclampsia, prolactinoma, idiopathic intracranial hypertension
Pain in the immunosuppressed patient	Neoplasm, opportunistic infections
Pain defined as acute, severe and the most severe pain in a person's life	Subarachnoid hemorrhage
Pain associated with head and neck trauma	Dissection of neck vessels, intracranial, epidural, subdural hematomas
Pain that increases in frequency and intensity	Increased intracranial pressure, chronic subdural hematoma, headache due to drug overuse
Pain associated with coughing and straining	Increased intracranial pressure
Increased pain when standing up	Low intracranial pressure

In headache that occurs during pregnancy, it is important to exclude secondary causes in order not to overlook important conditions such as eclampsia.[17]

There may be some secondary conditions that should be considered in the foreground in the association of some conditions, findings and symptoms such as onset period, comorbidities. Some examples of these secondary headaches are given in Table 5.[20]

LABORATORY AND IMAGING

Laboratory and imaging tests should be aimed at the preliminary diagnosis. If the cause of the headache is primary, blood tests, electroencephalography (EEG) and other imaging tests have no diagnostic value. These tests are of diagnostic importance in cases suggestive of secondary headache.[17] Extensive diagnostic tests ordered without a preliminary diagnosis will have low diagnostic value and high costs.

Radiologic examinations, lumbar puncture (LP) and CSF examination, laboratory tests, biopsy, EEG, ECG, fundoscopy, intraocular pressure measurement are among the examinations that can be considered specific to the preliminary diagnosis. Table 6 lists the tests that can be evaluated for some secondary causes.[20]

Table 6. Investigations to be requested for some specific reasons

Secondary Headache Cause	Audit to be Evaluated
Subarachnoid Hemorrhage	Computed tomography (CT), lumbar puncture (LP), cerebral angiography (DSA)
Intraparenchymal/Subdural/ Epidural Hemorrhage	CT, magnetic resonance imaging (MRI)
Ischemic cerebrovascular diseases	CT, MRI, MR venography
Temporal Arteritis	Sedimentation, CRP, doppler USG, temporal artery biopsy
Cervical Artery Dissection	MRI, magnetic resonance angiography, doppler ultrasound, CT angiography, DSA
Sinusitis	Waters radiograph, CT
Central nervous system infections	MRI, EEG, LP, blood and CSF microbiological examinations
Metabolic and Endocrine Causes	Prolactin levels, pituitary hormones, TSH, free T4

TREATMENT

In treatment, the etiology of the pain determines the approach route. In secondary headaches, treatment should be directed towards the cause. It should be noted that symptomatic treatment without excluding secondary causes may mask the underlying cause of the pain. In primary headache disorders, there are many different pharmacologic and non-pharmacologic treatment approaches to address the etiology.

Migraine Treatment

Migraine treatment is basically analyzed under two main headings: acute attack for the attack that has already started and prophylactic treatment to reduce the frequency of attacks. The main topics in migraine treatment are compiled and given in Table 7.

Table 7. Migraine treatment

Acute Attack Treatment
Non-steroidal anti-inflammatory drugs (NSAIDs) group
Triptan group drugs
Symptomatic treatments for nausea and vomiting
Prophylactic Treatment
Lifestyle changes
Antiepileptics, antidepressants, beta-blockers and calcium channel antagonists
Botulinum neurotoxin-A (BoNT-A)
Interventional methods
New Drug Therapies
Gepants and ditans

ACUTE ATTACK TREATMENT

The goal of acute treatment is to reduce the duration and severity of the onset of an attack and ideally to terminate it. The aim of treatment is not only to relieve the headache but also other accompanying symptoms. The International Headache society's recommendation for acute treatment clinical trials is that the headache should stop after 2 hours and that the headache and other accompanying symptoms should not recur for 24-48 hours.[21]

As a general principle, non-specific and easily accessible drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) may be preferred for mild to moderate attacks, and if these are not effective, more pathophysiology-specific drugs such as triptans may be preferred. Another symptom to keep in mind is nausea and vomiting, which can be more unpleasant than the headache itself .

In addition to NSAIDs or triptans, metoclopramide (10 mg) or domperidone (10 mg) are usually effective in symptomatic treatment of nausea. NSAIDs with proven efficacy in migraine

treatment are acetylsalicylic acid, ibuprofen, naproxen, ketorolac and diclofenac. Ergot alkaloids and triptans are migraine-specific drugs with agonistic effects on serotonergic 5-HT1B/1D receptors. In addition to symptomatic treatment of nausea and vomiting in migraine, they have been found to be effective against the primary migraine attack. Therefore, they are used as adjunctive therapy and intravenous metoclopramide is preferred in the treatment of acute attacks in emergency departments.[22]

While triptans are selective to 5-HT1B/1D receptors, ergot alkaloids bind to other serotonergic, dopaminergic and adrenergic receptors. For these reasons, ergot derivatives carry with them the potential for significant side effects. For example; since they also have a high affinity for vascular serotonergic receptors, systemic vasoconstriction and thus cardiovascular risks arise.[23]

PROPHYLACTIC TREATMENT

The goal of prophylactic treatment is to reduce the frequency of attacks by at least half. In general, the effect of prophylactic treatments appears 6-8 weeks after initiation and should be continued without interruption for at least 3-12 months for the effect to be permanent.[24]

Lifestyle Changes

In patients complaining of frequent and severe migraine attacks, in addition to pharmacological treatment approaches, regular nutrition, adequate sleep patterns and stress avoidance should be recommended.[25]

Antiepileptics, Antidepressants, Beta-Blockers and Calcium Channel Antagonists

Topiramate and valproic acid are antiepileptics approved by the United States Food and Drug Administration (FDA) for the prophylactic treatment of migraine. The effect of these drugs on migraine prophylaxis was discovered incidentally during their use in epilepsy and their mechanism of action in migraine is still unknown. When both topiramate and valproic acid are administered chronically to mice for several weeks, similar to migraine prophylaxis in patients, the threshold for triggering Cervicocephalic syndrome(CCS) increases and the propagation rate decreases.[24]

As with antiepileptics, the migraine prophylaxis effects of some antidepressants have been found to be incidental. There is insufficient evidence for the prophylactic effect of selective serotonin reuptake inhibitors, which are frequently used in the clinic.[26]

Flunarizine is a nonselective calcium channel antagonist, but also shows dopamine and histamine receptor antagonism. Although its mechanism of action in migraine prophylaxis is still unknown, there is evidence for an inhibitory effect on neurogenic inflammation.[27]

Botulinum neurotoxin-A (BoNT-A) inactives SNAP-25, a known presynaptic protein and suppresses neurotransmitter release from cholinergic terminals. Following local injection, BoNT-A enters the trigeminal nerve endings innervating the skin and is retrogradely transported by axonal transport mechanisms. In this way, it first reaches the trigeminal ganglion and then reaches the trigeminocervical complex by transcytosis. It has been suggested that BoNT-A suppresses the release of neuropeptides such as CGRP and P-substance at the site where it reaches, which may constitute a prophylactic effect.[28]

METHODS

Interventional methods can be used for acute and preventive purposes. The interventional methods can be summarized as large and small occipital nerve, supraorbital, supratrochlear nerve, auriculotemporal nerve blocks, sphenopalatine ganglion blocks.[29]

Different GON blockade techniques have been described. The most widely used and recommended technique is to place the sensitive point 1/3 medial to the imaginary line drawn between the protuberant a occipitalis externa and the mastoid process, medial to the occipital artery palpation. Local anesthetic volumes between 0.5-10 mL were used in the studies. The majority of researchers used 1.5-2 ml of 0.5% bupivacaine as local anesthetic and its efficacy has been shown.[30]

Acupuncture treatment method may have an analgesic effect and can be used during the treatment of migraine attacks, but studies on its usefulness in prophylactic treatment are mostly not statistically significant.For acupuncture, needles are inserted into the trigger points detected as a result of the examination. Although the effectiveness of dry needling has been proven in many musculoskeletal diseases, it has not been shown to be beneficial in migraine. It should not be considered as a treatment option in migraine cases.[31]

Trigger points occur as a result of abnormal depolarization of motor endplates leading to excessive release of acetylcholine at the neuromuscular junction. Prolonged contracted muscles lead to muscle shortening, hypoxia and metabolite accumulation. Algesic proinflammatory molecules such as substance P, CGRP and bradykinin have been detected in active trigger points. Trapezius, splenius capitis, levator scapula, temporal, and sternocleidomastoid muscles are the most common muscles in which trigger points occur. The association of primary headaches and myofascial pain is common and injections to these trigger points significantly reduce pain. In migraine patients, various studies have shown that the presence of trigger points and injections applied to these points provide a decrease in pain frequency and intensity.[32]

New Drug Therapies

The high prevalence of migraine and its high burden in terms of disability has increased the search for new migraine-specific treatments. This has led to the discovery of new drugs such as 5HT1F receptor agonists-ditans (lasmiditan), small molecule calcitonin gene-related peptide (CGRP) monoclonal antibodies.

These drug therapies may not be suitable for all patients due to their higher cost and limited accessibility. Lasmiditan and gepants are a good choice in the treatment of patients with severe migraine attacks who cannot use triptans for various reasons such as cardiovascular or cerebrovascular disease.

The anti-CGRP monoclonal antibodies should be considered as a last-line treatment for patients for whom other drug therapies have not been effective or who have side effects associated with these drugs and should be saved for last.[33]

TREATMENT OF TENSION HEADACHE

Acute Attack Treatment

Acute attack treatment to stop the attack and reduce its severity includes the use of simple analgesics and nonsteroidal anti-inflammatory agents alone or in combination (Table 8).[34]

Table 8. Drugs used in the treatment of attacks, their doses, and side effects.[35]

Attack treatment	Dose	Side effects
İbuprofen	200-800 mg	Gastrointestinal side effects
Flurbiprofen		
Paracetamol	1000 mg	Gastrointestinal side effects, Liver toxicity
Ketoprofen	25 mg	Gastrointestinal side effects
Aspirin	500-1000 mg	Gastrointestinal side effects
Naproxen	375-1000 mg	Gastrointestinal side effects
Diclofenac	12.5-100 mg	Gastrointestinal side effects
Dexketoprofen	25-75 mg	Gastrointestinal side effects

Metamizole

Metamizole has been shown to be effective in GTBA at doses of 0.5-1 g. However, its use is avoided because it causes agranulocytosis.[36]

Butalbital

Butalbital-containing drugs are recommended when first-line analgesics are ineffective or not used. Butalbital + acetaminophen + caffeine (esgic, floricet).[37]

Lumiracoxib

It is a new COX-2 receptor inhibitor and has been shown to be effective in tension headaches at doses of 200-400 mg.[38]

Flupirtine

Flupirtine is one of the non-narcotic analgesics and has effects on potassium channels and NMDA.[39]

Antiemetic Districts

Antiemetic drugs facilitate the absorption of analgesic drugs by providing rapid emptying of the stomach. Metoclopramide 10 mg (metpamide) and domperidone 10 mg (motilium) are among the drugs that are used and effective.[34]

Tension Headache Prophylaxis Treatment

The aims of prophylactic treatment are to decrease the frequency, severity, and duration of headache attacks and to ensure recovery in cases where acute attack treatments are unresponsive. In addition, prophylactic treatment may be started in advance during acute treatment due to lack of response to preventive treatment, side effects, overuse of the drug, and contraindications of the drug.(Table 9)[34]

Table 9. Dosage, side effects, and contraindications of antidepressant drugs.[40]

Primary treatment	Dose	Side effects	Contraindication
Amitriptyline	30-75 mg	Dry mouth, constipation, palpitations, blurred vision, weight gain, orthostatic hypotension	Hypersensitivity, arrhythmias, hypertension, mania, urinary retention and heart block, use with monoamine oxidase inhibitors
Secondary treatment			
Mirtazapine	30 mg	Weight gain, sedation, orthostatic hypotension, mania	Hypersensitivity
Venlafaxine	150 mg	GIS side effects, anorexia, irritability, insomnia, sexual dysfunction	Mania, use with monoamine oxidase inhibitors
Tertiary treatment			
Clomipramine	75-150 mg	Similar to amitriptyline side effects	Similar to amitriptyline
Maprotiline	75 mg	Headache, dizziness, seizures, ataxia, fatigue, sedation, similar to the side effects of amitriptyline	Use with monoamine oxidase inhibitors
Mianserin	30-60 mg	Seizures, hypomania, hypotension, arthralgia and edema	Use with monoamine oxidase inhibitors, DM, heart failure

In prophylaxis, amitriptyline is the first choice, venlafaxine and mirtazapine are the second choices.

Nonpharmacologic Therapies

Non-pharmacologic methods should also be considered in the treatment of primary headaches.[41]

Information about the disease

- Lifestyle change
- Regular sleep and nutrition
- Exercise
- Posture regulation
- Awareness and avoidance of triggers
- EMG- biofeedback
- Cognitive-behavioral therapies
- Psychological support
- Physical therapy
- Acupuncture
- Local injections
- TENS (Transcutaneous electrical nerve stimulation)

Cluster Type Headache Treatment

1- Acute attack treatment

- Oxygen inhalation: it has been shown that inhalation of 6-12 lt/min of 100% oxygen for 15-20 min with a mask during a headache attack was effective in approximately 2/3 of the patients.[42]
- Triptans:Subcutaneous sumatriptan (5-HT1B/D receptor agonist) was found to be superior to placebo at 6 mg and 4 mg doses. Response is obtained in 2/3 of patients within 15 minutes.[43]

2- Prophylactic treatment

- Verapamil: The first choice for prophylaxis for both episodic and chronic cluster headaches. It is started with 80 mg three times a day. If there is no response, 80 mg can be increased weekly up to 960 mg.[44]
- Lithium: It is used at a dose of 300-1200 mg/day. It has been found to be more effective in chronic cluster-type headaches.[45]

- Antiepileptic drugs: topiramate, sodium valproate, gabapentin are the main antiepileptic drugs used in cluster headache prophylaxis 46.

CONCLUSION

Headache is common in the community and is one of the most common causes of hospital admission. Although pain may have many etiologies, it is basically divided into primary and secondary headache disorders. The most important step in the evaluation of a patient presenting with headache is to differentiate between primary and secondary causes. The treatment approach should be directed towards the cause in secondary headache disorders. There are some traditional treatments for primary headache disorders and some newly developed drug therapies. Considering the prevalence and disability burden of primary headache disorders in the community, more studies are needed to develop effective drug therapies.

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Referee Evaluation Process

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The authors have no conflicts of interest to declare.

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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 presentation of uremia: akathisia

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ABSTRACT

Acute movement disorders associated with bilateral basal ganglia lesions are becoming more common in patients with diabetes mellitus and uremia. Pathophysiology is not fully known, although it is believed to be complex, with ischemic/microvascular as well as metabolic/toxic variables influencing lesions and symptoms. We have reported here a uremic diabetic patient who has sudden developed severe akathisia, in Magnetic Resonance Imaging (MRI) showed bilateral symmetric basal ganglia lesions with regression at follow-up. A condition linked with acute bilateral basal ganglia lesions in diabetic uremic individuals is uncommon, with clinical and imaging data demonstrating reversible alterations. Akathisia secondary to uremia is rarely seen in the literature. Our goal is to improve awareness of this condition among doctors and radiologists in order to identify more cases.

Keywords: Akathisia, uremia, diabetes mellitus, basal ganglia

INTRODUCTION

Uremia is a clinical and metabolic condition that develops in tandem with the decline of renal function. A well-known uremia consequence is brain involvement. The neurological effects of uremia are similar in many ways to the impact of other metabolic and toxic illnesses on the central nervous system.[1]

Acute movement abnormalities with bilateral basal ganglia involvement in diabetic uremic individuals have been reported in numerous recent case reports. The imaging features of this condition include symmetric bilateral basal ganglia lesions. The etiology behind it is yet unclear.[2-6]

Parkinsonism (bradykinesia, stiffness, postural instability, and gait abnormalities with no resting tremor) is the most frequent clinical symptom of bilateral basal ganglia lesions in uremic patients, followed by dysarthria, consciousness disturbances, dyskinesia, and dysphagia.[2,3]

Akathisia is a restless motor condition that most often occurs as a side effect of various medications in individuals receiving neuroleptic treatments. It's a neuropsychiatric disorder characterized by psychomotor restlessness. A person with akathisia will typically have a significant sense of discomfort or inner restlessness that affects their lower extremities.[7]

Akathisia secondary to uremia is rarely seen in the literature. We report here a case of sudden developed severe akathisia with basal ganglia lesions in a 63-years-old diabetic uremic patient. We discuss the possible etiology of this disease, as well as its clinical symptoms, laboratory results, Magnetic Resonance Imaging (MRI) findings, and clinical outcomes.

CASE

A 63 year old man was brought to our emergency department due to sudden acute motor restlessness, irritability, sleeplessness, dysphoria, as well as meeting the akathisia criteria. The most significant symptom was akathisia, which scored 10/14 on the Barnes Akathisia Rating Scale (BARS).[8]

Although cerebellar function tests were normal, akathisia was accompanied by minimal imbalance and extrapyramidal type dysarthria. His cranial nerves and peripheral nervous system were intact. Deep tendon reflexes were normal, and the Babinski reflexes were negative. The patient's vital signs

were normal, and there were no complaints of a headache, fever, impaired vision, or mental illness. He has never taken any medicine that has the potential to cause akathisia.

He had diabetes mellitus (DM), hypertension and uremia had received regular hemodialysis 3 times per week. There was no history of psychiatric or neurological illness in the family, including Huntington's disease.

Blood urea nitrogen (BUN:21.9 mg/dl) and creatinine (6.05 mg/dl) levels were high in the blood chemistry examination, but all other values were within reference limits. His blood glucose level was 120 mg/dl.Bilateral basal ganglia lesions were hyperintense on FLAIR-T2 weighted images according to brain MRI (Figure 1).

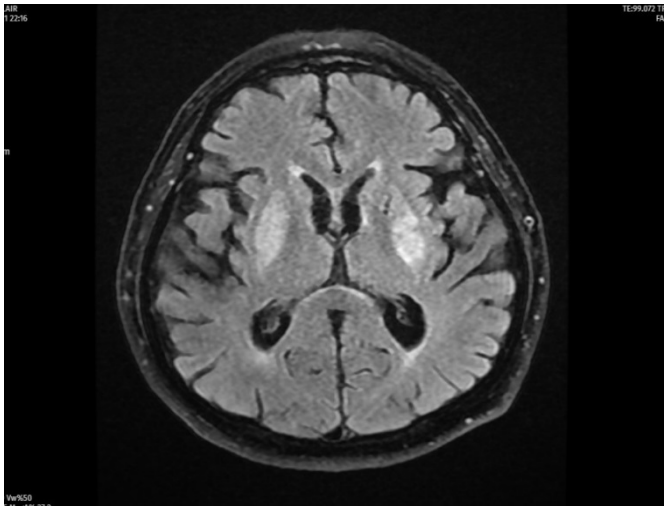

Figure 1. FLAIR image shows increased signal intensity in both basal ganglia lesions (white arrows indicate lesions).

He was not given any specific medication aside from hemodialysis. Hemodialysis was used more frequently. His irritability gradually improved in five days .One month following the initial MRI, a follow-up MRI of the brain was done, which revealed full remission of the basal ganglial abnormalities bilaterally (Figure 2). His neurological exam was normal.

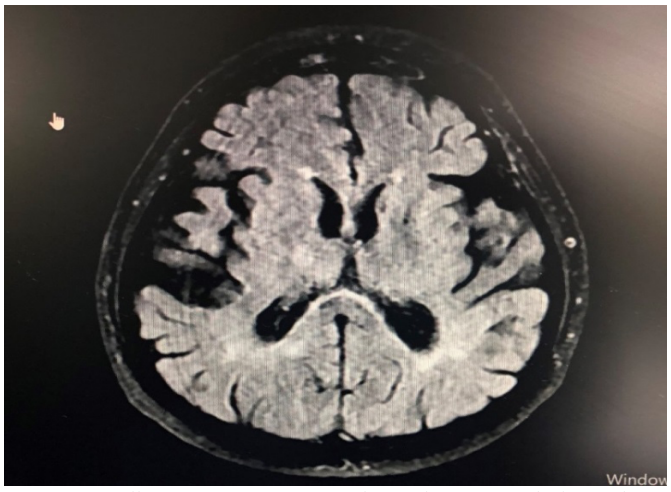

Figure 2. Follow-up FLAIR image obtained one month later shows significant regression of the lesions.

DISCUSSION

Acute movement disorders associated with bilateral lesions are increasingly described in patients affected by diabetes and uremia, it was first described by Wang et al.[3] The syndrome's most prevalent clinical symptoms are parkinsonism, gait abnormalities, dysarthria, and bradykinesia.[3,4,6] In our case the patient had akathisia.

The exact etiology of this condition is uncertain, and different researchers have suggested different theories. Uremic toxins, metabolic acidosis, and diabetic microangiopathy are only a few of the reasons that have been linked to it.[9]

Lee et al.[4] revealed the vasogenic origin of bilateral basal ganglia oedema, attributed it to localized hyperemia caused by abnormal small artery dilation, in 2006. Furthermore, they have demonstrated that diffusion-weighted imaging (DWI) may reveal tiny areas of cytotoxic oedema within confluent lesions of vasogenic oedema. Some areas of the basal ganglia lesions may undergo irreversible cytotoxic damage.

Furthermore, sympathetic dysautonomia, cerebrovascular reactivity impairment, and endothelial dysfunction in cerebral arteries may arise in people with long-standing diabetes. Hyperglycemia impairs endothelium-dependent vasoreactivity of cerebral arterioles, causes localized damaging endothelial lesions, leads to blood–brain barrier collapse, and increases free radical release.[10,11]

As a result, the cellular activity of the basal ganglia in these diabetic uremic individuals had already been impaired by long-term diabetes mellitus, either through microangiopathic alterations or energy usage failure. Furthermore, when the basal ganglia were exposed to significantly higher levels of uremic or metabolic toxins, regional cellular metabolism may have been disrupted, or a functional disturbance in smooth muscle cells of the vessels of the basal ganglia may have been induced, leading to vascular autoregulatory dysfunction and, ultimately, vasodilatation and focal hyperaemia.[2,4,12,13] Significant changes in cell metabolism and the collapse of vasogenic autoregulation occur as a result of this prolonged metabolic and toxic stress, resulting in tissue damage and oedema. Movement abnormalities are caused by alterations in physiological processes.[3]

In our patient rather than hyperglycemia, the most evident metabolic abnormality was significantly increased blood urea nitrogen and creatinine levels. The basal ganglia are especially vulnerable to a wide range of toxins and metabolic abnormalities. The acute exposure of the basal ganglia to uremic toxins was most likely caused by the worsening of the renal condition.[2-5] In our case, applying this hypothesis implies tissue oedema including the bilateral basal ganglia, and therefore full resolution with no lasting alterations. After increasing the number of hemodialysis treatments, our patient's neurological problems were completely resolved within 5 days. A month follow-up MRI revealed that the bilateral basal ganglia lesions had completely resolved.

The clinical result differs depending on the case series. According to a study of the literature, clinical abnormalities

may be resolved completely in one-fifth of the cases, partially in half of the cases, and not at all in 30% of the instances.[14] In over 90% of the instances, the radiologically detected abnormalities are resolved.[14,15]

Both basal ganglia are involved in many other disorders at the same time, including vascular abnormalities, toxic agent ingestion or inhalation, metabolic diseases, neurodegenerative diseases, demyelination, haemorrhage, infectious encephalitis, developmental anomalies, and neoplastic disease.[16-18] Our patients clinical symptoms, were not indicative of any of these diseases.

Acute akathisia is most common with neuroleptic and antidepressant therapy.[7] Akathisia is a disorder characterized by extreme restlessness. It consists mostly of two parts: i) a sensory component that includes feelings of inner restlessness, a desire to move, distress, and ii) a motor component, expressed as sensation-induced motions.[19]

Akathisia is diagnosed only on the basis of clinical observation and patient description because no confirming blood test, imaging examination, or neurophysiological investigation is available. The BARS, a 4-item scale in which the subjective and objective components of the disease are scored individually, then combined, is the most often used instrument for assessment.[8]

A movement disorder is the objective symptom of akathisia. When the condition is mild to moderate, the lower extremities are frequently the first to be affected. From the hips to the ankles, the motions are in the shape of standing in different postures and swaying or moving while sitting, the feet around. The fact that akathisia is more likely to affect the lower extremities than other antipsychotic-induced side effects that affect other body regions is sometimes useful in distinguishing it from other antipsychotic-induced side effects that affect other body regions. Although it is usually thought of as a sort of movement disorder or extrapyramidal system (EPS), akathisia is more of a sensorimotor disorder due to the strong sensory component that is a distinguishing feature of the illness. In reality, the sensory component might be the main issue, with motor indications emerging as a result of the restlessness and urge to move.[19]

Our patient have severe body restlessness, irritability, sleeplessness. And he said readily eased by altering posture or moving a limb. His motor symptoms were a result of his restlessness and need to move.

Although the etiology of akathisisa is unknown, positron emission tomography (PET) investigations have indicated that D2 (dopamine) receptor blockage in the striatum may play a significant role, and noradrenergic and serotonergic systems appear to be implicated.[5,7]

There appears to be dopamine receptor blockage in the mesocortical dopamine pathway as well the motor effect is inhibited by the mesocortical circuit. This pathway's postsynaptic blockage is considered to be the cause of akathisia.[20] Uremic toxins affect basal ganglia metabolism, including dopamine turnover. This might be aided by uncontrolled hyperglycemia. Akathisia might be caused by impaired dopamine turnover and increased sensitivity of postsynaptic dopamine receptors.[7,20] In literature there is only one case reported akathisia secondary to uremia.[21]

CONCLUSION

We provide a very uncommon case, it is the second case of reversible acute symmetrical basal ganglial lesions detected on MRI, which were linked to diabetic uremia and characterized as acute onset of akathisia. Our aim is to raise awareness of this disease among clinicians and radiologists so that more instances may be identified.

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.

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