CLINICAL NEUROSCIENCE

76. ÉVFOLYAM 11–12. SZÁM • 2023. november 30.

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OFFICIAL JOURNAL
of the
Hungarian Neurological Society,
Hungarian Neurosurgical Society,
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HIVATALOS LAPJA

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Ideggyógyászati Szemle/Clinical Neuroscience
havonta megjelenő szakfolyóirat
Impakt faktor: 0,8 (2022)
ISSN 0019-1442
Mailing address • A szerkesztőség postacíme
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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Is there any difference in mortality rates of atrial fibrillation detected before or after ischemic stroke?

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| | English | https://doi.org/10.18071/isz.76.0365 | www.elitmed.hu

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Érkezett:
2023. július 1.
Elfogadva:
2023. szeptember 17.

Background and purpose – Atrial fibrillation diagnosed after stroke (AFDAS) is a new term used for AF resulting from autonomic dysregulation. It is associated with a lower stroke recurrence compared to patients with known AF before a stroke (KAF). The aim of the study was to explore the characteristics and mortality rates in AFDAS patients.
Methods – 134 ischemic stroke patients (66.1±14.2 years old, n=73 male) were consecutively included in the study. While patients who had known AF with anticoagulant therapy were grouped as KAF, patients with newly documented AF rhythm (either by daily ECG or ambulatory ECG monitoring) were classified as AFDAS. All patients were followed for 1 year to obtain all-cause mortality, cardiac mortality, and neurogenic mortality.
Results – Of the 134 stroke patients, AF was detected newly in 38 patients and grouped as AFDAS. KAF patients had higher CHA_2DS_2VASc scores, hs-CRP and NT-proBNP levels, and more insular cortex involvement than the SR group. During the one-year follow-up, 35 stroke patients died. The mortality rate was significantly higher in patients with KAF (12/22; 54.5%) while the mortality rates were similar between AFDAS patients (11/38; 28.9%) and patients with sinus rhythm (SR) (12/74; 16.2%). KAF was an independent predictor when adjusted by

Van-e különbség az ischaemiás stroke előtt vagy után észlelt pitvarfibrilláció halálozási arányában?

Ileri C, MD; Dogan Z, MD; Ozben B, Prof. MD; Midi I, Prof. MD; Pazarci N, Assoc. Prof. MD

Háttér és cél – A stroke után diagnosztizált pitvarfibrilláció (AFDAS) egy új terminus, amit a vegetatív diszregulációból eredő pitvarfibrillációra használnak. Ez alacsonyabb stroke-recidívával jár a már a stroke előtt ismert AF-hez (KAF) képest. A vizsgálat célja az AFDAS-betegek jellemzőinek és halálozási arányának feltárása volt.
Módszerek – 134 ischaemiás stroke-beteget (66,1 ± 14,2 éves, n = 73 férfi) vontunk be a vizsgálatba. Míg az antikoaguláns-terápián lévő, ismerten AF-ben szenvedő betegeket a KAF-csoportba soroltuk, az újonnan dokumentált (akár napi EKG-val, akár ambuláns EKG-monitorozással) AF-ritmusú betegeket AFDAS-nak minősítettük. Minden beteget 1 éven keresztül követtünk a bármilyen okból bekövetkező halálozás, a cardialis, valamint a neurogén halálozás megállapítása céljából.
Eredmények – A 134 stroke-beteg közül 38 betegnél észleltek újonnan AF-et, és AFDAS-nak minősítették őket. A KAF-betegeknél magasabb volt a CHA_2DS_2VASc-pontszám, a hs-CRP- és NT-proBNP-szint, és nagyobb volt az insularis kéreg érintettsége, mint az SR-csoportban. Az egyéves követés során 35 stroke-beteg halt meg. A KAF-betegeknél szignifikánsan magasabb volt a mortalitás (12/22; 54,5%), míg hasonló volt a mortalitás az AFDAS-betegek (11/38; 28,9%) és a sinusritmusú (SR) betegek (12/74; 16,2%) között. A KAF független prediktor volt, ha az életkor,

age, sex, CHA_2DS_2VASc and NIHSS scores, and insular cortex involvement. While AFDAS had increased the mortality risk compared to SR, the difference was not significant in univariable and multivariable models.
Conclusion – AFDAS patients have similar CHA_2DS_2VASc scores and mortality rates to patients with SR, which implies that AFDAS might be a relatively benign form of AF.

Keywords: ischemic stroke, atrial fibrillation, atrial fibrillation diagnosed after stroke, AFDAS

a nem, a CHA_2DS_2VASc- és NIHSS-pontszámok, valamint az insularis kéreg érintettsége alapján korrigálták. Bár AFDAS esetén nőtt a halálozási kockázat az SR-hez képest, a különbség nem volt szignifikáns az egyváltozós és a többváltozós modellekben.
Következtetés – Az AFDAS-betegek CHA_2DS_2VASc-pontszámai és halálozási aránya hasonló az SR-betegekéhez, ami arra utal, hogy az AFDAS az AF viszonylag jóindulatú formája lehet.

Kulcsszavak: ischaemiás stroke, pitvarfibrilláció, stroke után diagnosztizált pitvarfibrilláció, AFDAS

A stroke may be the first presentation of atrial fibrillation (AF). Approximately one-fourth of ischemic stroke patients are newly diagnosed with AF[1]. The term, AF diagnosed after stroke (AFDAS) is used for both previously undetected, asymptomatic AF and poststroke AF[2].

In acute ischemic stroke, structural brain lesions, especially those with cortical involvement, may lead to autonomic dysregulation and inflammation[3]. Although the pathophysiology has not been defined clearly, autonomic dysfunction and inflammation may play a role in the development of AF by lowering the cardiac arrhythmogenic threshold[4]. AF has been detected in more than half of the cases within 3 days after admission for ischemic stroke[5]. The mean time of AF diagnosis has ranged between 3 to 77 days after stroke. Meanwhile, AF detected earlier after the stroke has been suggested to be the consequence of the stroke, not the cause of the stroke[2].

AFDAS patients are believed to have a more benign disease profile compared to patients with known AF (KAF). In a meta-analysis, it has been shown that AFDAS patients have a better vascular profile and lower comorbidities such as hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, and previous stroke[4]. The duration of AF periods diagnosed after stroke is less than 30 seconds in approximately half of the patients, which implies that AF burden is lower in AFDAS patients[6]. Moreover, the ischemic recurrence of AFDAS is shown to be less, compared to patients with KAF before stroke[7].

The aim of our study was to investigate the characteristics and mortality differences of the patients with strokes that preceded or occurred after the diagnosis of AF.

Methods

The investigation conformed to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent. The study was approved by the ethics committee of Marmara University School of Medicine.

Study population

One hundred and thirty-four patients presenting with acute ischemic stroke documented by cranial imaging were consecutively included in the study. The TOAST classification system was used to define the stroke subtypes[8]. National Institutes of Health Stroke Scale (NIHSS) scores of patients were noted at the time of hospitalization. Patients with transient ischemic attacks (TIA) were not included in our study.

Patients were evaluated for the presence of comorbidities, including hypertension, hyperlipidemia, diabetes, and coronary artery disease. Blood samples for high sensitive (hs) C-reactive protein (CRP), hs-cardiac troponin I (hs-cTnI), and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were noted. All patients underwent a transthoracic echocardiographic study by a Philips Epic echocardiography device (Philips Medical Systems, Andover, MA, USA) by an experienced cardiologist within the first three days following acute ischemic stroke. Conventional echocardiographic measurements were performed by the recommendations of the American Society of Echocardiography guidelines[9]. LVEF was assessed by biplane Simpson's method.

Electrocardiography (ECG) was obtained from each patient daily. Ambulatory ECG monitoring was performed in patients with sinus rhythm (SR) to explore

AF or other arrhythmias within the first seven days following acute ischemic stroke. The ECG recordings were analyzed by an experienced cardiologist. Patients who had newly documented AF rhythm lasting more than 30 seconds in ambulatory ECG monitoring or daily 12-lead ECG were classified as AFDAS, while patients who had known AF with anticoagulant therapy were grouped as KAF based on patient-reported medical history and prior available medical records. AFs that were detected at the time of hospitalization that had not been diagnosed and treated before this ischemic stroke event, and that also occurred during the hospitalization period were also categorized as AFDAS.

Cranial images of the patients were re-evaluated by experienced neurologists who were blind to patients' characteristics to determine whether there was an insular cortex involvement.

All patients were followed for 1 year to obtain all-cause mortality, cardiac mortality and neurogenic mortality.

Statistical analysis

Statistical analyses were performed by statistical software (SPSS 21.0 for windows, Chicago, IL). The distribution of data was assessed by using one-sample Kolmogorov–Smirnov test. Continuous data were expressed as mean ± SD while categorical data were expressed as numbers or percentages. Chi-squared test was used for the comparison of categorical variables. Student's t-test or ANOVA was used to compare the normally distributed continuous variables while the Mann-Whitney U test or Kruskal-Wallis test was used to compare the non-parametric continuous variables. Post hoc analyses were performed using the Bonferroni test when an overall statistical significance was determined. Logistic regression analysis was performed to explore the predictors of all-cause mortality. Statistical significance was accepted as a P-value less than 0.05.

Results

One hundred and thirty-four consecutive ischemic stroke patients (66.1 ± 14.2 years old, n=73 male) were included in the study. Twenty-two patients (16.4%) had KAF while AF was detected newly in 38 patients (28.4%), who were grouped as AFDAS. The remaining 74 patients (55.2%) had SR. The general characteristics of the patients according to cardiac rhythm are shown in **Table 1**. Patients with KAF and AFDAS were significantly older compared to the patients with SR, while there was no significant difference in age between KAF and AFDAS patients. KAF patients had higher CHA_2DS_2VASc scores and more insular cortex involvement than the SR group, while CHA_2DS_2VASc scores and insular cortex involvement were similar between AFDAS and SR patients. There were no significant differences in the comorbidities and NIHSS scores among patients. Stroke patients with KAF and AFDAS were using beta-blockers more than SR patients.

The laboratory and conventional echocardiographic parameters of the patients are listed in **Table 2**. hs-cTnI was elevated in all groups while the SR group had the highest mean. hs-CRP levels were higher in KAF patients compared to patients with SR. While AFDAS patients had also higher hs-CRP levels than patients with SR,

Table 1. *The characteristics of the patients*

	KAF (n = 22)	AFDAS (n = 38)	SR (n = 74)	P
Age (years)	75.2 ± 9.3*	71.6 ± 14.7*	60.6 ± 12.6	*<0.001*
Male sex (n – %)	12 (54.5%)	18 (47.4%)	43 (58.1%)	0.558
Body mass index (kg/m^2)	26.5 ± 5.7	26.6 ± 3.9	26.8 ± 4.5	0.970
CHA_2DS_2VASc	4.5 ± 1.8*	4.0 ± 1.9	3.2 ± 1.9	*0.013*
NIHSS	6.4 ± 3.9	6.1 ± 4.0	5.3 ± 4.0	0.454
Hypertension (n – %)	17 (77.3%)	29 (76.3%)	50 (67.6%)	0.507
Diabetes (n – %)	9 (40.9%)	14 (36.8%)	32 (43.2%)	0.808
Hyperlipidemia (n – %)	19 (86.4%)	27 (71.1%)	56 (75.7%)	0.404
Coronary artery disease (n – %)	9 (40.9%)	8 (21.1%)	23 (31.1%)	0.254
Insular cortex involvement (n – %)	11 (50.0)*	12 (31.6)	14 (18.9)	*0.013*
Beta-blocker usage (n – %)	10 (45.5)*	18 (47.4)*	15 (20.3)	*0.005*

KAF: known atrial fibrillation, AFDAS: atrial fibrillation diagnosed after stroke, SR: sinus rhythm, NIHSS: National Institutes of Health Stroke Scale
PostHoc analysis: * denotes statistical significance versus patients with sinus rhythm

Table 2. *The laboratory parameters and conventional transthoracic echocardiographic measures of the patients*

	KAF (n = 22)	AFDAS (n = 38)	SR (n = 74)	P
Glucose (mg/dL)	108 ± 51*	121 ± 57	135 ± 53	*0.023*
Creatinine (mg/dL)	1.18 ± 0.65	0.94 ± 0.34	0.94 ± 0.46	0.364
Total cholesterol	176 ± 43+	211 ± 52	197 ± 45	*0.042*
LDL cholesterol (mg/dL)	109 ± 37+	142 ± 45*	122 ± 37	*0.017*
hs-cTnI (ng/mL)	0.08 ± 0.16*	0.09 ± 0.24*	0.11 ± 0.47	*0.005*
hs-CRP (mg/L)	41.4 ± 48.2*	27.1 ± 37.7	12.4 ± 17.6	*0.004*
NT-proBNP (pg/mL)	7298 ± 10282*	2548 ± 6200	1241 ± 4750	*<0.001*
Left atrium (mm)	45.3 ± 7.1*,+	40.9 ± 7.7*	36.2 ± 5.1	*<0.001*
LAVI (mL/m^2)	39.2 ± 16.4*,+	29.3 ± 11.5*	20.9 ± 8.3	*<0.001*
LVEF (%)	54 ± 15	56 ± 11	59 ± 9	0.174
E/e'	11.6 ± 5.1*	9.7 ± 4.1	8.3 ± 3.1	*0.012*

KAF: known atrial fibrillation, AFDAS: atrial fibrillation diagnosed after stroke, SR: sinus rhythm, LDL: Low-density lipoprotein, hs-cTnI: High-sensitive cardiac Troponin I, hs-CRP: High-sensitive C-reactive protein, NT-proBNP: N terminal pro-brain natriuretic peptide, LAVI: Left atrial volume index, LVEF: left ventricular ejection fraction, E/e': the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity
PostHoc analysis: * denotes statistical significance versus patients with sinus rhythm
+ denotes statistical significance versus patients with atrial fibrillation diagnosed after a stroke

the difference was not statistically significant. KAF and AFDAS patients had significantly larger left atriums compared to patients with SR. Although there were no significant differences in the left ventricular ejection fraction values of the patients, the KAF group had significantly higher NT-proBNP and E/e' compared to the SR group, while AFDAS and SR patients had similar NT-proBNP and E/e'.

During the one-year follow-up period, 35 stroke patients died (12 patients in the KAF group, 11 in the AFDAS group, and 12 in the SR group). KAF patients had significantly higher all-cause and cardiac mortality rates compared to both AFDAS patients and SR patients, while the AFDAS group had similar all-cause and cardiac mortality rates to the SR group **(Table 3)**.

Table 3. *One-year mortality rates of the patients*

	KAF (n = 22)	AFDAS (n = 38)	SR (n = 74)	p
All-cause mortality (n – %)	12 (54.5%)+,*	11 (28.9%)	12 (16.2%)	*0.001*
Neurogenic mortality (n – %)	1 (4.5%)	5 (13.2%)	5 (6.8%)	0.400
Cardiac mortality (n – %)	11 (50.0%)+,*	6 (15.8%)	7 (9.5%)	*<0.001*

KAF: known atrial fibrillation, AFDAS: atrial fibrillation diagnosed after stroke, SR: sinus rhythm
PostHoc analysis: * denotes statistical significance versus patients with sinus rhythm
+ denotes statistical significance versus patients with atrial fibrillation diagnosed after a stroke

The characteristics, laboratory parameters, and conventional transthoracic echocardiographic measures of stroke patients according to mortality status are shown in **Table 4**. These patients were older, had higher CHA_2DS_2VASc and NIHSS scores, hs-cTnI, and hs-CRP levels, with more insular cortex involvement, and larger left atrium.

Univariable and multivariable logistic regression analyses were modeled to explore the predictors of all-cause of mortality **(Table 5)**. Logistic regression analysis revealed KAF as an independent predictor when adjusted by age, sex, CHA_2DS_2VASc and NIHSS scores, and insular cortex involvement. While AFDAS increased the mortality risk compared to SR, the differences were not significant in univariable and multivariable models.

Discussion

In our study, we explored the characteristics and mortality differences between KAF and AFDAS patients. We found that while both AFDAS and KAF patients were significantly older than the patients with SR, CHA_2DS_2VASc scores, insular cortex involvement, NIHSS scores, and comorbidities were similar between AFDAS and SR

Table 4. *The characteristics of the patients according to all-cause mortality*

	Deceased (n = 35)	Surviving (n = 99)	p
Age (years)	70.7 ± 10.9	64.5 ± 14.8	*0.026*
Male sex (n – %)	19 (54.3%)	54 (54.5%)	0.979
CHA_2DS_2VASc	4.4 ± 1.7	3.4 ± 2	*0.007*
NIHSS	6.6 ± 3.4	5.4 ± 4.1	*0.040*
Hypertension (n – %)	29 (82.9%)	67 (67.7%)	0.087
Diabetes (n – %)	18 (51.4%)	37 (37.4%)	0.146
Coronary artery disease (n – %)	15 (42.9%)	25 (25.3%)	0.050
Insular cortex involvement (n – %)	15 (42.9)	22 (22.2)	*0.019*
hs-cTnI (ng/mL)	0.19 ± 0.45	0.08 ± 0.36	*<0.001*
hs-CRP (mg/L)	34.0 ± 41.4	16.8 ± 27.1	*0.008*
LAVI (mL/m^2)	30.9 ± 15.4	24.5 ±11.1	*0.016*
LVEF (%)	57 ± 12	57 ± 10	0.880
KAF (n – %) AFDAS (n – %) SR (n – %)	12 (34.3) 11 (31.4) 12 (34.3)	10 (10.1) 27 (27.3) 62 (62.6)	*0.001*

NIHSS: National Institutes of Health Stroke Scale, hs-cTnI: High-sensitive cardiac Troponin I, hs-CRP: High-sensitive C-reactive protein, LAVI: Left atrial volume index, LVEF: left ventricular ejection fraction, KAF: known atrial fibrillation, AFDAS: atrial fibrillation diagnosed after stroke, SR: sinus rhythm

patients. Interestingly, only KAF was associated with mortality in both univariable and multivariable analysis, while AFDAS patients had similar mortality rates to SR patients.

Cardiovascular diseases are more common in both ischemic stroke and AF. However, cardiovascular disease and mortality rates are not the same in every AF patient. Underlying cardiovascular diseases and one-year composite cardiovascular outcomes were observed to be higher in KAF patients than in AFDAS patients, but KAF was not found to be an independent predictor of outcomes[10]. Since comorbidities and structural heart disease are noted less in AFDAS patients, it is believed to be triggered by neurogenic mechanisms developed after stroke[3, 11]. Major factors such as autonomic dysfunction, increased catecholamine discharge, neurogenic cardiac injury, and systemic inflammation leading to atrial electrical and structural remodeling after acute stroke may facilitate the occurrence and maintenance of AF[2]. In our study, coronary artery disease and other comorbidities such as hypertension, diabetes, and hyperlipidemia were found to be similar among groups.

There are conflicting results in the literature regarding the outcome of AFDAS. For example, in a study with 5-year follow-up of stroke patients, the highest annual mortality was found in patients with newly diagnosed AF within the first 6 months after stroke[12]. Also, *Yang XM* et al showed that AFDAS patients had similar stroke recurrence and mortality rates when compared to KAF but higher than SR[13]. In our study, mortality in the AFDAS group was found to be similar to sinus rhythm patients, which may be due to the more benign vascular profile of AFDAS as we predicted. In addition, little is known about the pathophysiology of AFDAS, but in recent studies, it is thought to have two subgroups, neurogenic and cardiogenic[14]. The cardiogenic AFDAS group with preexisting but newly diagnosed AF after stroke has atrial cardiopathy and structural heart disease[15]. In addition, in the neurogenic AFDAS group without structural heart disease, AF is thought to be triggered entirely by autonomic and inflammatory mechanisms[14]. The heterogeneity of AFDAS may explain the difference in outcome between studies.

Although it has not been revealed yet, it is hypothesized that large brain infarcts seen in moderate and severe strokes cause more autonomic dysregulation and inflammation and therefore cause more AFDAS[11, 15, 16]. We measured stroke severity, which correlates with infarct size, but we couldn't find any difference in NIHSS scores among the groups in our study. Studies about AFDAS showed a particularly remarkable involvement of the insular cortex, which plays a role in the regulation of the autonomic nervous system[3, 11]. Although there are conflicting reports on which of the right and left hemisphere

Table 5. *Univariable and multivariable logistic regression analysis showing the predictors of all-cause mortality*

	Odds Ratio	95% Confidence Interval	p
Univariable			
AFDAS versus SR	2.105	0.827 – 5.360	0.119
KAF versus SR	6.200	2.186 – 17.581	0.001
Multivariable Models			
Model 1			
AFDAS versus SR	1.755	0.637 – 4.833	0.277
KAF versus SR	4.484	1.427 – 14.089	*0.010*
Age	1.018	0.984 – 1.053	0.314
Male sex	1.073	0.469 – 2.457	0.868
Model 2			
AFDAS versus SR	1.847	0.662 – 5.156	0.241
KAF versus SR	4.518	1.406 – 14.515	*0.011*
Age	1.000	0.960 – 1.041	0.996
Male sex	1.218	0.521 – 2.843	0.649
CHA_2DS_2VASc	1.262	0.971 – 1.641	0.081
Model 3			
AFDAS versus SR	1.825	0.649 – 5.132	0.254
KAF versus SR	4.703	1.471 – 15.037	*0.009*
Age	1.019	0.984 – 1.055	0.295
Male sex	1.018	0.438 – 2.368	0.966
NIHSS	1.052	0.949 – 1.167	0.337
Model 4			
AFDAS versus SR	1.670	0.600 – 4.647	0.326
KAF versus SR	3.791	1.172 – 12.264	*0.026*
Age	1.015	0.980 – 1.050	0.405
Male sex	1.151	0.496 – 2.669	0.744
Insular cortex involvement	2.020	0.828 – 4.928	0.122
Model 5			
AFDAS versus SR	1.839	0.641 – 5.278	0.257
KAF versus SR	3.995	1.187 – 13.451	*0.025*
Age	0.998	0.957 – 1.041	0.926
Male sex	1.219	0.509 – 2.920	0.657
CHA_2DS_2VASc	1.264	0.962 – 1.662	0.093
NIHSS	1.021	0.916 – 1.138	0.708
Insular cortex involvement	2.129	0.822 – 5.514	0.120

KAF: known atrial fibrillation, AFDAS: atrial fibrillation diagnosed after stroke, SR: sinus rhythm, NIHSS: National Institutes of Health Stroke Scale

involvement increases sympathetic activity, increasing numbers of studies show that in insular cortex involvement the heart rate variability decrease and the risk of AF increase significantly[11, 17–19]. In our study, significantly higher insular cortex involvement was found in KAF patients while there was no difference between AFDAS and SR groups in terms of insular cortex involvement.

In addition, autonomic dysfunction is thought to cause not only post-stroke AF but also myocardial injury: so-called neurogenic myocardial stunning (NSM)[20]. There are opinions that myocardial damage presenting with troponin elevation after stroke may be a predictor of AF[21]. In our study, hs-cTnI was found to be high in all groups, while the SR group had the highest mean and EF values were similar between groups. Since NSM is a reversible myocardial damage diagnosed with reduced EF, regional wall motion abnormality, ECG changes, and high troponin values, it is not possible to make a conclusion based on the data available in our study[22, 23].

Approximately half of the ischemic strokes detected in the Penn Atrial Fibrillation Free study (PAFF) were detected within 6 months period before the diagnosis of AF. Most strokes occur on the day of diagnosis of AF and within the next 7 days[24]. In our study, approximately one-third of the patients were diagnosed with AFDAS, similarly in the first week. These patients had similar CHA_2DS_2VASc scores to patients with SR. However, the CHA_2DS_2VASc scores of KAF patients were higher than in the SR group. In another study investigating new AF with prolonged ECG monitoring more than one week after stroke, NIHSS and CHA_2DS_2VASc scores were found to be similar in groups with a previous diagnosis of AF and newly diagnosed AF[25]. It may be important on which day the diagnosis of AF is made after the stroke.

Limitations

First, a small sample size and a relatively short follow-up period are limitations of our study. Second, it has recently been revealed that AFDAS is a heterogeneous group and includes two different clinical entities as cardiogenic and neurogenic AFDAS. Due to the small number of AFDAS patients, we could not investigate the differences between these subgroups. Third, we excluded TIA because it was diagnosed with a subjective neurological evaluation, which might cause misdiagnosis of AFDAS. Fourth, AF might be underestimated as the patients did not undergo prolonged ambulatory ECG monitoring.

Conclusion

In summary, AFDAS patients were older but had similar insular cortex involvement, CHA_2DS_2VASc, and NIHSS

score to SR patients; the insular cortex involvement and CHA_2DS_2VASc score were higher in the KAF group than in SR patients; AFDAS patients had similar mortality rates to SR patients; KAF patients had increased mortality compared to SR patients; mortality of the KAF group was independent of age, sex, insular cortex involvement, CHA_2DS_2VASc, and NIHSS scores.

AFDAS patients have similar CHA_2DS_2VASc scores and mortality rates to patients with sinus rhythm, which supports the hypothesis that AFDAS might be a relatively benign form of AF. However, having a KAF diagnosis before an ischemic stroke is an independent predictor of all-cause mortality.

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CONFLICT OF INTEREST – The authors declare that they have no conflict of interest.

The study was presented as a poster presentation at the European Society of Cardiology Heart&Stroke Congress 2022 in Budapest and won the ‘Best Poster Prize’.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Changes in the hippocampal volume in chronic migraine, episodic migraine, and medication overuse headache patients

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| English | https://doi.org/10.18071/isz.76.0373 | www.elitmed.hu

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Érkezett:
2022. január 12.
Elfogadva:
2023. május 5.

Background and purpose – Hippocampi are the structures located in the medial depths of both temporal lobes, mainly responsible for memory, navigation and regulation of emotions, and activated during the processing of pain and the modification of nociceptive stimuli. Chronic pain is thought to have stress-like detrimental modulatory effects on the hippocampal neurogenesis, and adults with chronic pain have been showed to have lower hippocampal volumes. The present study aims to show the relationship between headaches and hippocampal volume by comparing the right, left and total hippocampal volumes of patients with Episodic Migraine (EM), Chronic Migraine (CM) and Medication Overuse Headache (MOH) to those of the healthy control group using the Magnetic Resonance Imaging (MRI) technique, also by looking into the correlation between the number of painful days and attacks and the current hippocampal volumes.

Methods – A total of 30 patients (10 EM, 10 CM, 10 MOH) from 18 to 45 years of age diagnosed with migraine and also followed up by the neurology outpatient clinic from February to May 2022 and 30 healthy volunteers of similar ages and sexes to the patient group were included in the study. In addition to the routine cranial MRI protocols of all the participants, further cranial images were taken with the addition of the T1W 3D FSPGR sequence adjusted to the hippocampal body in the coronal plane and covering the whole brain. Hippocampal volumes were measured manually.

A hippocampus-térfogat változásai krónikus migrénben, epizodikus migrénben és gyógyszer-túlhasználat miatti fejfájásban

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Háttér és cél – A hippocampusok a két halántéklebeny medialis mélyén elhelyezkedő struktúrák, amelyek elsősorban a memóriáért, a navigációért és az érzelmek szabályozásáért felelősek, és a fájdalom feldolgozása, valamint a nociceptiv ingerületek módosítása során aktiválódnak. A krónikus fájdalomról úgy gondolják, hogy stressz-szerű káros moduláló hatással van a hippocampalis neurogenezisre, és a krónikus fájdalomban szenvedő felnőtteknél kimutatták, hogy kisebb a hippocampalis térfogatuk. Jelen tanulmány célja, hogy bemutassa a fejfájás és a hippocampus térfogata közötti összefüggést az epizodikus migrénben (EM), krónikus migrénben (CM) és gyógyszer-túlhasználat okozta fejfájásban (MOH) szenvedő betegek jobb, bal és teljes hippocampalis térfogatának az egészséges kontrollcsoport hippocampalis térfogatainak összehasonlítása révén mágneses rezonancia képalkotó (MRI) technika segítségével, továbbá a fájdalmas napok, valamint a rohamok száma és az aktuális hippocampalis térfogat közötti összefüggés vizsgálatával.

Módszerek – A vizsgálatba összesen 30, 18 és 45 éves kor közötti, migrénnel diagnosztizált és a neurológiai ambulancián 2022 februárjától májusáig követett beteget (10 EM, 10 CM, 10 MOH), valamint 30, a betegcsoporthoz hasonló korú és nemű egészséges önkéntest vontunk be. Az összes résztvevő rutin koponya-MRI-protokolljain kívül további koponyafelvételeket készítettünk a hippocampus testéhez igazított T1W 3D FSPGR szekvenciával kiegészítve a coronalis síkban, az egész agyat lefedve. A hippocampus térfogatát manuálisan mértük.

Results – There were 27 females and 3 males in the patient group versus 28 females and 2 males in the control group, and no statistically significant differences in age and sex were found between the groups. The control group had higher average right, left and total hippocampal volumes than the whole patient group, but only the total hippocampal volume was significantly different between the groups. There was a negative correlation between the number of painful days and the measured right hippocampal and total hippocampal volumes; however, the measured values were not statistically significant.
Conclusion – It was concluded that the changes in the hippocampal volume in migraine might be associated with the pain characteristics of the disorder.

Keywords: episodic migraine, chronic migraine, medication overuse headache, hippocampus

Eredmények – A betegcsoportban 27 nő és három férfi volt, míg a kontrollcsoportban 28 nő és két férfi. A csoportok között nem volt statisztikailag szignifikáns különbség sem az életkor, sem a nem tekintetében. A kontrollcsoportban az átlagos jobb, bal és teljes hippocampus-térfogatok nagyobbak voltak, mint a teljes betegcsoporté, de csak a teljes hippocampus-térfogat különbözött szignifikánsan a kontroll- és a betegcsoport között. Negatív korreláció volt a fájdalmas napok száma és a jobb, valamint a teljes hippocampus-térfogatok között; a mért értékek azonban statisztikailag nem voltak szignifikánsak.
Következtetés – Arra a következtetésre jutottunk, hogy a hippocampus térfogatának változása migrénben összefügghet a betegség fájdalomjellemzőivel.

Kulcsszavak: epizodikus migrén, krónikus migrén, gyógyszer-túlhasználat okozta fejfájás, hippocampus

Hippocampi are the structures located in the medial depths of both temporal lobes and are mainly responsible for memory, navigation, and regulation of emotions. Hippocampus, together with the amygdala, the prefrontal cortex and the cingulate gyrus, makes up the limbic system. Furthermore, by keeping the cortisol at a certain level, the hippocampus controls the stress response triggered by the amygdala through negative feedback mechanism on the hypothalamic-pituitary-adrenal axis[1].

Animal studies have found some changes which are thought to cause post-stress loss of hippocampal volume, i.e. extensive cell shrinkage, apoptosis, loss of astrocytes, changes in the cerebrospinal fluid balance, reduced gliogenesis, and loss of neurogenesis capacity in the dentate gyrus, with dendritic debranching being the most common of them all[2].

Hippocampus is also one of the brain regions playing a key role in the modulation of pain signals; it is activated during the pain processing and the modification of nociceptive stimuli. Chronic pain affects the plasticity of the hippocampal mossy fiber-CA3 synapses and the neurogenesis in the dentate gyrus[3]. It has been shown that elderly adults having severe acute pain or chronic pain have lower hippocampal volumes and lower hippocampal N-acetylaspartate-to-creatine (NAA/Cr) ratio, which is an indicator of the loss of neuronal integrity and neurons[4]. These hippocampal changes suggest that chronic pain has stress-like detrimental modulatory effects on hippocampal neurogenesis[5]. Furthermore, it has been found that TNF-α, a proinflammatory cytokine, plays a role in neuropathic pain and is associated with the dysfunctions of the hippocampal neurogenesis. Neuropathic pain has been found to cause the development of symptoms of depression over time, and to be associated with impaired neurogenesis and also with the reduction in the expression of the neuroplasticity markers and myelin basic proteins[6].

Based on all the above data, the present study aims to show the relationship between headaches and hippocampal volume by comparing the right, left and total hippocampal volumes of the patients with Episodic Migraine (EM), Chronic Migraine (CM) and Medication Overuse Headache (MOH) to those of the healthy control group using the MRI technique, also by looking into the correlation between the number of painful days and attacks and the current hippocampal volumes.

Methods

Selection of patients

A total of 30 patients from 18 to 45 years of age diagnosed with no other neurological disorders than migraine by headache specialist and also followed up by the neu-

rology outpatient clinic from February to May 2022 were prospectively included in the study. The International Classification of Headache Disorders-3 (ICHD-3) was used for diagnoses[7]. The other group included in the study, i.e. the healthy control group, comprised 30 volunteers who presented to the neurology outpatient clinic with complaints like hypoesthesia in hands (carpal tunnel syndrome) or dizziness, had normal results from their neurological examinations with no known neurological disorders, were given cranial MRI scans, and were of similar ages to the migraine patient group. All the participants gave their informed consent for the present study.

Both for the patient and the healthy volunteer groups, individuals who were diagnosed with depression, had a history of chronic diseases such as diabetes and hypertension, chronic pain, or had malignancies, could not tolerate MRI scanning or had suboptimal MRI results due to artifacts, or could not undergo volumetric MRI were excluded from the study.

MRI protocol

The MRI scans for all the study participants were performed using General Electric's Optima™ MR450w 1.5T system. In addition to the routine cranial MRI protocols, further cranial images were taken with the addition of the T1W 3D FSPGR sequence adjusted to the hippocampal body in the coronal plane and covering the whole brain (TR/TE: 5412/1.94, flip angle: 15°, matrix: 192x256, FOV: 250 mm, number of sagittal slices: 284, slice thickness: 1 mm). Axial and sagittal multiplanar reconstructed images were acquired through coronal T1W 3D FSPGR sequence images.

The acquired MR images were evaluated using the software Volume Viewer, version 13.0 and the hippocampus was identified from the anatomical reference points[8]. The present study used 3D modelling for volumetric calculations and the hippocampal volume was measured manually by neurologist. The alveus for anterior and superior borders, the atrium of the lateral ventricle for posterior border, the white matter of the parahippocampal gyrus below the subiculum for inferior border, the cerebrospinal fluid (CSF) of the lateral ventricle for lateral border, the CSF of the cisterna ambiens for superior medial and the straight line that tracing with an angle of 45° from the most inferior part of the hippocampal body to the cisterna ambiens for inferior medial border were taken as reference points[9]. The hippocampal volume measurement unit was cm^3.

Statistical method

The software IBM SPSS™ (Version 22, New York/USA) was used for statistical analyses. Independent t-test was used to compare the migraine and non-migraine groups in terms of age, and sex. Due to the small number of subjects in the groups, the volume comparison of the right hippocampus, left hippocampus and total hippocampus was made with the One-Way ANOVA test and Bonferroni correction was applied. Within the migraine group, Spearman's correlation test was used to determine the correlation between the number of painful days in a month and the right hippocampal volume, left hippocampal volume, and total hippocampal volume. The value $p \leq 0.05$ was accepted as the measure of statistical significance.

As a result of power analysis, it was planned to work with at least 27 individuals in each group and a total of 54 people as a result of minimum 80% power and maximum 5% type error.

Results

The study group comprised 60 individuals. It was divided into the sub-groups of 30 healthy controls (50%), 10 EM patients (16.7%), 10 CM patients (16.7%), and 10 MOH patients (16.7%). The patient group consisted of 27 females and 3 males while the control group comprised 28 females and 2 males. Mean ages were 30,27±5.98 years in the control group and 33.47±7.75 years in the patient group, and there were no statistically significant differences in sex and age between the groups.

The average numbers of painful days in a month were 3.3±2.21, 16.3±1.77, and 18±2.31 for the EM, CM, and MOH groups, respectively, and the total average number of painful days in a month for 30 patients was 12.53±6.98. Across the whole patient group, the average right hippocampal volume was 2.51±0.33 cm^3, the average left hippocampal volume was 2.43±0.38 cm^3, and the total hippocampal volume was 4.93±0.67 cm^3. In the control group these volumes were 2.59±0.36, 2.51±0.36, and 5.1±0.67 cm^3, respectively, which showed that all the volumetric values of the control group were higher compared to those of both the whole patient group comprising 30 patients and the sub-groups **(Table 1)**.

The correlation analysis performed to determine the correlation between the number of painful days and the measured right, left and total hippocampal volumes revealed that there was a negative correlation between the number of painful days and the measured right hippocampal and total hippocampal volumes, which meant that the hippocampal volume decreased as the number of painful days increased; however, the measured values were not statistically significant (p=0.847, 0.496, 0.842, respectively).

When only the patient group and the control group were considered without any sub-group analysis, the control group had higher average right, left and total hip-

Table 1. *Descriptive statistics of the patient and control groups*

	Control	Episodic migraine	Chronic migraine	Medication overuse headache	Total (Patient)
	Avg. ± Std.	Avg. ± Std.	Avg. ± Std.	Avg. ± Std.	Avg. ± Std.
Number of painful days (days/month)		3.3±2.21	16.3±1.77	18±2.31	12.53±6.98
Right hippocampal volume (cm^3)	2.59±0.36	2.41±0.31	2.52±0.37	2.35±0.2	2.43±0.30
Left hippocampal volume (cm^3)	2.51±0.36	2.23±0.46	2.5±0.35	2.29±0.29	2.34±0.38
Total hippocampal volume (cm^3)	5.1±0.67	4.64±0.72	5.02±0.67	4.64±0.44	4.77±0.63

pocampal volumes than the whole patient group, and the average total hippocampal volume was found to be significantly different between the control and patient groups (p=0.05) **(Table 2)**.

The sub-group analyses further showed that there was no statistically significant difference in the right, left and total hippocampal volumes between the EM, CM, and MOH sub-groups **(Table 3)**.

Table 2. *Comparison of right, left and total hippocampal volumes of the groups*

	Control	Patient	t	p
Right hippocampal volume (cm^3)	2.59±0.356	2.43±0.297	1.876	0.066
Left hippocampal volume (cm^3)	2.51±0.359	2.34±0.377	1.803	0.077
Total hippocampal volume (cm^3)	5.10±0.672	4.77±0.63	1.964	*0.05*

Table 3. *Comparison of right. left and total hippocampal volumes of the sub-groups with One-Way ANOVA. bonferroni correction*

		N	Mean	Std. Deviation	F	p
Right hippocampal volume (cm^3)	Control	30	2.59	.36	1.628	.193
	EM	10	2.41	.31		
	CM	10	2.52	.37		
	MOH	10	2.35	.20		
Left hippocampal volume (cm^3)	Control	30	2.51	.36	2.090	.112
	EM	10	2.23	.46		
	CM	10	2.50	.35		
	MOH	10	2.29	.29		
Total hippocampal volume (cm^3)	Control	30	5.10	.67	2.063	.115
	EM	10	4.64	.72		
	CM	10	5.02	.67		
	MOH	10	4.64	.44		

Discussion

Migraine is known to be a common neurological disorder and characterized by the attacks of throbbing headaches accompanied by phonophobia, photophobia, and nausea[10]. It has conventionally been reported to be a disorder with no long-term effects on the brain. However, the recent data show that migraine increases the risk of the development of silent brain findings in the patients such as white matter lesions, ischemic lesions and volumetric changes in both gray and white matter seen in MRI. These changes have been found to progress together with an increased number of migraine attacks which represent a form of the anatomical progression of the disorder[11, 12].

Studies using the structural and functional imaging of CM have found changes in the cortex, basal ganglia, brain stem and the hypothalamus involved in pain modulation. While these changes may be associated with the severity and/or duration of headaches, it has also been suggested that they might be linked with the cognitive status, sleep pattern and/or mood of the person[13]. *Gudmundsson* et al. found that patients with migraine and depression had reduced total brain volumes, white matter and gray matter volumes compared to healthy controls and also to migraine alone or depression alone groups[14]. While the detected changes indicated the neural plasticity occurring in migraine, it could not be determined whether these changes represented the etiology or the result of the chronicity. A study by *Naguib* et al. showed that chronic migraine patients had significantly lower total brain

volumes, and thickness of gray matter, cerebellum and frontal lobe compared to episodic migraine patients[15]. On the other hand, the same study could not determine the mechanism of the reshaping of the brain in migraine; it suggested that the mechanism might be associated with the variations related to the number, size and synapses of neurons and glial cells, various interstitial fluids or blood flow, and caused by neuroinflammation, vasoconstriction or vasodilation, and neuronal degeneration.

The accumulated evidence suggests the role of a maladaptive stress response in the migraine mechanism especially in chronic migraine[16]. Although previous studies have detected the changing volume of the hippocampus time and time again, the aspects of this change are not entirely consistent. Patients experiencing 1-2 painful days a month have been shown to have higher hippocampal volumes on both right and left sides compared to patients experiencing 8-14 painful days a month and to healthy controls, and it has been determined that there is a negative correlation between the hippocampal volume and the estimated number of attacks. Another study categorizing patients into 8 different sub-groups based on the number of painful days from 1 to 30 a month found the highest hippocampal volume in the patients having 5-7 painful days[17] . These two studies suggested that the hippocampus showed an adaptive plasticity in lower frequencies of headaches and higher frequencies caused a maladaptive reduction in the hippocampal volume[16, 17]. Our study, as well, highlighted a negative correlation between the number of painful days and the right and total hippocampal volumetric values investigated without any sub-group analyses; however, the values were not statistically significant. On the other hand, our study did not find any correlation with the left hippocampal volume.

While *Hubbard* et al. found increased left hippocampal volumes in migraine patients compared to healthy controls, Chong et al. reported the opposite and could not associate the hippocampal volumes with the duration of disorder or frequency of headaches[18, 19]. Another study showed that hippocampal volumes of the healthy controls were lower than those of the EM group while higher than those of the CM group. This finding was found to be consistent with the findings of the two aforementioned cross-sectional studies suggesting an adaptive increased volume in low frequencies of headache and a maladaptive reduced volume in higher frequencies, and it also proved the necessity of comparing the migraine patients having different frequencies of headache while investigating the changes in brain circuits related to the hippocampus[20]. While our study did not find any statistically significant results from the comparison of the right, left and total hippocampal volumes of the EM and CM patients with those of the healthy controls, the volumetric values for both sub-groups were lower compared to the healthy controls with the EM subgroup having the lowest values.

The pathogenesis of MOH, which is still difficult to understand, involves central sensitization and the dysfunction of the endogenous serotonin system[21, 22]. Considering neuroimaging studies, the study by *Lai* et al. comparing the MOH patients with healthy controls showed gray matter atrophy in the gyrus rectus, inferior frontal gyrus, medial frontal gyrus, and precuneus[23]. Supporting the findings of our study, *Mehnert* et al. discovered the MOH-related gray matter atrophy in the medial orbital gyrus, hippocampus, inferior frontal gyrus, and precuneus[24]. On the other hand, several studies reported they could not find any gray matter changes in the MOH group compared to the control group[25]. In conclusion, there have been only few volumetric brain imaging studies related to the MOH so far. Our study compared the hippocampal volumes of the MOH patients with those of the healthy controls and found that the volumetric values for MOH were lower compared to the control group's values but there were no statistically significant differences.

It was though that the hippocampal volume changes in migraine might be associated with the pain characteristics of the disorder and the amount of medication used, however it was found that factors such as migraine subtype, frequency of attacks, cumulative number of migraine attacks, anxiety, and depression affected the hippocampal volume and there were inconsistent findings in the literature. Further studies would ensure a clearer determination of the relationship between the hippocampus and migraine by way of careful selection of sub-groups and eliminating the influencing factors.

Limitations

Disease duration was not included in the study because patients declared a wide range of disease duration. The number of patients in the subgroups were underpowered compared to the control group; we couldn't separate the subgroups according the type of medications like triptans or non-steroidal anti-inflammatory drugs. We also could not evaluate whether the presence or absence of aura had an effect on hippocampal volume. This study was cross-sectional; we could not comment on the effects of the preventive drugs that the patients used before or after the diagnosis, on hippocampal volume.

This study was presented as an oral presentation at the 6. MENA Meeting in November 2022.

ACKNOWLEDGEMENTS – We thank Abdullah Karaakın from Beykent University for translating this study from Turkish into English.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

The effectiveness of organic vegetable oils with high biocompatibility in preventing epidural fibrosis: An experimental study

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English | https://doi.org/10.18071/isz.76.0379 | www.elitmed.hu

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Érkezett:
2022. október 17.
Elfogadva:
2023. március 26.

Background and purpose – Epidural fibrosis after all spinal surgeries is an important surgical issue. Various biological and non-biological materials have been tried to inhibit epidural fibrosis, which is deemed to be the most important cause of pain after spinal surgery. Olive oil, nigella sativa oil and soybean oil employed in oral nutrition in clinics involving liquid fatty acids, palmatic acid, linoleic acid, stearic acid and palmitoleic acid. The effectiveness of olive oil, nigella sativa oil and soybean oil on epidural fibrosis was researched on for the first time in laminectomy model.

Methods – Fifty adult male Wistar albino rats weighing between 300 and 400 grams were used in the research. A total of 5 groups were formed: sham (Group I) (n = 10), no application was created; Group II (n = 10) 1 cc saline; Group III (n = 10) 1 cc olive oil; Group IV (n = 10) 1 cc nigella sativa oil; Group V (n = 10); 1 cc soybean oil was applied topically to the epidural region after laminectomy. The total spine of the rats was dissected, histopathological and immunochemical measurements were conducted. Neuro-histopathological results were scored semi-quantitatively in terms of vascular modification, neuron degeneration, gliosis and bleeding criteria.

Results – The lowest level of fibrosis and connective tissue proliferation was observed in the group where nigella sativa oil was used after the operation, followed by the group treated with olive oil and lastly with the group given soybean oil.

A magas biokompatibilitású szerves növényi olajok hatékonysága az epiduralis fibrosis megelőzésében: Kísérleti tanulmány

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Háttér és cél – Az epiduralis fibrosis minden gerincműtét után fontos sebészeti probléma. Különböző biológiai és nem biológiai anyagokkal próbálták gátolni az epiduralis fibrosist, amit a gerincműtétek utáni fájdalom legfontosabb okának tartanak. Az olívaolaj, a *Nigella sativa* (fekete kömény) olaj és a szójaolaj a klinikákon a táplálásban szájon át alkalmazott, palmatinsav-, linolsav-, sztearinsav- és palmitoleinsav-tartalmú folyékony zsírsavak. Az olívaolaj, a *Nigella sativa*-olaj és a szójaolaj hatékonyságát az epiduralis fibrosisra kutatócsoportunk vizsgálta először laminectomiás modellben.

Módszerek – Ötven felnőtt, 300–400 gramm közötti súlyú hím Wistar albínó patkányt használtunk a kutatásban. Összesen öt csoportot alakítottunk ki: sham (I. csoport) (n = 10), nem volt kezelve; II. csoport (n = 10) 1 koncentrált sóoldat; III. csoport (n = 10) 1 koncentrált olívaolaj; IV. csoport (n = 10) 1 koncentrált *Nigella sativa*-olaj; V. csoport (n = 10); 1 koncentrált szójaolajat helyileg alkalmaztunk az epiduralis régióra a laminectomia után. A patkányok teljes gerincét felboncoltuk, szövettani és immunkémiai méréseket végeztünk. A neurohisztopatológiai eredményeket félkvantitatív módon pontoztuk az érrendszeri elváltozás, a neuronok degenerációja, a gliosis és a vérzési kritériumok alapján.

Eredmények – A fibrosis és a kötőszöveti proliferáció legalacsonyabb szintje abban a csoportban volt megfigyelhető, ahol a műtét után *Nigella sativa*-olajat használtak, ezt követte az olívaolajjal kezelt csoport, végül pedig a szójaolajjal kezelt csoport.

Conclusion – Nigella sativa oil and olive oil are very efficient for lowering the degree of epidural fibrosis and adhesions following laminectomy and can be employed as a simple, inexpensive and highly biocompatible material in clinical practice.

Keywords: epidural fibrosis, laminectomy, nigella sativa, olive oil , soybean oil

Következtetés – A *Nigella sativa*-olaj és az olívaolaj nagyon hatékonyan csökkenti a laminectomiát követő epiduralis fibrosist és az összenövések mértékét, és egyszerű, olcsó és nagymértékben biokompatibilis anyagként alkalmazhatók a klinikai gyakorlatban.

Kulcsszavak: epiduralis fibrosis, laminectomia, *Nigella sativa,* olívaolaj, szójaolaj

Intervertebral disc degeneration is a physiological process. A higher number of people pass through surgery of the lumbosacral area, and laminectomy is a kind of surgery where part of the vertebral lamina is deducted for decompression of the spinal cord or roots. The formation of epidural fibrosis can be seen normally following surgery[1, 2]. However, it causes some compression symptoms and reduces the progress of spinal surgery with compression and/or stretching the nerve root or the dura mater. Furthermore, neuronal atrophy and axonal degeneration have been reported under the scar tissue[3].

Epidural fibrosis is a challenging topic in neurosurgery. In clinical practice, epidural fibrosis is a component of "post-laminectomy syndrome" or "failed-back surgery" which is a main source of strain and anxiety in daily activities, as well as of a decreased quality of life following spinal surgery. About 8% to 48% of patients who had surgery for lumbar disc herniation experienced post-laminectomy syndrome or failed-back surgery[4]. Re-operation to excise fibrotic tissues has a danger of dural tears, nerve injuries and excessive bleeding[5].

Considering the high complication rates and the gradually reduced progress rates of repetitive operations, it was concluded that the most significant approach is to hinder the advancement of epidural fibrosis. Presently, there is no efficient treatment of epidural fibrosis, and prophylaxis is a suggested alternative. In the recent years, a number of studies have been carried out and biological and non-biological constituents to hinder epidural fibrosis have been investigated in various experiments[6, 7].

In the literature, to our knowledge, there is no study about clinical or experimental research on the effectiveness of organic vegetable oils on epidural fibrosis following spinal operations. The major reason for selecting organic vegetable oils is that they can be employed as a simple, inexpensive and greatly biocompatible material in clinical practice. As a result, our research might be a guide for a prospective clinical trial.

Materials and methods

All the experimental processes employed in this research were unveiled and offered by the local Animal Research Ethics Committee of Kirikkale University. Animal care and all the tests followed the European Union Council Directive of November 24, 1986 (86/609/EEC) associated to the care of animals for experimental use. This research was carried out at Kirikkale University School of Medicine, Experimental Animals Research Laboratory.

Fifty male Sprague–Dawley rats weighing approximately 250–300 g were employed. Animals were housed with a single animal per cage at the Animal Experimental Research Centre and fed a standard rodent chow diet and water ad libitum and kept at a consistent temperature (22°C) on a 12:12 h light/ dark cycle. Maximum effort was expended to minimise the discomfort of the animals during surgery and sacrifice. The rats were randomly assigned to five groups with 10 rats per group.

The groups were as following: Group 1: Sham (n = 10); Group 2: Control (n = 10), laminectomy was conducted, as explained below, afterwards, 1 cc of saline was used topically to the epidural region; Group 3: Olive oil (n = 10), laminectomy was conducted, and afterwards, 1 cc of olive-oil was used topically to the epidural region; Group 4: Nigella sativa oil (n = 10), laminectomy was carried out, and afterwards, 1 cc of nigella sativa-oil was used topically to the epidural region; Group 5: Soybean oil (n = 10), laminectomy was conducted, and afterwards, 1 cc of soybean-oil was used topically to the epidural region.

Every rat had the same surgical process. One dose of 50 mg/kg ceftriaxone (Rocephine, Roche, Turkey) was given through the intraperitoneal route for prophylaxis 30 min before the operation. Rats were placed on an operating board in a prone position after receiving intraperitoneal injections of ketamine hydrochloride (90 mg/kg, Ketalar; Pfizer, Istanbul, Turkey) and xylazine

hydrochloride (10 mg/kg, Rompun 2%; Bayer, Istanbul, Turkey). The dorsal hair was shaved off from the skin and the surgical field was disinfected with povidone-iodine and draped with sterile towels. A longitudinal midline skin incision was created between the LII and LIII spinous processes. The lumbosacral fascia was uncovered longitudinally, and the paraspinous muscles were dissected bilaterally in a subperiosteal fashion to open the laminae of the LIII–LV vertebrae. LIII–LV laminectomy and flavectomy were performed, and epidural fat was removed, leaving the dura mater clean and dry. Haemostasis was achieved using cotton pads. No cautery or bipolar coagulation was used. The wounds were closed in an anatomical fashion via a propylene suture (Prolene polypropylene sutures; Ethicon; Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA). There were no comorbidities or adverse effects due to the materials used. For postoperative analgesia, all of the rats were provided ketorolac (50 mg/kg, intraperitoneal) for 5 days. Rats were sacrificed 6 weeks later with an overdose of intraperitoneal sodium thiopental (100 mg/kg). When obtaining the samples, the animals were inspected for dura tear, nerve damage and illnesses. There was no spotted dura tear or illnesses in the rats. The lumbar spine, including the surgical site, was removed en bloc and then fixed in 10% formic acid.

After postfixation in 10% formaldehyde solution, the vertebral samples were placed in fixation and decalcification solution (Biocal C, code RRDC3/G, composition: EDTA <1%, potassium sodium tartrate <1%, sodium tartrate <1%, hydrochloric acid <1%, Biostain [UK]) for 36 hours. The tissues were trimmed, washed, dehydrated and embedded in paraffin wax for histopathologic examination. Using standard histological protocols, axial sections of 4 μm thickness were obtained and stained with hematoxylin–eosin. Furthermore, sections were stained with Masson's trichrome (Bio Optica, Italy) to assess fibrosis. All sections were examined by a pathologist who was blinded to the rats' treatment. Light microscopy (Leica DFC450C, Germany) was used to examine the slides, and digital photomicrographs were taken. Histomorphometric examinations were conducted using Leica QWin image analysis software. The fibrosis density was determined using Leica QWin image analysis software and 20 × objective lens (Leica Microsystems Imaging Solutions, N Plan). The incorporated optical density of all progressive staining was measured, and the mean fibrosis-positive area/total area was calculated using Leica QWin Plus v4. After calculating the proportion (% pixels) of the stained area to the whole field, the mean (in % pixels) staining area for each slide was determined[8].

Statistical analysis

IBM SPSS Statistics for Windows Version 24.0. was used to analyse the data (IBM Corp., Armonk, New York, USA). The Shapiro–Wilk test was employed to evaluate whether the representation of continuous variables was normal. The nonparametric Kruskal–Wallis test was used to compare differences in groups, while the difference between subgroups was analysed using the Mann–Whitney U Test. A likelihood ratio test was used to determine the presence of arachnoidal involvement. A p-value less than 0.05 was considered statistically significant.

Results

No mortality or morbidity happened after the procedure. The application of the study oils had no adverse effects on the surrounding tissue or on wound healing in any rat. We observed no wound infections, haematomas or cerebrospinal fluid leaks. The evaluation of tissue fibrosis response and the results of the histomorphometric analysis of the degree of fibrosis between the groups are demonstrated in **Table 1** and **Table 2**.

Histopathological evaluations of connective tissue formation and fibrosis in dura mater-related tissues after surgery revealed that the highest degree of connective tissue and fibrosis was formed in the Control group (Group 1) ($p = 0.001$). However, dura mater, spinal cord and vertebral bone tissue were detected in normal histological appearance in the sham group (Group 2). The lowest level of fibrosis and connective tissue proliferation was seen in the nigella sativa oil group (Group 4) , followed by the olive oil applied group (Group 3) and finally, the soybean oil applied group (Group 5) ($p < 0.05$). Although there was no statistically significant difference in fibrosis between the nigella sativa oil and olive oil group ($p > 0.05$), both groups had significantly less fibrosis than the soybean oil group ($p < 0.05$). The histopathological evaluation results of the fibrotic changes formed in the operation area, as well as the degree of fibrosis between the dura mater and the dorsal fascia and the bone roof are given.

In Group 2, fibrosis was diffusely concentrated in the dorsal vertebral region, and dense collagen tissue content

Table 1. *Evaluation of tissue fibrosis response*

Items	Tissue fibrosis response scores			
	0	1	2	3
Fibrosis	No	Few fibroblasts	Fibroblastic proliferation and increased collagen	Fibrosis, collagen bundles

was detected with a cellular appearance due to fibroblastic activity, particularly in regions where adhesions were formed. In areas of severe fibrosis, newly formed capillaries and enlarged venous vessels filled with erythrocytes were observed. Despite all of these findings, almost no inflammatory cells were found.

The most severe histopathological changes were observed in the soybean oil group. Connective tissue repair activities at the dorsal vertebral level were characterised by advanced fibroblastic activity and collagen matrix. The collagen matrix was unusually stained in dark blue. In addition, multiple neovascularisation activities were also present in this group. In the connective tissue and healing areas, polymorphous nuclear leukocytes and macrophage activity were outlined, although their numbers were variable. In particular, the intense macrophage activity can be assessed as the inflammation-increasing effect of soybean oil.

Table 2. *Histomorphometric analysis results of the degree of fibrosis between groups*

	Control	Sham	Soybean-oil	Olive-oil	Nigella-sativa-oil
Case 1	1.14	0.05	0.93	0.17	0.47
Case 2	2.09	0.26	1.00	0.24	0.07
Case 3	2.22	0.12	0.63	0.25	0.21
Case 4	2.03	0.16	1.09	0.52	0.27
Case 5	1.41	0.22	1.18	0.14	0.25
Case 6	1.42	0.03	1.04	0.10	0.21
Case 7	2.14	0.04	0.77	0.31	0.03
Case 8	2.06	0.06	1.15	0.13	0.07
Case 9	2.15	0.10	1.05	0.24	0.20
Case 10	1.78	0.14	0.78	0.18	0.09
Mean	1.78	0.13	0.95	0.25	0.22

It was outlined that in the nigella sativa and olive oil groups, minimal fibrosis was formed similarly to each other. In particular, it was characterised by focal or mild fibroblastic activity in the dorsal area. All rats survived during the clinical follow-up. The histopathological changes are shown in **Figure 1**.

Discussion

The degenerative spine, seen with today's industrial working conditions and increasing life expectancy, has made low back pain one of the most common medical problems in clinical practice[9]. Additionally, more spine procedures are being performed for a variety of reasons, including spinal stenosis, lumbar disc herniation, spondylolisthesis, fracture and infectious diseases. One of the most often used operations is laminectomy[10]. Epidural fibrosis is a well-known complication and is widely seen after conducting laminectomy[11]. It is known that fibrosis develops as a result of fibroblast activation secondary to the increase in inflammatory cytokines in the operation area. These fibroblasts produce mounts of collagen fibres in the laminectomy defect sites[12]. It has been found that fibroblasts turn into fibrocytes with the formation of collagen fibres before the scar tissue is formed from fibrous connective tissue[12]. Although it has been reported that the post-laminectomy membrane is formed due to the invasion of fibroblasts originating from spinal muscles, the exact mechanism behind the formation of postoperative peridural fibrosis has not yet been fully elucidated[13].

Developing fibrosis is among the causes of postoperative low back pain and failed-back syndrome[14]. It is believed that by limiting the growth of fibrosis, this difficult problem for surgeons can be greatly avoided. It is believed that traction in the dura and nerve roots as a result of fibrosis are the causes of pain[15]. Prolongation of hospitalisation, increase in hospital costs and development of neurological deficits occur due to this epidural scar malformation[16]. It is stated that after the development of fibrosis, the surgical operation will be complicated due to the risk of dural tear and haematoma, and the correct approach is the attempt to prevent the development of fibrosis[16].

Potential fibrosis development varies depending on the patient's metabolic activity and surgical circumstances. Well-known fibrosis-increasing surgical agents defined so far are the anatomical region, the surgical style, the development of postoperative infection and the amount of peri/postoperative haemorrhage. Transforming growth factor-1b (TGF-1B) is thought to play a leading role in fibrosis formation[17, 18]. Consequently, the inhibition of the migration of fibroblasts from the paraspinal muscles or haematoma related to surgery could prevent or reduce epidural fibrosis formation.

Many studies have been performed, and many substances have been used to prevent epidural fibrosis developing after spinal surgery. They examined the effectiveness of other compounds for the prevention of epidural fibrosis[19], such as steroids, non-steroidal anti-inflammatory drugs, pedicle fat grafts, synthetic membranes, haemostatic sponges, and anti-adhesion barrier gels[20, 21]. The use and results of anti-inflammatory agents that prevent the induction of TGF-1B and haemostatic agents that provide efficient control of bleeding have also been reported in the literature[22]. It has

been stated that quite satisfactory results were collected. Olive oil and nigella sativa oil, which are employed in our study, two well-known Mediterranean foods whose consumption has been associated with beneficial effects on human health. There are current studies in the literature that these healthy foods can modulate inflammation through antioxidant and epigenetic mechanisms[23]. Furthermore, the major difference between soybean and olive/nigella sativa oil lies between their fat type, i.e. soybean oil contains polyunsaturated fat, while olive oil contains monounsaturated fats. The outcomes of these natural ingredients, which are popular and have various structures, were compared in our study.

Ozkan et al. examined the effects of 5-fluorouracil (5-FU) and bevacizumab (BV), alone and combined, on epidural fibrosis in rat laminectomy model[24]. *Savran* et al. analysed the prevention of epidural fibrosis in rats by local or systemic administration of citicoline[25]. *Bahrami* et al. investigated the effect of N-acetyl-cistein[26]. According to some studies, alpha-tricalcium phosphate (α-TCP) may prevent the development of fibrosis not only through its direct actions on fibroblasts but also by lowering TGF-β levels because of the crucial role that TGF-β plays in collagen synthesis[22].

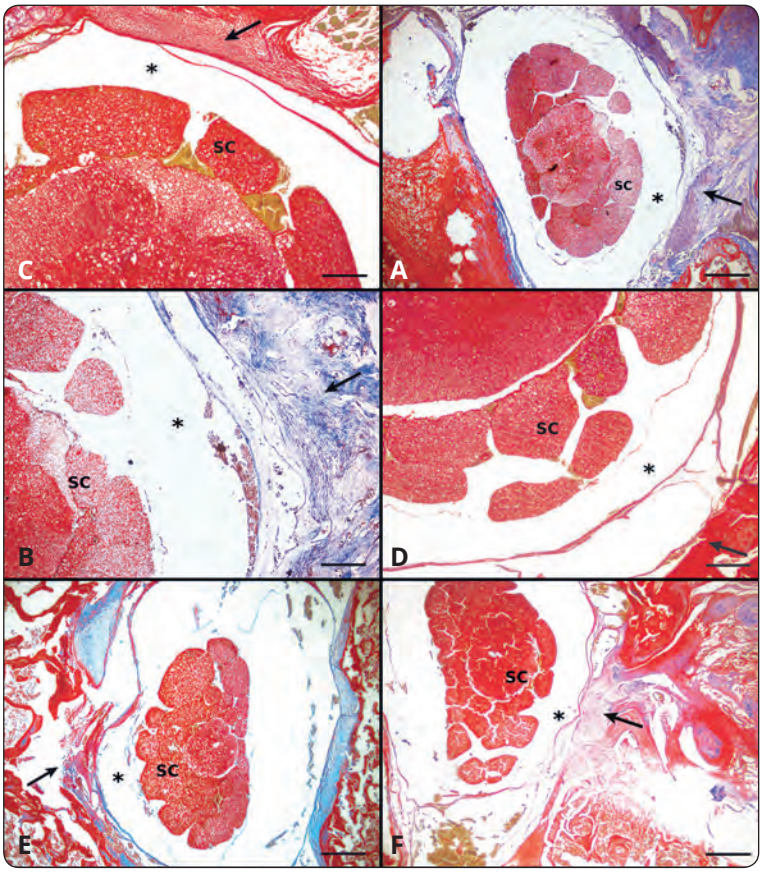

Figure 1. *Histopathological sections of the spinal cord. All sections were stained with Masson's trichrome. In the group without laminectomy (Group 1), normal structure of spinal cord (SC) and subdural space (asterisk) are seen, bar=320 μm* **(A)**.
In the group that did not receive any treatment after laminectomy (L3-4) (Group 2), intense fibroblastic activity (arrow) and local osteoid differentiation are observed in the dorsal root laminectomy area, bar=210 μm **(B and C)**.
In the group in which olive oil was applied after laminectomy (L3-4) (Group 3), a low level of fibroblastic activity (arrow) is seen, with the exception of minimal fibrous adhesions, bar=210 μm **(D)**.
In the group using Nigella sativa oil after laminectomy (L3-4) (Group4), mild to moderate fibrosis and fibroblastic activity (arrow) with collagen are seen in the regeneration area, bar=320 μm **(E)**.
In the group given soybean oil after laminectomy (L3-4) (Group 5), an area of fibrosis (arrow) in the dorsal laminectomy region that progresses further into the spinal space, bar=320 μm **(F)** *is seen*

The fact that more and more information has been gained about the fundamental uses of vegetable oils and their positive contributions to human health, thanks to the bioactive components they contain, has led to an increasing interest of consumers in vegetable oils produced by cold pressing and consumed without refining. It is well recognised that the main cause of these effects is the oxidative stability of vegetable oils[23].

In our study, we analysed the effects of relatively inexpensive organic vegetable oils, which are easy to obtain and are frequently used in daily life. Since they are organic, biocompatible and inexpensive, their use as raw materials in the production of active substances and their involvement in clinical practice will be relatively easy. Nigella sativa oil is also among the oils with high oxidation stability. A significant decrease in fibrosis rates was found in all of the active ingredients we used, and the best result was obtained with nigella sativa oil. More detailed cohort studies are needed to apply our satisfactory results in clinical practise.

Limitations

First, there are likely to be species differences in the inflammatory reaction to surgery. Second, sacrificing time is another limitation of the study. Epidural fibrosis level may be higher after a long-time period. Finally, to improve the statistical power of the data, more rats should be included in each group.

Conclusion

Based on our study, organic oils reduce epidural fibrosis after laminectomy in rats. It is proposed that these natural products can safely be used in other species, including human.

DECLARATION OF CONFLICTING INTERESTS – The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.
FUNDING – The authors received no financial support for the research, authorship and/or publication of this article.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Personality traits and psychological complaints under patients suffering from headaches

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PRINT | English | https://doi.org/10.18071/isz.76.0385 | www.elitmed.hu

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Érkezett:
2023. január 9.
Elfogadva:
2023. január 23.

Background and purpose – Although headaches are often comorbid with psychological symptoms, the underlying psychological processes, e.g. the role of personality dimensions as headache determinants remains unclear. Studies found associations between headaches and various personality traits; according to the Big Five model of personality, persons suffering from headaches exhibit a higher rate in neuroticism, while a lower rate in extraversion, openness to experiences and positive emotions. This is the first study to clarify the associations among duration, intensity, and frequency of headaches and personality dimensions. Through this study we could get into the personality dimensions in the background of pain experience and that which personality dimensions bear a part in the behaviour of the persons, who suffered from headache, but do not seek treatment through this complaint.
Methods – Treated (Group1) and untreated (Group2) headache patients and healthy controls (Group3) were investigated (total of 360 participants). The main headache components of intensity, duration, and frequency were used as dependent variables with personality dimensions in the Big Five concept investigated by the NEO-PI-R Personality Inventory.

Személyiségfaktorok és pszichológiai eltérések vizsgálata fejfájás esetén

Hal M; Hal V, MD; Vécsei L, MD, DSc; Balog A, MD; Majláth Zs, MD; Tajti J, MD, DSc; Ertsey Cs, MD, PhD; Bozsik Gy, MD; Zsombók T, MD, PhD; Purebl Gy, MD, DSc

Háttér és cél – Egyértelmű a kapcsolat a pszichológiai tünetek és a fejfájás között, mégsem tiszta a személyiségfaktorok és a fájdalom, valamint a „fájdalom-viselkedés" kapcsolata. Korábbi tanulmányok a Big Five faktorait alapul véve kimutatták, hogy a fejfájással küzdők esetén magasabb neuroticizmus, alacsonyabb extroverzió, nyitottság és pozitív érzelmek mérhetőek. Tanulmányunk az első olyan vizsgálat, amely a fejfájás időtartamát, erősségét és gyakoriságát – külön-külön – figyelembe véve összefüggést állít fel a háttérben húzódó személyiségdimenziókkal. Közelebb kerülhetünk a személyiségdimenziók megismeréséhez általa, valamint egy olyan típus viselkedésének megértéséhez, akinek jelentős fejfájása van, mégsem fordul szakemberhez a probléma miatt.
Módszerek – Kezelt (Csoport1) és kezeletlen (Csoport2) fejfájással küzdő páciensek csoportjait, valamint egészséges kontrollcsoportot (Csoport3) vontunk be vizsgálatunkba (összesen 360 vizsgálati alany). A fejfájást leginkább meghatározó erősség-, időtartam- és gyakoriságváltozókat függő változóként vontuk be a NEO-PI-R Személyiség Leltár alapján a statisztikai eljárásba. Összehasonlító vizsgálatot is végeztünk a csoportok között. A vizsgálatban részt vevő személyek önkéntes, anonim, önkitöltős formában töltötték ki kérdőívcsomagunkat.

Results – Employing multiple regression analysis, facets of personality described 14.7% of headache intensity, 10.9 % of duration, and 18.7 % of frequency variance. Group1 and Group2 reached significantly higher values on the dimension of anxiety, depression, and vulnerability to stress than Group3. Group1 showed a significantly higher value on *trust* personality dimension than Group3 and Group2. Group3 exhibited a significantly higher value in the *trust* dimension than Group2. Concerning *vulnerability to stress,* the highest value was yielded by the "treated and suffering from headaches" group and there was a significant difference also with the "untreated and suffering from headaches" group and with the control group. In this dimension, the "untreated and suffering from headaches" group's point value was significantly higher than the control group's ($p<0.01$, $U=-4.501$).
Conclusion – Our study demonstrates that the three headache components are not independent from personality traits, and personality traits may interact with treatment seeking behavior even in the presence of significant headache complaints. The role of the personality traits are significant in the intensity, duration and frequency of headaches.

Keywords: pain, headache, personality traits, treatment

Eredmények – Eredményeink alapján a többváltozós regressziós elemzés szerint a személyiségdimenziók 14,7%-át magyarázzák a fejfájáserősség varianciájának, 10,9%-át a fejfájás-időtartam varianciájának, míg 18,7%-át a fejfájás gyakorisági varianciájának. A Csoport1 és Csoport2 szignifikánsan magasabb értéket ért el a szorongás, a depresszió és a sebezhetőség aldimenziókon, összevetve a kontrollcsoporttal. A Csoport1 mindkét csoporthoz viszonyítva magasabb bizalommal rendelkezik, ugyanakkor a Csoport3 ugyanezen dimenzión szignifikánsan magasabb értéket mutat a második, vagyis a kezeletlen fejfájással küzdő csoporthoz képest. A sebezhetőség aldimenzión a Csoport1 szignifikánsan eltér pozitív irányba mindkét csoporttól, és a Csoport2 is mérhetően magasabb értéket ér el a kontrollcsoporttal összevetve.
Következtetés – Vizsgálatunk alátámasztja, hogy a három, fejfájást leginkább meghatározó változó nem független a személyiségdimenzióktól, és a személyiségváltozók összefüggésben állnak a kezelés során jelentkező vagy a kezelés elutasítását támogató viselkedésben. A személyiségváltozóknak jelentős szerepe van az erősség, az időtartam és a gyakoriság alakulásában fejfájás esetén.

Kulcsszavak: fájdalom, fejfájás, személyiségfaktorok, kezelés

Headaches signify a major everyday complaint worldwide[1, 2], and this not only concerns the individual, but public mental health as well[1]. Migrain is the third medical complaint in the population[3]. According to various surveys, 46 – 91.3% of people experience headaches on a regular basis[4–6]. The distribution of primary headache syndromes can be specified as ca. 30 – 78% tension-type headaches[2], 11.0 – 17.7% migraines[4, 7], and cca. 0.1% cluster headaches[8]. Secondary headaches are most commonly caused by alcohol, fever, hunger, and rhinosinusitis[9, 10], or can be generated by a medication overuse headache (MOH) with a 1 – 1.5 % prevalence[11].

Albeit headaches denote the most common neurological problem worldwide[4, 12], there are considerable difficulties in estimating the exact prevalence of different headache types. Many patients are treated by a primary care physician (PCP)[13], while presumably a considerable number of patients employ self-treatment and do not seek medical help. Headaches are often comorbid with psychological features and mental disorders, namely: anxiety[14–16], depression[14–16], chronic fatigue[17], insomnia[18], distress[19–21], inadequate coping strategies[19–21] and low quality of life[6, 14, 15]. Other studies found associations between headaches and various personality traits; according to the Big Five model of personality, persons suffering from headaches exhibit a higher rate in neuroticism[22, 23], while a lower rate in extroversion[22], openness to experiences[23, 24] and positive emotions[23–25].

The aim of our study is to clarify the associations among headaches and multifactorial psychological background. Our study could be the first research, which explains the differences between intensity, duration and frequency of headache with personality traits. Through this study we could get into the questions:

1. "Can we identify a headache sufferer personality profile?"

2. "Which personality dimensions show differences between the "suffered from headache groups" and "control group"?

3. "Which personality dimensions bear a part in the behavior of the "suffered from headache, but non-treated" group?"

According to our first hypothesis, the variance of the appearance of primary headaches (including the frequency, duration, and intensity of the headache) can be widely explained with personality factors.

According to our second hypothesis, patients with significant headache complaints who do not seek treatment show different personality trait patterns compared to those who do seek treatment. Thus, personality traits, as trust or positive emotions or neuroticism might be background factors in the treatment gap of headaches.

Methods

Participants and procedure

Our research was conducted in accordance with the ethics permit number 44712-2/2014/EKU, granted by the Scientific Research Ethics Committee of the Medical Research Council in Hungary. 360 participants (above age of 18) were enrolled in the study, 126 individuals were recruited by neurologists and 234 persons were involved with convenience sampling with online, or paper and pencil tests. Subjects participated anonymously and voluntarily; they received no compensation for taking part. The subjects were divided into three groups:

Group 1: Treated and suffering from headaches (headaches, treated)

Subjects enrolled by their neurologist; received primary headache diagnosis –migraine, TTH, cluster headache; partaking in ongoing pharmacological treatment in three neurology center in Hungary.

Group 2: Untreated and suffering from headaches (headaches, untreated)

Subjects suffering from significant headaches based on Headache Questionnaires; have not sought treatment; do not have a specific headache diagnosis.

Group 3: No reported headaches (control group)

Subjects have no significant headache complaints and are not being treated.

Those who were enrolled by their neurologist (Group1) filled out a paper-based test; all other participants were approached with convenience sampling and were asked to fill out an online test. Thus, Group2 and Group3 were divided based on the results of the online test and the Headache Questionnaire. **Table 1** and **Table 2** show the distribution of the participants before and after adjustment for age, sex, and level of education.

Table 1. *360 participants before adjustment*

360 participants before adjustment			
	Group1 (headaches, treated)	Group2 (headaches, untreated)	Group3 (control)
N	119	113	128
male	35	48	60
female	84	65	68
primary school	8	4	6
secondary school	61	58	65
university degree or higher	50	51	57
Mean age	44.1	38.81	37.45
SD	13.11	14.12	13.92

Table 2. *210 participants following adjustment*

210 participants following ADJUSTMENT			
	Group1 (headache, treated)	Group2 (headache, untreated)	Group3 (control)
N	70	70	70
male	18	18	18
female	52	52	52
primary school	2	2	2
secondary school	35	35	35
university degree or higher	33	33	33
Mean age	41.51	40.33	39.77
SD	12.71	13.99	12.45

Instruments

Sociodemographic questions: sex (male, female), age (year of birth), level of education (3-point Likert-type scale).

In case of the three groups, we inquired about previous psychiatric diagnoses and treatments based on self-disclosure. We also asked whether the participant is presently receiving psychological or psychiatric or psychotherapeutic treatment or medication with regard to their headache.

Headache Questionnaire: The intensity, duration, and frequency of headaches was measured in the following way:

Intensity: 10-cm Visual Analogue Scale (VAS).

Frequency: The mean frequency was measured by the mean value of the last 3 months' headache frequency.

The question was: "How frequently do you experience headaches in the last 3 months?" 1. month:...; 2. month:…; 3. month:... The mean value of the last three months' headache frequency was used in the analyses.

Duration: The question was "Usually how long does a headache episode last (without medication)? (Minutes, hours or days)". The duration of headache was used in minutes to create a continual scale in the analyses.

In Group1 (headache, treated), the neurologist completed a medical data sheet as well, which contained the headache diagnosis and the prescribed medicine.

Personality traits: The Hungarian version of the NEO-PI-R personality questionnaire was employed to identify personality traits. It contains 256 questions based on the Big Five (5 main personality dimensions: openness to experience, conscientiousness, extroversion, agreeableness, and neuroticism) and includes 31 sub-dimensions[26]. Just the Hungarian version of the NEO-PI-R is disposed with the dimension of endurance, as the 31. sub-dimension. The subjects classified how much a given statement was inherent to them on a 5-point Likert-type scale. The point values attained in the main and sub-dimensions of the NEO-PI-R refer to the highest attained value in a given personality dimension, which denotes that the specified personality dimension is characteristic of the given person.

Statistical methods

SPSS 24.0 was utilized for statistical analysis. To estimate the internal reliability of scales, we employed the Cronbach's alpha-index and descriptive statistics. The groups were compared along categorical variables with the Chi-Square test (for example level of education); in case of normal distribution we used a one-way analysis of variance along the continuous variables, while in case of non-normal distribution, we utilized the Kruskal-Wallis test (where 3 groups were compared). Aside from employing Bonferroni correction, we compared variables in pairs with the Mann-Whitney U test, where the Kruskal-Wallis test yielded a significant difference. Independent-Samples T Test was used to compare 2 groups with normal distribution and Mann-Whitney U test by non-normal distribution of the values. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normal distribution of the values or the standardized residual. The homoscedasticity and linearity were checked by plots and Breusch-Pagan test. Before the multiple regression analyses, Spearman correlation were used to select 10 relevant sub-scales from NEO-PI-R, which showed high associations with headache intensity, duration or frequency. These 10 sub-scales were involved to the regression models: anxiety, depression, vulnerability to stress, excitement seeking, positive emotions, values, trust, altruism, modesty and tendermindedness. Multicollinearity diagnostic was tested before the analyses. Multiple regression analyses were used to determine the personality dimensions background of the headache intensity, duration and frequency. The criterias of multiple regression were filled by our data.

Results

Formation of the study groups and outlier filtration

During the process of outlier filtration, we removed all persons who completed any part of the test package incorrectly. From the total number of subjects (N=360), 119 participants belonged to Group1 (headaches, treated). The 234 participants were divided into two groups: Group2 (headaches, untreated) and Group3 (control). The control group (N=128) comprised persons who reported no headaches and persons who have experienced headaches once a year with a maximum intensity of 2 (on VAS) for an hour (60 minutes) at most. The reason for the latter is that the use of painkillers, and/or the aid of a psychologist, and/or a lack of regular contact with a physician may have affected the test results of headache questionnaires. To ensure the homogeneity of the sample, we aimed to create the groups accordingly taking socioeconomic factors into consideration during adjustment. During inclusion and the formation of groups, apart from sociodemographics, we took into consideration whether the person has a headache diagnosis, is undergoing treatment, as well as the intensity, frequency, and duration of their headaches. All of these criteria were based on the Headache Questionnaire's questions (frequency and duration), the Visual Analogue Scale and the diagnosis of a specialist. Group1 (headaches, treated) and Group2 (headaches, untreated) differed in merely one respect: in the latter group, individuals did not seek treatment for their headaches, thus they had not come into contact with a neurologist and had not received a diagnosis, although, it is evident from the questionnaire that these individuals suffered from headaches of significant intensity, duration and frequency. Subjects in Group2 (headaches, untreated) had a minimum intensity of 2 (on VAS), the minimum frequency was "monthly 1 episode" (mean value in the last 3 months), and the duration was usually more than an hour (mean: 60 minutes or more). Due to a lack of diagnosis, the criteria of The International Classification of Headache Disorders-3 (2018)[27] and other diagnostic systems could not be applied in their case, as without a personal visit to a specialist, we could not form a diagnosis concerning headache type.

Subsequent to placing the subjects into the three groups described above, we sorted participants within the groups according to sex, age and education. With regard to psychiatric or psychological care, 42 of the 210 persons included in the study retained a previous psychiatric diagnosis. Twelve of these participants received

a diagnosis of anxiety disorder, 10 received a diagnosis of mood disorder, and 11 retained a diagnosis of mixed anxiety and depressive disorders (category International Statistical Classification of Diseases and Related Health Problems 10th Revision, 2019[28]). A further 9 participants had other psychiatric diagnoses or could not divulge their diagnosis. Based on self-disclosure, 5 of the 42 persons take antidepressants, which were prescribed by a psychiatrist. Of the 210 participants, 13.33% (N=28) is presently receiving psychological care; 15 persons approached a psychologist or psychotherapist due in part or completely to their headaches. Only participants in Group1 retained a diagnosis from a neurologist that also specified the type of headache; these diagnoses were: migraine without aura (N=17, 24.29%); migraine with aura (N=15, 21.43%); tension-type headache (N=36, 51.43%); cluster headache (N=2, 2.86%).

The year of birth could only differ by a maximum of 5 years between the 3 groups, with this we aimed to decrease the influential effect of sociodemographic variables. We utilized data from 210 participants, 70 people (18 men and 52 women) per group. The mean age of the groups was as follows: "Treated and suffering from headaches": 41.51 years (SD = 12.71 years); "Untreated and suffering from headaches": 40.33 years (SD = 13.99); Control group: 39.77 years (SD = 12.45 years).

Based on our hypotheses, to precisely identify the personality dimensions behind headaches we needed to adjust the sample regarding sex, age, and education as these factors may influence the factors of the NEO-PI-R Questionnaire[29–31]. The age variable showed a non-normal distribution on the Kolmogorov-Smirnov Test ($p<0.01$). There were no significant differences between the 3 groups after adjusting for age as measured with the Kruskal-Wallis Test ($p=0.20$, df=2, Chi-Square=3.20). Level of education was represented with a 3-point Likert-type scale. There were no significant differences among the 3 groups concerning the level of education as measured with the Chi-Square test ($p=0.089$; df=2; Chi-Square=10.97).

Before the analyses, the intensity, duration and frequency of headache were compared between the groups. The 3 values (intensity, duration and frequency of headache) are a non-applicable concept regarding the control group.

A normal distribution was detected in Headache Intensity on the VAS with the Kolmogorov-Smirnov test ($p>0.05$). The average value of headache intensity on the 10-cm Visual Analogue Scale (VAS) for Group1 was 6.87 (SD=1.65), the median was 7.00. The average value of the "untreated and suffering from headaches" group (Group2) was 6.84 (SD=1.63) and the median was 7.00, as the value of the control group (Group3) was very low, the average amount was 0.97 (SD=0.56) and the median was 1.00. Headache intensity did not show any significant differences between the treated and untreated headache groups ($p=0.56$, df=139, $t=0.58$) on the Independent Samples T test.

The duration and frequency variables showed a non-normal distribution on the Kolmogorov-Smirnov Test ($p<0.01$). There were no significant differences between the two groups regarding the duration of headache ($p=0.14$, $U=3171.00$; $Z=-4.18$) and frequency of headache ($p=0.26$, $U=3513.00$; $Z=-3.09$) as measured with Mann-Whitney U test. The average value of headache duration for Group1 was 31.00 hours (SD=18.34), the median was 28.5. The average value of the "untreated and suffering from headaches" group (Group2) was 30.21 (SD=16.63) and the median was 24.00. The average value of headache frequency for Group1 was 13.23 episodes/month (SD=7.05), the median was 12.00. The average value of the "untreated and suffering from headaches" group (Group2) was 11.21 (SD=6.49) and the median was 10.00. **Table 3** shows the descriptive statistics for the measured variables.

Table 3. *Descriptive statistics and Cronbach's alpha for the measured scales*

Variable	Item number	Cronbach-α	Total sample		Group 1		Group 2		Group 3	
			mean	SD	mean	SD	mean	SD	mean	SD
NEO-PI-R Neuroticism	48	0.93	138.05	28.32	152.98	30.34	145.45	22.43	115.04	27.06
NEO-PI-R Extraversion	48	0.93	156.46	26.99	142.82	28.67	157.21	20.20	159.15	27.60
NEO-PI-R Openness to Experiences	48	0.92	158.75	25.44	148.40	22.08	163.86	19.10	160.32	28.47
NEO-PI-R Agreeableness	48	0.92	161.93	25.23	170.15	19.67	155.49	17.61	161.51	28.86
NEO-PI-R Conscientiousness	48	0.94	168.72	26.06	169.05	22.77	169.01	19.10	166.49	30.13

We employed the Kolmogorov-Smirnov Test to verify the normality analysis of the measured variables. The variables do not follow normal distribution ($p<0.05$) in the case of the NEO-PI-R. Making a distinction between Group2 (headaches, untreated) and Group3 (control) required a more thorough approach as headaches are a common complaint, but their conceptualization – whether they require medical attention or not – is very individual. Headaches can be conceptualized on the basis of three, clinically relevant dimensions: frequency, duration, and intensity – the patient's perception of the dimensions is highly subjective and individual. In order to include all three dimensions in our research, we analyzed these 3 dimensions separately.

We used multivariate regression analysis with a stepwise method to identify personality dimensions capable of explaining the largest variance in intensity, duration, and frequency of headaches. In the first multiple regression analysis, we took the intensity of headaches to be the dependent variable.

Multiple regression analysis

In the first multiple regression analysis, we took the intensity of headaches to be the dependent variable. The first model, *anxiety* ($p<0.01$; $F=41.44$; $df=1$) showed 11.8%; the second model, *values* ($p<0.01$; $F=23.55$; $df=2$) explained 13.2% and with the third model, *excitement seeking* ($p<0.01$; $F=17.69$; $df=3$), 14.7% of intensity of headache's variance was explained. **Table 4** shows the results of the first multiple regression analysis.

In the second multiple regression analysis, we took the duration of headaches to be the dependent variable. The first model, *modesty* ($p<0.01$; $F=19.41$; $df=1$) showed 5.8%; the second model, *positive emotions* ($p<0.01$; $F=15.31$; $df=2$) explained 8.9%. With the third model, *altruism* ($p<0.01$; $F=12.75$; $df=3$) 10.9 % was explained of the duration's variance. **Table 5** shows the results of the second multiple regression analysis.

In the third multiple regression analysis, we took the frequency of headaches to be the dependent variable. The first model, *vulnerability to stress* ($p<0.01$; $F=54.19$; $df=1$) showed 14.7%; the second model, *positive emotions* ($p<0.01$; $F=31.61$; $df=2$) explained 16.8% and with the third model, *modesty* ($p<0.01$; $F=23.95$; $df=3$), 18.7% of the variance was explained. **Table 6** shows the results of the third multiple regression analysis.

After multiple regression analysis, the Kruskal Wallis Test was used to detect the significant differences between the 3 groups. Among the NEO-PI-R dimensions, neuroticism ($p<0.01$, $df=2$, $\chi^2= 25.95$), agreeableness ($p<0.01$, $df=2$, $\chi^2= 16.79$), and extraversion ($p<0.01$, $df=2$, $\chi^2= 20.40$) showed significant differences; at least one group was significantly different from the others in these dimensions.

Table 4. *Multiple regression analysis, dependent variable: Intensity of headache (on VAS)*

Model		Unstandardized coefficients		Standardized coefficients	Sig.
		B	SE B	Beta	
1	(Constant)	2.35	0.52		0.00
	anxiety	0.13	0.02	0.34	0.00
2	(Constant)	0.42	0.99		0.67
	anxiety	0.13	0.02	0.34	0.00
	values	0.07	0.03	0.12	0.02
3	(Constant)	1.41	1.07		0.19
	anxiety	0.12	0.02	0.32	0.00
	values	0.10	0.03	0.17	0.01
	excitement seeking	-0.07	0.03	-0.13	0.02

R^2=0.118 for Step1; ΔR^2=0.014 for Step2 ($p<0.001$); ΔR^2=0.015 for Step3 ($p<0.001$)

Table 5. *Multiple regression analysis, dependent variable: Duration of headaches*

Model		Unstandardized coefficients		Standardized coefficients	Sig.
		B	SE B	Beta	
1	(Constant)	-662.43	456.84		0.15
	modesty	77.18	17.52	0.24	0.00
2	(Constant)	713.62	617.09		0.25
	modesty	75.71	17.26	0.24	0.00
	positive emotions	-48.63	14.92	-0.18	0.00
3	(Constant)	403.09	622.34		0.52
	modesty	45.31	20.58	0.14	0.03
	positive emotions	-73.23	17.45	-0.27	0.00
	altruism	57.11	21.53	0.19	0.00

R^2=0.058 for Step1; ΔR^2=0.031 for Step2 ($p<0.001$); ΔR^2=0.020 for Step3 ($p<0.001$)

Table 6. *Multiple regression analysis, dependent variable: Frequency of headaches*

Model		Unstandardized coefficients		Standardized coefficients	Sig.
		B	SE B	Beta	
1	(Constant)	-2.99	1.51		0.04
	vulnerability to stress	0.51	0.07	0.38	0.00
2	(Constant)	3.53	2.77		0.20
	vulnerability to stress	0.47	0.07	0.35	0.00
	positive emotions	-0.20	0.07	-0.15	0.01
3	(Constant)	-0.13	3.05		0.97
	vulnerability to stress	0.36	0.08	0.27	0.00
	positive emotions	-0.22	0.07	-0.02	0.00
	modesty	0.25	0.09	0.16	0.00

R^2=0.147 for Step1; ΔR^2=0.021 for Step2 ($p<0.001$); ΔR^2=0.019 for Step3 ($p<0.001$)

Concerning the *trust* personality dimension, Group1 (headaches, treated) showed a significantly higher value than Group3 (control group) ($p<0.01$, U=-5.51) and Group2 (headaches, untreated) ($p=0.02$, U=-3.10). Also, when compared to Group2, the control group exhibited a significantly higher value in the *trust* dimension of the NEO-PI-R. ($p=0.04$, U=-2.51). In sum, all three groups showed a significant difference compared to each other, the lowest of these in the *trust* dimension was Group2.

Concerning *vulnerability to stress*, the highest value was yielded by the "treated and suffering from headaches" group and there was a significant difference also with the "untreated and suffering from headaches" group ($p=0.035$, U=-2.103) and with the control group ($p<0.01$, U=-3,223). In this dimension, the "untreated and suffering from headaches" group's point value was significantly higher than the control group's ($p<0.01$, U=-4.501).

Discussion

Previous headache research principally focused on clinically significant anxiety, depression, and other emotional disturbances, providing a large amount of data for further research[14–16]. Since these studies do not provide a more profound explanation regarding the complex nature of the interactions, the role of deeper, underlying psychological processes or entities have scarcely been studied, and the role of personality dimensions or character profiles as possible headache determinants remains unclear. Convincing data has been published concerning those struggling with headache-related pain and their experiences with negative emotional impact, a decaying quality of life, and maladaptive coping mechanisms[19, 22].

Our study clearly demonstrated that the three main headache characteristics (intensity, duration, frequency) are not independent from personality traits. These findings suggest that further longitudinal research is needed to clarify the nature of the triadic (perhaps circular) interactions between personality traits, psychological symptoms, and headache complaints. However, it is also noteworthy that the three main modalities of pain experience (intensity, duration, frequency) related differently to the Big Five personality dimension facets. Intensity was significantly more associated to the facets of anxiety, values and excitement seeking, and together they explained 14.7% of the variance. Duration was associated with 3 facets: modesty, positive emotions and altruism which together explained 10.9% of the duration's variance. Frequency was associated to three facets: vulnerability to stress, positive emotions and modesty, which together explained 18.7% of headache frequency's variance **(Figure 1)**.

The identification of Group2 (headaches, untreated) also lead our research to noteworthy findings. We have shown that there is a significant subgroup of headache sufferers, which remains untreated and differs from the other two groups (treated headaches and control) on the basis of personality traits. The distinction of the three groups ensures the possibility to examine which personality facets may contribute to the behavior of Group2,

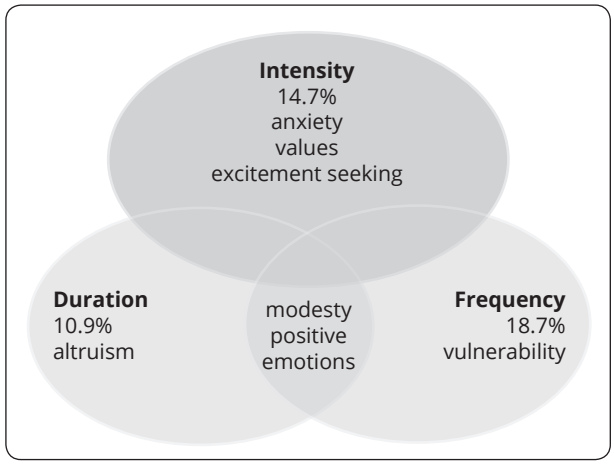

Figure 1. *The explained variance of intensity, duration, and frequency of headaches with personality dimensions*

whose members suffer as much as Group1 in all three pain experience modalities and yet do not seek treatment. According to our results, all three groups differ in the trust facet significantly (the lowest level of trust was distinctive in the case of Group2), and one group differs significantly from the other two in the main dimensions of neuroticism and agreeableness. Furthermore, it is noteworthy that both Group1 and Group2 have significantly higher values in the vulnerability to stress facet compared to Group3.

Regarding the reasons behind people not seeking treatment despite of being afflicted with significant pain, our results may lend a preliminary explanation in at least two respects. Firstly, a theoretical explanation might be that these individuals do not seek help due to psychological reasons (perhaps based on a low level of trust as our study has shown). Secondly, a viable explanation might be that these people might be characterized with poor compliance and withdraw themselves from treatment. Further research is needed to clarify these conjectures, nevertheless, our findings suggest that there is a substantial treatment gap in a common medical complaint: the headache. However, the identification of the personality factors associated with headaches may provide a basis not only for further theoretical research, but also for psychosocial strategies enhancing compliance and bridging this treatment gap.

Clinical implications

The personality dimensions underlying headaches are easier to grasp, as long as we are not examining the patient based on diagnosis, but rather the frequency, duration, and intensity of their headaches.

The psychosomatic affliction of headaches is more accurately interpreted with the bio-psycho-social approach when we know the personality dimensions residing in the background.

Our study was one of the first to approach applicability from the perspective of personality factors and the partially subjective experience of headaches (frequency, intensity, duration). Congruently, we are planning the implementation of a new, concise instrument that is apt for screening and may aid in planning the most effective treatment protocol.

DECLARATION OF CONFLICTING INTERESTS – The authors declared no potential conflicts of interest with respect to research, authorship and/or publication of this article.

FUNDING – The authors received no financial support for the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENTS – We would like to thank all persons who filled out questionnaires and participated in the tests for providing us with their data in order to make our research more exact and reliable. We would also like to thank our participating colleagues: Szent Rokus Hospital, Department of Psychiatry, University of Szeged, Faculty of Medicine, Department of Neurology, Semmelweis University, Department of Neurology and Institute of Behavioural Sciences.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Cerebellar antibodies in post-stroke sera of acute ischemic stroke patients

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PRINT | English | https://doi.org/10.18071/isz.76.0394 | www.elitmed.hu

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Érkezett:
2023. február 5.
Elfogadva:
2023. március 15.

Background and purpose – Although serum anti-neuronal antibodies are found in acute ischemic stroke (AIS) patients, it is not completely clear whether they are already present before the cerebrovascular event or emerge thereafter.
Methods – Sera of 21 consecutive first-ever AIS patients were collected within the first day of AIS (baseline), as well as 1 and 6 months after AIS. Well-characterized and novel anti-neuronal antibodies were investigated by cell-based assays, immunoblotting and indirect immunohistochemistry.
Results – None of the AIS sera collected at different time points showed well-characterized antibodies. In 7 patients, 1- and 6-month sera (but not baseline sera) showed IgG mostly reacting with soma and dendrites of cerebellar Purkinje cells. Antibody-positive patients did not differ in terms of clinical and etiological features.
Conclusion – Our results provide evidence for the antibody-triggering action of AIS. Although anti-cerebellar antibodies are not associated with the severity of stroke, they may potentially contribute to chronic post-stroke complications and disability.

Keywords: stroke, ischemic stroke, antibody, cerebellar, autoimmunity

Kisagyi antitestek akut ischaemiás stroke-on átesett betegek szérumában

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Háttér és cél – Bár akut ischaemiás stroke-os (AIS) betegeknél előfordulnak a szérumban antineuronalis antitestek, nem teljesen világos, hogy ezek már a cerebrovascularis esemény előtt jelen vannak, vagy csak később alakulnak ki.
Módszerek – Huszonegy, első AIS-ében szenvedő beteg szérumát gyűjtöttük össze az AIS utáni első napon belül (kiindulási állapot), valamint 1 és 6 hónappal az AIS után. Jól jellemzett és új antineuronalis antitesteket vizsgáltunk sejtalapú vizsgálatokkal, immunoblottinggal és indirekt immunhisztokémiával.
Eredmények – A különböző időpontokban gyűjtött AIS-szérumok egyike sem mutatott jól jellemzett antitesteket. Hét betegnél az 1 és 6 hónapos szérumok (de nem a kiindulási szérumok) IgG-t mutattak, ami főként a kisagyi Purkinje-sejtek szómájával és dendritjeivel reagált. Az antitestpozitív betegek nem különböztek a klinikai és etiológiai jellemzők tekintetében.
Következtetés – Eredményeink bizonyítékot szolgáltatnak az AIS antitest-indukáló hatására. Bár a kisagyellenes antitestek nem állnak összefüggésben a stroke súlyosságával, potenciálisan hozzájárulhatnak a stroke utáni krónikus szövődményekhez és a rokkantsághoz.

Kulcsszavak: stroke, ischaemiás stroke, antitest, kisagyi, autoimmunitás

Acute ischemic stroke (AIS) causes damage to neurons and glia causing disruption of the blood-brain barrier and release of damage associated proteins. These events facilitate activation of the resident innate immune cells of the brain, infiltration of immune cells into the central nervous system and access of brain-derived antigens into the lymphoid tissue[1]. Overall, these factors result in activation of the adaptive immune system characterized by activated T and B cells, increased production of IgG, IgM and IgA in cerebrospinal fluid and emergence of antibody-producing B cells in the brain[1, 2].

Adaptive immune system activation may also lead to production of anti-neuronal antibodies, which have been reported to be associated with impaired cognition, increased clinical severity of stroke and infarct size[3, 4]. However, it is still not entirely clear whether these immunoglobulins merely represent pre-existing and naturally occurring antibodies or AIS may actually trigger the production of novel anti-neuronal IgG.

Materials and methods

Participants

We consecutively enrolled 21 first-ever AIS patients admitted to our inpatient clinic within a few hours after the onset of cerebrovascular event. Clinical scores, clinical severity scores and inflammation-related blood count/biochemistry parameters (white blood cells [WBC], lymphocytes, neutrophils, C-reactive protein [CRP], sedimentation) were noted **(Table 1)**. AIS patients with a previous history of stroke or any other neurological disorder, with any coexisting disease or infection (shortly before AIS and during the 6-month follow-up period) and under immunosuppressive treatment (before AIS or during the 6-month follow-up period) were excluded. Also, patients showing serum anti-neuronal antibodies in baseline sera were not included. Sera of 30 age/gender matched healthy volunteers were used as controls in antibody assays.

AIS was diagnosed on the basis of clinical features and cranial MRI (T1-, T2-, FLAIR- and diffusion-weighted) findings. All AIS patients underwent Doppler ultrasonography of the carotid arteries, electrocardiogram (ECG), transthoracic echocardiogram, 24-hour Holter monitoring, cranial and cervical computed tomography angiography (CTA) investigations on a routine basis. Patients with no pathological findings in these investigations were considered as AIS of undetermined etiology. Intracranial hemorrhage was ruled out by neuroimaging in all participants. All patients received a standard treatment protocol, as per international guidelines for AIS management[5]. Ethical approval was obtained from the Institutional Review Board.

Antibody assays

Sera of AIS patients were collected within the first day of stroke (baseline sample), 1 month and 6 months after AIS and were kept frozen at -80°C until use. Well-characterized anti-neuronal antibodies were investigated in 1:30 diluted sera by commercial kits (Euroimmun, Luebeck, Germany) using cell-based (NMDA receptor, LGI1, CASPR2, $GABA_B$ receptor, AMPA receptor, glutamic acid decarboxylase antibodies) or immunoblotting (Yo and Tr/DNER antibodies) assays. To investigate anti-neuronal antibodies directed against novel antigens, indirect immunohistochemistry was performed with frozen 10-µm-thick sections of rat brain fixed in paraformaldehyde overnight, using patient and control sera (1:200, overnight incubation at 4°C), secondary biotinylated anti-human IgG (1:1000, 2 h at room temperature) and the avidin-biotin-peroxidase method[6]. Brain sections incubated with healthy human sera and only secondary anti-IgG were used as controls. Intensity of immunolabeling was scored visually on a range from 0 (negative) to 4 (very strong) by two independent observers. In cases the scores of the two observers did not overlap, we took the average of two separate scores.

Statistics

Data of anti-neuronal antibody positive and negative patients were compared by Student's t, Mann Whitney U or chi-square tests, as required. $p < 0.05$ was considered statistically significant.

Results

Cerebellar antibodies in AIS

None of the AIS patients showed well-characterized antibodies in sera collected at baseline, 1 and 6 months after the cerebrovascular accident. Likewise, baseline serum samples of AIS patients did not show any specific staining pattern on frozen rat brain sections. By contrast, both 1st and 6th month serum IgGs of 7 AIS patients reacted with the dendritic projections and soma of Purkinje cells and the molecular and granular layers of the cerebellum **(Figure 1)**. Serum IgG of AIS patients did not react with the white matter of the cerebellum. Intensity of immunolabeling was scored through assessment of 5 randomly selected cerebellar cortex fields under the microscope for each participant. There was no difference between 1st (mean, 3.6±0.5; range, 3-4; median, 4) and 6th month (3.4±0.5; 3-4; 3) serum samples of 7 antibody positive AIS patients in terms of intensity and binding pattern (p=0.313 by Mann-Whitney U). By contrast, antibody positive AIS patients showed significantly higher IgG

Table 1. *Comparing characteristics of acute ischemic stroke patients with and without cerebellar neuropil antibodies (Ab)*

	Neuropil-Ab positive (n=7)	Neuropil-Ab negative (n=14)	p value
Age	66.1 ± 11.8	68.6 ± 11.3	0.325*
Sex (men/women)	5/2	9/5	0.743**
TOAST (n)			
Large artery atherosclerosis	1	2	0.732**
Cardioembolism	3	6	
Small-vessel occlusion	0	2	
Undetermined etiology	3	4	
Other determined etiology	0	0	
Large vessel occlusion	0	0	
OCPS classification (n)			
TACI	4	4	0.392**
PACI	3	6	
POCI	0	2	
LACI	0	2	
Localization (n)			
MCA	7	11	0.417**
PCA	0	2	
BA	0	1	
Brainstem infarct (n, %)	0 (0%)	2 (14%)	0.293**
Cerebellar infarct (n, %)	0 (0%)	0 (0%)	NA**
Vascular risk factors (n)			
Hypertension	4	12	0.945**
Type 2 diabetes mellitus	3	8	
Coronary artery disease	1	3	
Atrial fibrillation	1	1	
Hyperlipidemia	0	1	
Cigarette use	1	3	
Congestive heart failure	0	2	
ICU admission (n, %)	4 (57%)	7 (50%)	0.757**
Death in ICU (n, %)	0 (0%)	1 (7%)	0.469**
Maximum NIHSS	10.1 ± 8.1	8.9 ± 5.0	0.355***
Maximum mRS	3.7 ± 1.6	3.9 ± 1.4	0.422***
Increased inflammation findings (n, %)	5 (71%)	3 (21%)	0.026**

TOAST: trial of ORG 10172 in acute stroke treatment classification, ICU: intensive care unit, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale, OCPS: the Oxfordshire Community Stroke Project, LACI: lacunar infarct, PACI: partial anterior circulation infarct, TACI: total anterior circulation infarct, POCI: posterior circulation infarct, MCA: medical cerebral artery, PCA: posterior cerebral artery, BA: basilar artery, n: number, NA: not applicable.
Numeric data is presented as average ± standard deviation. Significant p value is denoted by bold characters.
* Student's t-test, ** chi-square test, *** Mann Whitney U test.

binding scores than the remaining AIS patients (0.4±0.1; 0-1; 0; p<0.001) and the healthy controls (0.3±0.1; 0-1; 0; p<0.001). No appreciable staining was observed in other parts of the rat brain. Serum IgG of healthy controls did not react with brain sections.

Comparison of anti-cerebellar antibody positive and negative patients

AIS patients with and without cerebellar antibodies did not differ in terms of stroke etiology, vascular risk factors, prevalence of ICU admission/death and clinical severity scores of stroke. All AIS patients with anti-cerebellar antibodies had partial or total anterior circulation infarcts due to the occlusion of the middle cerebral artery. Since they had moderate to severe hemiplegia, cerebellar signs and symptoms could not be assessed on the hemiplegic body side. No cerebellar signs were elicited on the non-hemiplegic sides of the antibody-positive patients during the initial admission or 6-month follow-up. Notably, one of the patients with posterior circulation-associated AIS (Table 1) exhibited a cerebellar lacunar infarct. However,

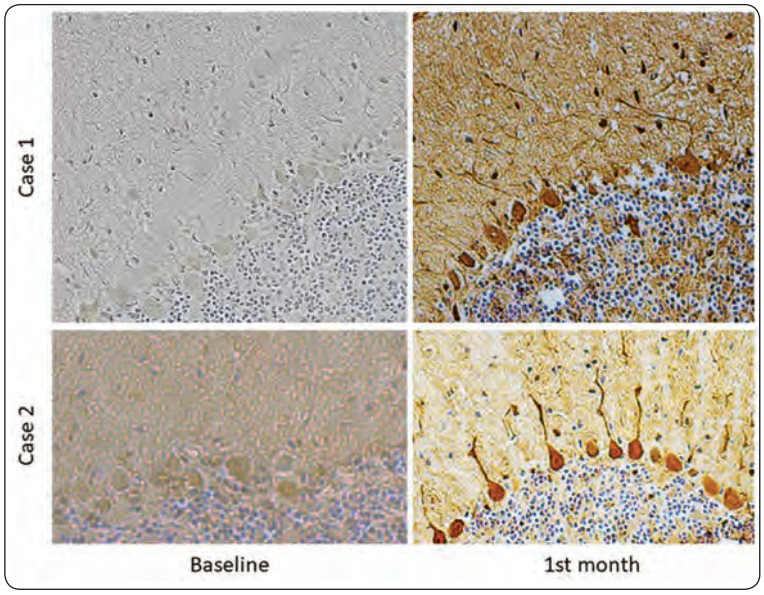

Figure 1. *Section of rat cerebellum immunolabeled with sera of two acute ischemic stroke patients. IgG of sera obtained at the 1st month of follow-up shows intense reactivity with the somata and dendritic projections of Purkinje cells and with the molecular and granular layers of the cerebellum (right panels), whereas those obtained from the same patients shortly after stroke occurrence (baseline) do not show an appreciable immunoreactivity with the brain tissue (left panels). Staining was performed with the avidin-biotin-peroxidase technique (brown) with hematoxylin counterstaining (blue); original magnification x20*

this patient exhibited neither cerebellar symptoms nor anti-cerebellar antibodies. Eight AIS patients showed mildly elevated sedimentation, CRP and WBC. Significantly higher ratio of AIS patients with cerebellar antibodies displayed increased sedimentation (1 antibody-positive), CRP (3 antibody-positive, 2 antibody-negative) or WBC (2 antibody-positive, 1 antibody-negative) levels than antibody negative patients **(Table 1)**. None of the AIS patients showed altered lymphocyte or neutrophil counts.

Discussion

Our results indicate that AIS is associated with the presence of circulating anti-neuronal antibodies, in line with previous studies[3, 4, 7–9]. However, these studies have often used the ELISA method which might detect antibodies to non-linear epitopes in both patient and healthy control groups. Also, previous studies have often found IgA/IgM antibodies to neuronal surface antigens, which are often not pathogenic and might be found in non-immune disorders[10]. Most importantly, these antibodies were mostly detected in the first few hours to days of the post-stroke period[8, 9]. Production of IgG antibodies usually takes several weeks. Also, in the rodent model of stroke, antibody producing B cells emerge 2 weeks following stroke occurrence[1]. Thus, stroke-associated antibodies reported so far putatively represent rapid amplification of pre-existing naturally occurring antibodies[1].

To investigate the antibody boosting effect of AIS, we collected baseline and post-stroke sera and included only patients who had not displayed antibodies shortly after AIS. Emergence of anti-neuronal IgGs with similar cerebellar staining pattern 1 month after the cerebrovascular event indicates that AIS promotes production of antibodies directed mostly against the layers of the cerebellar cortex. This effect is not temporary and persists at least for 6 months indicating the presence of long-lived plasma cells and memory cells. In a recent study with a similar design[9], authors have shown a very similar cerebellar staining pattern with the sera of AIS patients lending further support to our results. However, authors have failed to detect novel anti-neuronal antibodies in the post-stroke 30- and 90-day samples. This discrepancy might be due to the sensitivity difference between the immunofluorescence method used in the previous study and the indirect immunohistochemistry method used in the present study. Since minute details of the immunofluorescence method have not been provided, a thorough comparison is not possible. However, we believe that overnight fixation with paraformaldehyde and overnight incubation with patient sera might have increased the chances of detecting cell membrane antibodies and low-affinity antibodies, respectively.

A drawback of our study was unavailability of AIS patients with pure cerebellar infarcts. However, none of the seropositive patients of our cohort had a cerebellar or brainstem infarct, suggesting that antibodies did not necessarily occur as a result of increased exposure of the immune system to cerebellar antigens. Also, the single patient with a cerebellar lacunar infarct did not display cerebellar antibodies. It is fairly possible that anti-cerebellar antibodies found in our study develop against a different antigen and merely cross-react with antigen(s) found predominantly in the cerebellar tissue.

The immunostaining pattern obtained in our study is somewhat reminiscent of the so-called "Medusa head" staining pattern[11]. Two well-characterized antibodies yielding this immunohistochemistry pattern (anti-Yo and anti-Tr/DNER) were found negative in our patients. As a limitation of this study, we were unable to investigate other antibodies showing the same pattern. Antibodies with this staining pattern are associated with severe subacute cerebellar symptoms leading to prominent cerebellar atrophy and underlying cancer and have not been previously related with AIS. Since our patients did not exhibit

findings of apparent cerebellar involvement or systemic cancer, we did not consider the screening of other rarely detected paraneoplastic cerebellar antibodies[11].

Only one third of the AIS patients developed cerebellar antibodies. This might be a reflection of the different responsiveness of the immune system to the antigenic challenge. Putatively, AIS patients with antibodies might have genetic features leading to increased pro-inflammatory lymphocyte activation, enhanced antigen presentation, blood-brain barrier disruption or neuroinflammation. A notable finding in support of this argument was the increased prevalence of inflammation marker elevation in antibody positive patients, possibly indicating an immunogenetic background causing an overall propensity to antibody production.

Diffuse staining observed in granular and molecular layers of cerebellum is suggestive of cell surface antibodies that often have a pathogenic action[10], whereas the Medusa head pattern might be associated with both intracellular and cell surface antibodies[11]. However, there was no apparent difference in the overall severity of stroke in seronegative and seropositive patients and antibody-positive patients did not exhibit cerebellar signs. These results exclude a major pathogenic impact for anti-cerebellar antibodies and indicate that they are putatively directed against both intracellular and cell membrane antigens. An attractive hypothesis is that a mixed group of antibodies are produced in the weeks following stroke putatively as a bystander effect of the blood-brain barrier breach and increased access of the immune system to the brain. However, given the persistence of these antibodies, one may argue that long-term exposure to these antibodies might contribute more or less to post-stroke chronic disability. Unavailability of human brain tissue was a limitation of our study. Use of human brain tissue in future studies may provide a more useful perspective in terms of antibody binding and functionality of AIS-associated cerebellar antibodies.

In brief, why cerebellar antibodies are preferentially produced in AIS, whether these antibodies might contribute to overall long-term disability in AIS and whether our antibody assay may be used as a method to interpret the extent of post-stroke activation of the antigen-specific immune system need to be further studied. Our immediate plan for future exploration of cerebellar antibodies is to identify the target autoantigens using advanced molecular techniques including immunoprecipitation and mass spectrometry. Our second plan is to conduct long-term follow-up of antibody positive AIS patients with more extensive measures of cognitive and physical disability for more precise assessment of the long-term impact of cerebellar antibodies on stroke outcome.

FINANCIAL SUPPORT – This project was funded by Istanbul University Scientific Research Fund-BAP-TYO-2022-38583.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Vestibular evoked myogenic and auditory brainstem evoked potentials in a female migraine population

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| English | https://doi.org/10.18071/isz.76.0399 | www.elitmed.hu

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Érkezett:
2023. február 11.
Elfogadva:
2023. március 21.

Background and purpose – The purpose of the present study was to evaluate ocular vestibular evoked myogenic potential (oVEMP), cervical vestibular evoked myogenic potential (cVEMP), and brainstem auditory evoked potential (BAEP) response characteristics and to understand the pathophysiology of vestibular dysfunction in female migraineurs with vertigo symptoms. We also aimed to assess the electrophysiological diagnostic significance of the VEMP responses in vestibular migraine (VM).
Methods – 23 patients with migraine without aura (MoA), 23 patients with VM, and 20 sex-and age-matched healthy controls, a total of 66 female participants were enrolled in this study. The outcome parameters were asymmetry ratios (ARs), amplitudes of oVEMP, cVEMP, N1P1, P13N23, and the respective latencies (mean ± SD). From the BAEP graphs, absolute and interpeak interval latencies of waves were analyzed.
Results – 30.4% of the MoA group and 21.7% of the VM group had uni- or bilaterally absent cVEMP responses which were statistically significant only in the MoA group (p=0.035) in comparison to control group. Both groups displayed statistically insignificant absent or asymmetrical responses for oVEMP (13.1%). Cervical VEMP P13 and N23 latency, peak-to-peak amplitude, interaural latencies, and amplitude ARs did not show any significant difference between MoA and VM patients and healthy controls. No significant difference was detected among the three groups in the oVEMP and BAEP parameters.
Conclusion – Although absent cVEMP responses were more common in MoA and VM patients than in healthy individuals, the

Vestibularisan kiváltott myogen és auditív agytörzsi kiváltott potenciálok női migrénes populációban
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Háttér és cél – A jelen vizsgálat célja az volt, hogy értékelje az ocularis vestibularis kiváltott myogen potenciál (oVEMP), a nyaki vestibularis kiváltott myogen potenciál (cVEMP) és az agytörzsi auditív kiváltott potenciál (BAEP) válasz jellemzőit, valamint hogy segítsen megérteni a vestibularis diszfunkció patofiziológiáját a szédüléses tünetekkel járó migrénben szenvedő nőknél. Célunk volt továbbá, hogy értékeljük a VEMP-válaszok elektrofiziológiai diagnosztikai jelentőségét a vestibularis migrénben (VM).
Módszerek – A vizsgálatba 23 aura nélküli migrénes (MoA) beteget, 23 VM-es beteget és 20, nemben és életkorban illesztett egészséges kontrollt, összesen 66 női résztvevőt vontunk be. A kimeneti paraméterek az aszimmetriaarányok (AR), az oVEMP, cVEMP, N1P1, P13N23 amplitúdói és a megfelelő latenciák (átlag ± SD) voltak. A BAEP-gráfokból a hullámok abszolút és csúcsok közötti intervallumlatenciáit elemeztük.
Eredmények – A MoA-csoport 30,4%-ának és a VM-csoport 21,7%-ának egy- vagy kétoldali cVEMP-válaszai hiányoztak, ami statisztikailag csak a MoA-csoportban volt szignifikáns (p = 0,035) a kontrollcsoporthoz képest. Mindkét csoport statisztikailag nem szignifikáns hiányzó vagy aszimmetrikus oVEMP-válaszokat mutatott (13,1%). A nyaki VEMP P13 és N23 latencia, a csúcs-csúcs amplitúdó, az interaurális latenciák és amplitúdó-AR-ek nem mutattak szignifikáns különbséget a MoA- és a VM-betegek, valamint az egészséges kontrollok között. Az oVEMP- és a BAEP-paraméterek tekintetében nem volt szignifikáns különbség a három csoport között.
Következtetés – Bár a hiányzó cVEMP-válaszok gyakoribbak voltak a MoA- és a

VEMP and BAEP test results should not be used in the differential diagnosis of VM and MoA.

VM-betegeknél, mint az egészségeseknél, a VEMP és BAEP vizsgálati eredményeket nem szabad felhasználni a VM és a MoA differenciáldiagnózisában.

Keywords: migraine, vestibular migraine, vestibular evoked myogenic potential, vertigo, migraine without aura

Kulcsszavak: migrén, vestibularis migrén, vestibularis kiváltott myogen potenciál, vertigo, aura nélküli migrén

Migraine without aura (MoA) is a primary headache disorder characterized by unilateral, recurrent, and pulsatile headaches associated with nausea, vomiting, and phono-photophobia without aura[1]. Patient with migraine frequently has vestibular complaints, such as dizziness, unsteadiness, or head motion intolerance[2, 3]. Many studies have identified subclinical vestibular dysfunction in migraineurs who do not complain of vestibular symptoms[4].

Vestibular migraine (VM) is a clinically common disease that presents recurrent dizziness/vertigo, with or without headache. VM is one of the most common causes of episodic vertigo in adults, with a lifetime prevalence of 1%[5, 6].

The pathophysiology of VM remains unclear. Altered neural activity in the trigeminal vascular system (TVS) is one of the initial mechanisms underlying migraine. Calcitonin gene-related peptide (CGRP) and substance P are neuropeptides expressed in the TVS. These neuropeptides cause vasodilation and inflammation, which exposes the throbbing pain of migraine. It has also been reported that some neuropeptides, such as CGRP and serotonin, may be involved in the VM pathway. This pathway starts from the TVS, goes to the brainstem and vestibular nuclei, and connects the contralateral thalamus and cortical pain-related areas. Besides this pathway, nociceptive centers of the brain are also associated with pain centers and vestibular nuclei[7, 8]. Part of the pathway that modulates neuronal hyperexcitability remains obscure. While some studies have found a higher incidence of central vestibular dysfunction in patients with VM[9], others have reported a higher incidence of peripheral vestibular dysfunction[10–13].

Cervical and ocular vestibular evoked myogenic potentials (cVEMP/oVEMP) have been widely used to analyze vestibular dysfunction in patients with MoA and VM. These are short-latency, vestibular-dependent reflexes recorded from the sternocleidomastoid (SCM) and the inferior oblique (IO) extraocular muscles. Electromyographic responses derived from vestibular labyrinths can be evoked by sound delivered through headphones, vibration applied to the skull, or electrical stimulation. It has been reported that they reflect otolith function rather than semicircular canals[14-16].

The cVEMP, representing the vestibulo-collic reflex, originates from the saccule. It is transmitted to the inferior vestibular nerve and descends via the vestibulospinal tract through the lower brainstem to the motor neurons of the SCM muscle[17, 18]. oVEMP, a manifestation of the vestibulo-ocular pathway, appears to be mainly utricular in origin. It is transmitted to the superior vestibular nerve and ascends via the medial longitudinal fasciculus through the upper brainstem to the oculomotor nuclei[17-19].

Since oVEMP and cVEMP provide information about both ascending and descending vestibular pathways in the brainstem, combined VEMP measures have been studied in several peripheral and central vestibular disorders[20, 21]. Delayed reflex latencies have been attributed to central pathology, whereas the absence of responses and reduced amplitudes have been accepted to localize peripheral causes[22, 23]. VEMP findings in the literature with regard to MoA and VM do not appear to be homogenous.

Auditory symptoms are generally considered to be less common than vestibular symptoms in migraine[24]. Specific auditory symptoms such as phonophobia and hearing loss and tinnitus suggest impairment of auditory pathways in migraine cases[25]. Brainstem auditory evoked potential (BAEP) is an important neurophysiological method for evaluating peripheral and central nerve functions from the cochlea to the brainstem[26]. BAEP responses were reported to have some abnormalities in the form of absolute or interpeak latencies or both in MoA and VM patients, thereby demonstrating that these abnormalities might be the earliest indicator of the auditory nerve and/or brainstem dysfunctions[24, 27].

The present study aimed to analyze the auditory and vestibular profile differences of patients with VM and MoA through BAEP and VEMP testing and to help understand the pathophysiology of vestibular dysfunction. We also aimed to assess the electrophysiological diagnostic significance of the VEMP responses.

Methods

Participants

Between May 2020 and August 2020, 66 female participants (aged 20-56 years) were enrolled in this prospective, controlled study. The subjects were divided into 3 groups: The first group consisted of 23 female VM patients (mean age 40.15±10.47 years; range, 20– 60 years) based on the criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3)[28] and the International Classification of Vestibular Disorders (ICVD) of the Barany Society[29].

The second group consisted of 23 female MoA patients (mean age 41.56 ± 7.84 years; range, 29– 54 years) based on the criteria of the ICHD-3. The third group, the control group, consisted of 20 healthy female subjects age-matched to the patients' group (mean age 38.85 ± 9.89 years; range, 25-65 years). Patients with headache and vestibular symptoms underwent electrophysiological tests on headache-free and vertigo-free days.

All participants underwent a thorough neurological workup, that is, history taking, clinical examination, and a basic audiological evaluation, including pure tone audiometry (250-8000 Hz) (Interacoustics AC 40 Clinical Audiometer; Assens, Denmark) to rule out any hearing loss, and brain magnetic resonance imaging (MRI) performed to exclude other neurological problems.

The exclusion criteria included the history of prolonged noise exposure, ototoxic medication, ear discharge, otosclerosis, head or ear trauma, diabetes mellitus, and hypertension or ischemic heart disease. The control group showed no neurological or vestibular symptoms.

The study protocol was approved by the local ethics committee (reference number 2020/514/177/34; approval date May 13th, 2020). Informed consent was obtained from all participants.

Audio-vestibular workup

BAEP and VEMP recordings were performed using an EMG/EP measuring machine (MEB-2300K, Nihon Kohden, Tokyo, Japan) while the subjects were seated, in a dim and quiet environment.

BAEP recordings were performed using a montage consisting of Cz-ipsilateral mastoid (M1) and Cz-contralateral mastoid (M2) derivations. Auditory stimuli presented to each ear separately via earphones were clicks with a duration of 0.1 ms, a frequency of 10 Hz, and an intensity of 60 dB higher than the hearing threshold initially established for each subject. The responses were analyzed with a 100–3000 Hz bandpass filter and a sweep time of 10 ms. Two hundred responses were averaged in each run and two runs were performed for each ear. Absolute latencies of waves I, III, and V and interpeak latencies (IPL) of waves I–III, III–V, and I–V were noted.

VEMPs were recorded following stimulation with a 500Hz tone burst (1ms rise/fall time, 2 ms plateau) presented through headphones (air-conducted-AC-sound) at an intensity of 95 dB NHL and a stimulus presentation repetition rate of 5 Hz. The electrode impedances were less than 5 kΩ.

cVEMP test

The active electrode was placed on the upper one-third of the SCM muscle, ipsilateral to the sound stimulation, with the reference electrode over the sternum and the ground electrode on the forehead. Patients were tested in a seated position. While the subjects turned their heads to the counter-lateral side to contract the SCM, the responses were recorded from the ipsilateral SCM. A total of 200 sweeps were averaged. Myogenic signals were amplified and band-pass-filtered at 20-2000 Hz. The procedure was repeated twice on both sides.

The results of VEMP were evaluated by the existence of the initial successive positive and negative polarities termed P13 and N23 based on their respective latencies. If they were not detected in two consecutive runs of the unrectified trace at 95 dB stimulation, the result was accepted as the absence of VEMP. In the unrectified trace, interpeak (P13-N23) latency and amplitude, and after rectification, the absolute peak latencies and amplitudes of P13 and N23 were measured. Intersite differences in P13 and N23 latencies were calculated. Interaural P13-N23 amplitude asymmetry ratio (AAR) was calculated as follows: (larger response - smaller response) / (larger response + smaller response) × 100. Greater than 30 % asymmetry was accepted as abnormal. VEMP parameters were compared among the three groups.

oVEMP test

The active electrode was placed ~1 cm below the center of the inferior eyelid contralateral to the sound stimulation, with the reference electrode located 2 cm below the active electrode and ground electrode on the forehead. Patients were tested in a seated position. During the recording, the participants were asked to keep their heads at a midline position and look upward to a fixed point of 30° above the horizontal line.

Myogenic signals were amplified and band pass-filtered between 30 Hz and 3000 Hz. 200 stimuli were applied to each ear twice.

The unrectified signals from 200 trials were averaged from the oVEMP traces. The first negative and positive responses were designated as the N10 and P15 waves, respectively. In the unrectified trace, the interpeak (N1-P1) latency and amplitude, and after rectification, the absolute

Table 1. *Comparison of BAEP results between left and right ears in the three groups*

	MoA group			VM group			Control group				
	Left	Right	Pa value*	Left	Right	Pb value*	Left	Right	Pc value*	Pd value**	Pe value**
PL I	1.34 ± 0.12	1.37 ± 0.13	0.851	1.21 ± 0.14	1.17 ± 015	0.889	1.73 ± 0.11	1.66 ± 0.11	0.645	0.331	0.811
PL III	3.58 ± 0.14	3.65 ± 0.16	0.668	3.35 ± 0.21	3.35 ± 0.23	0.568	3.62 ± 0.17	3.72 ± 0.15	0.335	0.167	0.220
PL V	5.26 ± 0.14	5.39 ± 0.19	0.309	5.15 ± 0.27	5.25 ± 0.31	0.354	5.21 ± 0.22	5.21 ± 0.21	0.565	0.472	0.110
IPL I-III	2.14 ± 0.35	2.10 ± 0.26	0.578	2.18 ± 0.31	2.12 ± 0.32	0.484	2.07 ± 0.19	2.08 ± 0.30	0.840	0.184	0.430
IPL III-V	1.91 ± 0.32	1.86 ± 0.36	0.879	1.83 ± 0.28	1.80 ± 0.28	0.891	1.83 ± 0.26	1.67 ± 0.30	0.088	0.370	0.188
IPL I-V	4.05 ± 0.33	3.97 ± 0.47	0.862	4.03 ± 0.41	3.92 ± 0.25	0.260	3.89 ± 0.30	3.75 ± 0.40	0.064	0.159	0.123

p value* Dependent samples Wilcoxon signed- rank test; p value** Independent samples Kruskall-Wallis Test.
MoA: migraine without aura, VM: vestibular migraine, Pa: comparison between left and right ears in the MoA group, Pb: comparison between left and right ears in the VM group, Pc: comparison between left and right ears in the control group, Pd, comparison of left ears among the groups, Pe: comparison of right ears among the groups

peak latencies of N1 and P1 and the amplitude of N1 were measured. Intersite differences in the latencies were also calculated. The interaural N1 AAR was calculated using the same method that was mentioned for cVEMP; greater than 30% asymmetry was accepted as abnormal. VEMP parameters were compared among the three groups.

Statistical analysis

Data were entered into Excel and analyzed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Numbers (n) and percentages (%) were used to describe categorical data. Continuous data are expressed as mean ± standard deviation (SD) values. Three groups were compared in the analysis: VM, MoA, and control. Wilcoxon signed-rank and Kruskal Wallis tests were used to compare group differences in the VEMP and BAEP variables. Of note, the absence of a VEMP response was assigned an amplitude of zero microvolts, and latency was considered as missing data. The associations of VEMP response rates with both MoA and VM were compared separately with the those of control group using Fisher's exact test. Statistical significance was set up at $p<0.05$.

Results

Demographics

All participants were female to avoid a gender bias. There was no statistical difference in age between the study and control groups. The duration of the disease was 13.7±9.05 years for the MoA group and 10.43±6.85 years for the VM group; there was no statistical difference in disease duration between MoA and VM groups. None of the groups had any patients with sensorineural or conductive hearing loss in the pure tone audiometry test.

BAEP results

There were no statistically significant differences in any groups between the right and left peak latency differences of waves I, III, V, and IPL I-III, III-V, and I-V waves **(Table 1)**. In addition, there were no significant differences between the groups in terms of right and left sides.

VEMP results

cVEMP findings

Seven patients in the MoA group (4, 17.4% unilateral; 3, 13% bilateral) demonstrated absent cVEMP responses, while responses could not be obtained for five patients in the VM group (2, 8.7% unilateral; 3, 13% bilateral) and one in the control group (1, 5% unilateral; 0.0% bilateral). A statistically significant low response rate was observed in the MoA group (Fisher' exact test, p=0.035) **(Table 2)**.

No statistically significant differences were observed for any of the peak latencies, interpeak intervals, and interaural latency differences between the patient and control groups. In addition, P13-N23 interpeak and rectified P13 and N23 amplitudes of cVEMP in paitents VM and

Table 2. *VEMP responserates in patients and healthy controls*

	VM (n:23)	MoA (n:23)	Controls (n:20)
cVEMP			
Bilateralresponse, n (%)	18 (78.3%)	16 (69.16%)	19(95%)
Unilateralresponse, n (%)	2 (8.7%)	4 (17.4%)	1(5%)
No response, n (%)	3 (13%)	3 (13%)	0 (0%)
oVEMP			
Bilateralresponse, n (%)	20 (86.9%)	20 (86.9%)	19 (95%)
Unilateralresponse, n (%)	2 (8.6%)	2 (8.6%)	1 (5%)
No response, n (%)	1 (4.5%)	1 (4.5%)	0 (0%)

VM: vestibular migraine, MoA: migraine without aura, cVEMP: cervical vestibular evoked myogenic potential, oVEMP: ocular vestibularevoked myogenic potential

MoA did not differ significantly from those of healthy controls. Moreover, the amplitude ARs did not differ between the groups (p> 0.05) **(Table 3)**.

oVEMP findings

Three patients in the VM group (2, 8.6% unilateral; 1, 4.5% bilateral), three patients in the MoA group (2, 8.6% unilateral; 1, 4.5% bilateral) and one in the control group (1, 5% unilateral; 0, 0% bilateral) showed no oVEMP responses. There was no statistically significant difference between the groups in terms of oVEMP response rate **(Table 2)**.

In oVEMP, there were no significant differences in the peak, interpeak, and interaural latencies among the groups. In addition, no statistically significant difference was found when comparing the amplitude of all waveforms and ARs between patients and healthy controls (p> 0.05) **(Table 4)**.

Discussion

In the present study, we found no significant differences in the VEMP and BAEP parameters between the patient and control groups. However, low cVEMP response rates were observed in the MoA group.

Despite the increasing amount of published data on VM-related VEMP studies in recent years, the findings appear to be contradictory, and migraine-related published data are limited as well. While some studies have found a higher incidence of central vestibular dysfunction in VM patients[9, 30], others have reported peripheral

Table 3. *cVEMP results of patients and healthy controls*

Parameters	VM	MoA	Controls	p*
Leftside				
Latency P13 (ms)	14.33±2.75	14.45±2.45	13.93±1.81	0.960
Latency N23 (ms)	20.61±3.00	30.8+-2.80	20.65±2.40	0.396
P13-N23 interpeak latency (ms)	4.21±1.19	3.84±1.06	4.09±1.56	0.613
P13-N23 amplitude (μV)	10.713±7.12	13.34±10.10	17.13±16.39	0.313
P13rectified amplitude (μV)	4.64±3.64	5.42±5.65	7.57±11.81	0.880
N23 rectified amplitude (μV)	4.22±3.16	4.41.±4.12	5.54±4.49	0.628
Right side				
Latency P13 (ms)	14.46±2.41	14.16±2.73	14.23±2.32	0.562
Latency N23 (ms)	20.38±2.48	19.78±2.81	20.78±3.06	0.356
P13-N23 interpeak latency (ms)	4.00±1.48	4.11±1.60	4.40±1.84	0.356
P13-N23 amplitude (μV)	12.93±11.93	12.2±9.22	16.47±18.05	0.890
P13 rectified amplitude (μV)	5.45±6.11	4.85±3.92	7.12±7.27	0.606
N23 rectified amplitude (μV)	4.66±4.87	3.98±4.08	6.27±7.35	0.356
Interside difference				
Interaural latency diff, P13	2.13±1.89	2.21±1.87	1.78±1.13	0.983
Interaural latency diff, N23	1.67±1.13	2.06±1.40	2.70±2.22	0.511
P13-N23 amp asymmetry ratio, %	29.53±22.88	21.87±15.91	29.63±26.10	0.868

* Kruskal-Wallis Test. VM: vestibular migraine, MoA: migraine without aura

Table 4. *oVEMPResults of patients and healthy controls*

Parameters	VM	MoA	Controls	P value*
Leftside				
Latency N1(ms)	10.79±2.17	10.35±1.71	10.81±1.88	0.752
Latency P1(ms)	15.00±1.99	14.19±1.71	15.00±1.88	0.405
N1-P1 interpeak latency (ms)	4.21±1.19	3.84±1.06	4.09±1.56	0.627
N1-P1 amplitude (μV)	1.64±1.34	1.82±1.77	2.69±5.70	0.908
N1 rectified amplitude (μV)	1.10±1.24	0.95±1.20	1.08±2.39	0.766
Right side				
Latency N1 (ms)	10.92±2.40	10.35±1.63	10.11±1.39	0.632
Latency P1 (ms)	14.92±2.32	14.46±1.95	14.72±1.60	0.875
N1-P1 interpeak latency (ms)	4.00±1.48	4.11±1.60	4.40±1.84	0.910
N1-P1 amplitude (μV)	4.57±5.42	2.38±2.53	4.56±4.56	0.262
N1 rectified amplitude (μV)	1.84±2.57	1.05±1.38	1.94±3.48	0.726
Interside difference				
Interaural latency diff, N1	1.82±1.42	1.46±0.97	1.29±1.05	0.880
Interaural latency diff, P1	1.79±1.55	1.66±1.36	1.26±1.04	0.637
Amp. Asymmetry ratio, %	44.96±30.06	43.30±30.92	36.90±27.92	0.861

*Kruskal-Wallis Test. VM: vestibular migraine, MoA: migraine without aura

vestibular dysfunction in VM patients[10, 11, 31]. Such variance suggests that the migraine mechanism may act on the vestibular system at various levels[32]. Although the pathophysiology is not clear, altered neural activity within the trigeminovascular system and vestibular hyperexcitability are considered the primary mechanisms of vestibular dysfunction in patients with migraine[33, 34].

We found no significant differences in cVEMP or oVEMP parameters between patient and control groups. The findings in the literature on VM and cVEMPs do not appear homogenous. Some authors reported abnormalities in latency, amplitude, and the presence or absence of a response[2, 17, 35–37]. Our results are concordant with the results of the studies performed by *Taylor* et al. and *Kandemir* et al. revealing cVEMPs with similar latencies and amplitudes in patients with VM and healthy controls[13, 38]. Although we could not demonstrate the diagnostic significance of c- and oVEMP, some researchers have considered VEMP findings to be effective markers in VM diagnosis. *Makowiec* et al. reported that patients with VM exhibited normal cVEMP and abnormal oVEMP responses, suggesting that such a VEMP pattern might be a biomarker of VM[39]. Additionally, many investigators have reported that VM patients often manifest oVEMP but not cVEMP abnormalities. They reported that higher rates of abnormal oVEMPs may suggest greater vulnerability within the ascending utricular ocular pathway in patients with VM[40–42]. Whereas, Taylor et al. detected no significant c/oVEMP abnormalities in VM patients, which is consistent with our results[13]. Based on these previously published reports in the literature and the results of the present study, we think that the variability of VEMP results of VM patients prevent these responses from being used as a definitive biomarker.

The VEMP profiles of patients and controls in our study differed in the bilateral presence of c- and oVEMP responses. A high absent cVEMP responses in migraineurs was observed compared to the controls in our study, although the difference was not statistically significant. In line with our findings, *Hong* et al. stated that neither an abnormality in latencies nor a cVEMP asymmetry was present but 60% of the patients had bilaterally absent cVEMP responses[12]. A significant low response rate was also observed in the MoA group in the present study, but there was no statistically significant difference among the groups concerning the VEMP response rate. This finding may suggest a subclinical dysfunction within the descending saccular pathway in patients with MoA and might be related to pathophysiological similarities between MoA and VM. Moreover, Taylor et al. concluded that peripheral vestibular function is usually preserved in VM and that central mechanisms must be the cause of vertigo[13]. There are several hypotheses about absent VEMP responses, such as reduced serotonergic control of the saccular reflex pathways in the brainstem and insufficiency of glutamate, the major neurotransmitter of the vestibular system[35, 39, 42]. Although VEMP results in patients with MoA are contradictory, *Boldingh* et al. re-

ported uni- or bilaterally absent cVEMPs in 44% of their patients with VM and 25% of their patients with migraine as compared to 3% of the healthy controls[43].

Various vestibular function test studies have been conducted in patients with migraine during the interictal period. Several studies have reported vestibular abnormalities in the form of involvement of peripheral or central vestibular pathways or both[3, 43]. One study reported dysfunction in the vestibulo-ocular reflex, whereas another indicated underlying dysfunction in the vestibulospinal system. These findings suggest that migraineurs without vestibular symptoms exhibit vestibular abnormalities, generally indicating subclinical vestibulopathy[44, 45]. *Allena* et al. recorded normal latency cVEMPs with reduced amplitude, which suggested reduced serotonergic control of the VEMP pathways[46]. *Yetiser* et al. also recorded normal latency with a unilaterally reduced amplitude of P13 in 30 female migraine patients[47]. *Moallemi* et al. reported no meaningful difference between migraine patients and a healthy group in cVEMP asymmetry measures. Furthermore, they claimed that unilateral headaches in migraine patients do not result in abnormalities in VEMP side difference measures[48]. *Kandemir* et al. also reported a normal interictal cVEMP profile in migraineurs which is consistent with our results[38].

Although oVEMP abnormalities are reported more frequently in VM, cVEMP abnormalities have been reported to be more reliable than oVEMP in assessing vestibular dysfunction in migraineurs indicating subclinical vestibulo-collic pathway dysfunction[2]. In a study evaluating the diagnostic value of cVEMP in VM and migraine, the absence of VEMP responses was found to be numerically higher in the migraine group than in the VM group. The increased rate of absent VEMPs was associated with hypoperfusion of the sacculo-collic reflex pathway in migraine patients. In addition, it was concluded that the VEMP reflex responses appear to be insufficient for the differential diagnosis of VM and migraine[49]. However, some authors reported an abnormal interictal oVEMP profile in migraineurs, suggesting pathology within the vestibulo-ocular reflex[4]. They reported that oVEMP is a more reliable measure than cVEMP to evaluate vestibular function in migraineurs. Moreover, the significantly prolonged oVEMP latencies in their study suggested an underlying functional abnormality in the central vestibular system.

There was no statistically significant difference in the absolute and interpeak latencies obtained for BAEP among the groups consistent with some previous reports[50]. *Dash* et al. evaluated the audiovestibular functions in 50 cases of migraine with or without vertigo[24]. They reported that all patients showed some abnormalities in the form of prolonged absolute latency or prolonged interwave peak latencies or both consistent with the findings of *Zhang* et al.[27]. These results demonstrated that BAEP abnormalities might be the earliest indicator of impending auditory involvement in migraine. Moreover, in the studies of Zhang et al. compared with the migraine group, the peak latencies of I, III, and V waves in the VM group were prolonged, but the V wave changes were still within the normal range, indicating that brainstem dysfunction was more serious in VM patients than in migraine patients and VM patients have both central nervous system damage and peripheral nerve damage. Prolongation of wave V latency in VM patients has been indicated as a physiological dysfunction in the auditory system up to the brainstem level in another study[37].

In conclusion, the VEMP and BAEP tests are easy, noninvasive, and convenient to use in daily clinical practice with minimal discomfort. In our study, we provide evidence of the possible involvement of the descending saccular pathways in MoA and VM, as shown by the higher absent cVEMP responses in migraineurs than in healthy individuals. However, based on the findings of the present study, it is possible to state that VEMP and BAEP findings should neither be used in the differential diagnosis of VM and MoA. Futher studies are needed to determine whether MoA and/or VM are disorders of central or peripheral pathology.

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DISCLOSURE – Financial support: None.
CONFLICTS OF INTEREST – None.

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EREDETI KÖZLEMÉNY
ORIGINAL ARTICLE

The significance of neutrophil/lympocyte ratio and platelet/lymphocyte ratio in predicting diabetic polyneuropathy and neuropathic pain severity as inflammatory factors

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PRINT | English | https://doi.org/10.18071/isz.76.0408 | www.elitmed.hu

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Érkezett:
2023. augusztus 11.
Elfogadva:
2023. augusztus 25.

Background and purpose – Neuropathic pain may appear as one of the first symptoms that take the patient to the physician in type 2 diabetes, which can be asymptomatic for years. Although it is accepted that diabetes is a trigger for vascular inflammation, it has been suggested that inflammation itself may trigger diabetes. In our study, we aimed to investigate the relationship between diabetic polyneuropathy and neuropathic pain and inflammatory markers.
Methods – The study included 44 healthy controls, 46 diabetic patients with normal electroneuromyography (ENMG) and 44 diabetic patients with polyneuropathy detected in ENMG. Sedimentation, C-reactive protein (CRP), Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLO) and mean platelet volume (MPV) values were recorded in the sera of the patients. The Douleur Neuropathic 4 (DNP4) Questions was used to evaluate the presence of neuropathic pain in the patients, and the Visual Analogue Scale (VAS) was used to evaluate the severity of pain.
Results – NLR, CRP, sedimentation levels were statistically significantly higher in the DMP+ and DMP– patient groups compared to the control group. PLO and MPV levels were significantly higher in the DMP+ patient

A neutrophil-lymphocyta arány és a thrombocyta-lymphocyta arány mint gyulladásos faktorok jelentősége a diabeteses polyneuropathia és a neuropathiás fájdalom súlyosságának előrejelzésében

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Háttér és cél – A neuropathiás fájdalom az egyik első tünet lehet, ami orvoshoz viszi a beteget 2-es típusú cukorbetegségben, ami évekig tünetmentes lehet. Bár elfogadott, hogy a cukorbetegség érrendszeri gyulladást kiváltó tényező, felmerült, hogy maga a gyulladás is kiválthatja a cukorbetegséget. Tanulmányunkban a diabeteses polyneuropathia és a neuropathiás fájdalom, valamint a gyulladásos markerek közötti kapcsolat vizsgálatát tűztük ki célul.
Módszerek – A vizsgálatba 44 egészséges kontroll, 46 diabeteses beteg normális elektroneuromiográfiás (ENMG) lelettel és 44, ENMG-vel kimutatott polyneuropathiás diabeteses beteg került bevonásra. A betegek szérumából a szedimentáció, a C-reaktív fehérje (CRP), a neutrophil-lymphocyta arány (NLR), a thrombocyta-lymphocyta arány (PLO) és az átlagos thrombocyta-térfogat (MPV) értékeit rögzítettük. A betegeknél a neuropathiás fájdalom jelenlétének értékelésére a Douleur Neuropathic 4 (DNP4) Kérdőívet használtuk, míg a fájdalom súlyosságának értékelésére a vizuális analóg skálát (VAS).
Eredmények – Az NLR, a CRP és a süllyedés szintje statisztikailag szignifikánsan magasabb volt a DMP+ és a DMP– betegcsoportban, mint a kontrollcsoportban. A PLO- és MPV-szintek szignifikánsan magasabbak

group compared to both the DMP– patient group and the control group.

The means of VAS and DN4 scores were statistically significantly higher in the DMP+ patient group than in the DMP– patient group. In the DMP– patient group, the NLR levels of those with neuropathic pain according to the DN4 scale were statistically significantly higher than those without neuropathic pain.

Conclusion – Diabetic neuropathy is one of the common complications of diabetes, affecting about half of patients. Our study shows that NLR, PLO, MPV values can be used as parameters to help us make an easy and fast diagnosis in diabetic polyneuropathy. However, their reliability in the diagnosis of diabetic polyneuropathy should be evaluated with studies to be conducted with larger patient and control groups.

Keywords: diabetic peripheral neuropathy, neuropathic pain, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLO)

voltak a DMP+ betegcsoportban mind a DMP– betegcsoporthoz, mind a kontrollcsoporthoz képest.

A VAS- és a DN4-pontszámok középértékei statisztikailag szignifikánsan magasabbak voltak a DMP+ betegcsoportban, mint a DMP– betegcsoportban. A DMP– betegcsoportban a DN4-skála szerint neuropathiás fájdalomban szenvedők NLR-szintje statisztikailag szignifikánsan magasabb volt, mint a neuropathiás fájdalomban nem szenvedőké.

Következtetés – A diabeteses neuropathia a cukorbetegség egyik gyakori szövődménye, a betegek mintegy felét érinti. Vizsgálatunk azt mutatja, hogy az NLR-, PLO- és MPV-értékek segítségével könnyen és gyorsan felállítható a diabeteses polyneuropathia diagnózisa. Mindazonáltal, ezen értékek megbízhatóságát a diabeteses polyneuropathia diagnózisában nagyobb beteg- és kontrollcsoportokon elvégzendő vizsgálatokkal kell értékelni.

Kulcsszavak: diabeteses perifériás neuropathia, neuropathiás fájdalom, neutrophil-lymphocyta arány (NLR), thrombocyta-lymphocyta arány (PLO)

Type 2 diabetes mellitus (DM) is a worldwide health problem and it is expected that 783.2 million people will be affected with type 2 diabetes mellitus (DM) by 2045[1]. Diabetic polyneuropathy (DPN) and neuropathic pain (NP) due to DPN is one of the most common complications of diabetic neuropathy. Its lifetime incidence in type 2 DM patients is approximately 45%[2]. Neuropathic pain can be asymptomatic for years and it can be one of the first symptoms that can cause the patient with type 2 diabetes to see a physician[3].

Although it is accepted that diabetes is a trigger for vascular inflammation, it has been suggested that inflammation itself may trigger diabetes. It has been proven that increased C-reactive protein (CRP), body mass index (BMI), triglyceride, and glucose levels increase the risk of developing type 2 diabetes[4]. There is some evidence that low-level systemic inflammation is an important determinant in the development and follow-up complications of type 2 DM[5, 6].

Recently, multiple markers and hematological indices, including neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), have been used as markers of the systemic inflammatory response[7, 8]. An increase in NLR levels has been reported as an important marker for the diagnosis of diabetic retinopathy and a risk factor for major cardiovascular cases[9, 10]. In a recent study, NLR has been associated with non-arteritic anterior ischemic optic neuropathy[11]. In our literature review, it is seen that there are studies reporting a significant relationship between NLR and peripheral polyneuropathy in Type 2 DM patients[1, 12]. However, no study was found that evaluated the relationships between NLR and PLR ratio with NP and DPN.

In our study, it is aimed to investigate the relationships between diabetic polyneuropathy and neuropathic pain and NLR and PLR, which are new markers of inflammation.

Methods

Study participants

The study was conducted with 90 patients who visited the neurology clinic of Medical Faculty Hospital at Harran University between January 2017 and May 2017 and were diagnosed with type-2 diabetes by the Polyclinic of endocrinology and metabolism diseases in our hospital. As control groups the study also involved 44 healthy people who were at the same age.

The patients and the control group were informed about the procedure to be performed before the study and they were asked to sign consent forms. The patient and control groups were examined for polyneuropathy by using electroneuromyography (ENMG). Forty six patients with diabetes with normal ENMG and 44 patients with diabetes who were diagnosed with polyneuropathy as a result of ENMG were determined as the patient group. Nerve conduction studies were performed with ENMG to exclude the presence of any polyneuropathy in the healthy control group.

The patients with chronic or acute infection, chronic renal failure, extremity amputation, previous or existing malignancy, entrapment neuropathy detected by ENMG, plexopathy, radiculopathy or having undergone surgery due to it, and other risk factors for peripheral neuropathy (B12 deficiency, hypothyroidism, amyotrophic lateral sclerosis, amyloidosis, connective tissue diseases, vasculitis, chronic alcohol use, drug use, etc.) were excluded from the study. The control group included healthy volunteers who did not have any systemic diseases including diabetes, acute or chronic infection, any long-term drug use (immunosuppressive, antibiotics, antiepileptic drugs etc.), and polyneuropathy, which was excluded by ENMG.

Measurements

The neutrophil/lymphocyte ratio was calculated by dividing the number of neutrophils obtained in the complete blood count of the patient group and the control group by the number of lymphocytes. Similarly, platelet/lymphocyte ratio was calculated by dividing the platelet count by the lymphocyte count. Mean serum glycosylated hemoglobin (HbA_{1c}), sedimentation, CRP, MPV, NLR and PLR values of the patient and control groups were recorded.

Douleur Neuropathique 4 Questions (SN-4) was used to evaluate neuropathic pain and Visual Analogue Scale (VAS) was used to evaluate pain management in patients with diabetes. VAS is a scale used in understanding the severity of pain and in its clinical follow-up. VAS is used to digitize values that cannot be measured numerically. To do so, a line of 10 cm was drawn. The initial endpoint of this line, namely the zero point, was defined as "no pain" and the last endpoint as "severe pain". The patients were asked to indicate where his or her condition fits along this line[13].

The DN4 questionnaire consists of 10 questions, 7 of which are related to symptoms and 3 of which reflect clinical examination findings. In this questionnaire, each yes answer is evaluated as 1 point. Neuropathic pain is acknowledged in patients with a total score of 4 and above[14].

Keypoint electromyography device (Version 2.38, Medtronic Dantec, Skovlunde, Denmark) was used for recording, data saving and analysis. In line with the protocol, more than one motor and sensory nerve conduction studies were performed in both lower extremities and at least one upper extremity. In this context, motor nerve conduction of both peroneal and tibial nerves, and sensory conduction of both medial plantar and peroneal superficial nerves were examined. Likewise, motor and sensory conductions of the median and ulnar nerves in at least one upper extremity were examined.

Statistical analysis

Statistical analyses were performed using the SPSS computer program for Windows Version 11.5 (Statistical Package for the Social Sciences). The metadata were represented with averages ± standard deviations, numbers and percentages. Categorical variables were compared using chi-square test. In the normally distributed constant data comparison, the Student's t-test was used. The patient group was compared with control group via One-Way Anova. In the non-normally distributed group, the Mann-Whitney U test was used. The Kruskal-Wallis test was used to compare more than two independent groups. The correlation among variables was found through Pearson Correlation Test. The results were evaluated at 95% confidence interval and significance was thought at $p<0,05$ level.

Results

The mean age of DM patients with polyneuropathy (DMP+) was 54.59±10.26, the mean age of DM patients without polyneuropathy (DMP–) was 54.69±10.05, and the mean age of the control group was 51.95±9.14. The clinical and demographic characteristics of the patients are given in **Table 1**.

NLR level in DMP+ and DMP– patient group was significantly higher when compared to control group (p=0.020, p1=0.036). NLR level in DMP+ patient group was higher than that of DMP– patient group, but it was not statistically significant. PLR level in DMP+ patient group was significantly higher when compared to both DMP– patient group and control group (p=0.000, p=0.002). Mean serum HbA_{1c} level was significantly higher in DMP+ patient group than in DMP– patient group (p=0.000). Serum CRP level was found significantly higher in both DMP+ patient group and DMP– patient group when compared to control group (p=0.000, p=0.002). However, no statistical significance was seen between DMP+ and DMP– patient groups. DMP+ and DMP– patient groups had significantly higher sedimentation levels than control group. The sedimentation level in DMP+ patient group was higher than in the DMP– patient group, but it was not statistically significant. The MPV level was significantly higher in DMP+ patient

Table 1. *Demographic and clinical characteristics of the groups*

		DMP+ n=44	DMP– n=46	Control n=38	P
Age		54.59 ± 10.26	54.69 ± 10.05	52.60 ± 6.17	0.637
Gender	Male	23 (18.0%)	14 (10.9%)	22 (17.2%)	0.236
	Female	21 (16.4%)	32 (25.0%)	16 (12.5%)	
BMI		26.60 ± 3.66	30.97 ± 5.10	29.21 ± 3.31	0.134
Duration of DM (years)		12.22 ± 6.34	8.54 ± 4.12		0.026
	Drugs used				
	Insulin	7 (15.9%)	2 (4.3%)		
	OAD	18 (0.9)	30 (65.2%)		
	Insulin+OAD	16 (6.4%)	9 (19.6%)		
	Diet	3 (6.8%)	5 (0.9%)		

DMP+: diabetic patients with polyneuropathy, DMP–: diabetic patients without polyneuropathy, BMI: body mass index, OAD: oral antidiabetic drugs

group when compared to DMP– patient group and control group (p=0.018, p=0.001). Mean VAS score was significantly higher in DMP+ patient group than in DMP– patient group (p=0.000, p=0.000). Likewise, mean DN4 score was significantly higher in DMP+ patient group than in DMP– patient group **(Table 2)**.

In DMP– patient group, the NLR levels of those with neuropathic pain (2.52±1.25) according to the DN4 scale were statistically significantly higher than those without neuropathic pain (1.84±0.70) (p=0.023).

There was a significant positive correlation between the VAS scale and DN4 scale results applied to the patients. No significant correlation was observed between other biochemistry markers and VAS **(Table 3)**.

In DMP+ patient group, 7 patients (%15,9) had normal DN4 scale score while 37 patients (%84,1) were found to have NP. In DMP– patient group, 30 patients (65.2%) had normal DN4 scale score whereas 16 patients (34.8%) were found to have NP. Regarding NLR levels, a statistical significance was found between patients with normal DN4 scale score and patients with pathologies (p=0,045). No statistically significant difference was found between other biochemistry markers **(Table 4)**. A significant positive correlation was found between DN4 scores and HbA1c levels (p=0.042) **(Table 5)**.

Discussion

In the development of diabetic polyneuropathy, hyperglycemia, duration of diabetes, old age, hypertension, hypoinsulinemia, hyperinsulinemia, smoking and alcohol use, albuminuria, body mass index, hypercholesterolemia and genetic factors are regarded as major risk factors. Diabetic polyneuropathy is more common in men

Table 2. *Biochemical parameter of the groups*

Parameter	DMP+	DMP–	Control	*P*-value	*P1*-value	*P2*-value
HbA_{1c} (%)	11.24 ± 2.40	8.07 ± 2.18	5.47 ± 0.34	*0.000*	*0.000*	*0.000*
ESR (mm/h)	26.56 ± 16.13	21.97 ± 10.41	13.93 ± 7.93	*0.000*	*0.005*	0.168
CRP (mg/dl)	0.69 ± 0.32	0.60 ± 0.41	0.41 ± 0.20	*0.000*	*0.002*	0.392
MPV	8.58 ± 2.24	7.42 ± 1.07	7.96 ± 1.59	*0.018*	0.798	*0.001*
NLR	2.12 ± 0.97	2.08 ± 0.97	1.62 ± 0.35	*0.020*	*0.036*	*0.965*
PLR	128.58 ± 33.08	109.90 ± 20.19	97.19 ± 20.56	*0.000*	0.063	*0.002*
VAS	5.54 ± 2.06	3.54 ± 2.50				*0.000*
DN4	5.95 ± 2.11	3.26 ± 2.05				*0.000*

HbA_1: glycosylated hemoglobin, ESR: erytrocyhte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, VAS: Visual Analogue Scale, DN-4: Douleur Neuropathic 4 Question , P: comparison between those with polyneuropathy and the control group, P1: comparison between those without polyneuropathy and the control group, P2: comparison between the patient groups with and without polyneuropathy

Table 3. *Correlation between VAS and other variables*

		Variables							
		NLR	HbA1c	CRP	ESR	MPV	DN4	PLR	WBC
VAS	R	0,127	0,037	–0,009	0,049	0,152	*0,750*	–0,066	0,121
	P	0,235	0,732	0,936	0,648	0,152	*0,000*	0,535	0,257

than in women[4, 15]. Similarly, in our study, duration of the disease and male gender were found to be statistically significantly correlated with the development of diabetic polyneuropathy.

Hemoglobin A_{1c} is a marker that shows glucose tolerance and glucose regulation in diabetes, formed by slow and non-enzymatic glycosylation of hemoglobin[16]. In a study involving 1077 diabetic patients, *Abougalambou* et al. found the prevalence of diabetic neuropathy as 54.7%. The average HbA_{1c} levels of the patients in the study were high, and the HbA_{1c} value was a modifiable risk factor for the development of diabetic polyneuropathy[17]. Similarly, in our study, the differences of mean HbA_{1c} value in DMP+ patients was found to be statistically significant when compared to the DMP– patient group and to the control group. In addition, a significant positive correlation was found between DN4 scores and HbA_{1c} levels. These findings show that increased Hba_{1c} levels may pose a risk for the development of polyneuropathy in diabetic patients and that increases in HbA_{1c} levels are associated with the emergence of neuropathic pain symptoms.

Table 4. *Biochemical markers according to DN4 scale results*

Biochemical Markers	DN4 Scale Results	Mean ± SD	*P*-value
HbA1c (%)	Normal	9.09 ± 2.75	0.131
	Neuropathic pain	9.99 ± 2.76	
CRP (mg/dl)	Normal	0.61 ± 0.43	0.548
	Neuropathic pain	0.66 ± 0.31	
ESR (mm/h)	Normal	21.18 ± 15.22	0.091
	Neuropathic pain	26.33 ± 12.11	
MPV	Normal	7.54 ± 1.76	0.053
	Neuropathic pain	8.30 ± 1.83	
NLR	Normal	1.87 ± 0.67	*0.045*
	Neuropathic pain	2.26 ± 1.10	
PLR	Normal Neuropathic pain	119.33 ± 28.79 118.82 ± 28.89	0.934

HbA_1:glycosylated hemoglobin, ESR: erytrocyhte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, P: comparison between the biochemical markers and DN4 Scale results

There are many theories on the pathogenesis of diabetic neuropathy. One of them is oxidative stress and inflammation stemming from it. In many studies, diabetic patients are reported to have high levels of CRP, interleukin (IL) -1, IL-6 and inflammatory cytokine such as tumour necrosis factor (TNF) -α[18–20]. It is a well-known fact that low-level systemic inflammation plays an important role in the development of type 2 DM and microvascular and macrovascular complications of diabetes, including diabetic polyneuropathy[6, 7]. In our study, serum CRP and sedimentation rates were found to be higher in the DMP+ patient group than in the DMP– and control groups.

In a study by *Zaccardi* et al., patients with and without diabetes were compared in terms of MPV levels and it was found that patients with diabetes have significantly higher levels of MPV[21]. In another study by Özşenel et al., patients with diabetes-induced retinopathy and nephropathy and patients without any diabetes-induced complications were compared in terms of MPV rates, but no statistically significant difference was found[22]. Recently, NLR has widely been accepted as biomarker as it shows both high neutrophil levels demonstrating acute inflammation and negative effects of low lymphocyte levels illustrat-

Table 5. *Correlation between DN4 and other variables*

		Variables							
		NLR	HbA_{1c}	CRP	ESR	MPV	DN4	PLR	WBC
DN4	R	0.127	0.037	–0.009	0.049	0.152	*0.750*	–0.066	0.121
	P	0.235	0.732	0.936	0.648	0.152	*0.000*	0.535	0.257

ing physiological stress. The combination of NLR and PLR levels with other inflammatory markers has been reported as a good marker of inflammatory status. In a study by Ünal et al., a close relationship between NLR, PLR, anemia and albuminuria was reported in diabetic patients[23]. In another study by *Peng Luo* et al., NLR rates were examined in Type 2 DM patients as it was thought that chronic systemic inflammation contributes to the development of cardiovascular cases, and DM is a systemic inflammation. It has been suggested that NLR may be an independent risk factor for cerebrovascular diseases[24]. It has also been reported that PLR has a predictive effect for diabetes mellitus and its complications[25, 26].

In our study, NLR, PLR, and MPV levels were found to be statistically significantly higher in the DMP+ patient group compared to the control group. Likewise, PLR and MPV levels were found to be statistically significantly higher in the DMP+ group compared to the DMP– group. However, the NLR value was found to be higher in the DMP+ group than in the DMP– group, but not statistically significantly. These findings demonstrate that NLR, PLR and MPV levels, which are easily and cheaply obtained parameters, can be used as markers to predict the development of diabetic polyneuropathy. We think that the insignificant NLR difference may be due to the small size of our patient group and thus we recommend that it should be investigated in larger patient groups.

Diabetic peripheral neuropathy usually develops gradually and insidiously. It can manifest as pain, numbness, tingling, weakness and balance disorders, which can even lead to amputation[27]. Some patients are asymptomatic at the early stage and EMG examination may be normal even if they have clinical findings, which can lead to neglecting the disease. Neuropathic pain seen in patients with DPN negatively affects their quality of life. Involvement of unmyelinated C, thin myelinated Aδ, thick myelinated Aα, and Aβ-type neuronal fibres are typical. Although the exact order in which these fibres are affected is not known, there is evidence that thin fibres are involved earlier and that neuropathic pain precedes sensory losses and decreased nerve conduction velocity[28]. It has much negative effect on working life, sleeping pattern and life pleasure. Patients with diabetic neuropathy develop anxiety disorders (35%) and depression (28%)[29]. In our study, the VAS pain score was found to be statistically significantly higher in DMP+ patients compared to DMP– patients. The DN4 score was found to be higher in the DMP+ group. When the whole patient population was examined in terms of NLR and DN4 questionnaire, it was found that the NLR levels of the patients with a pathological DN4 score and neuropathic pain were statistically significantly higher than that of the patients with a normal DN4 score. In the DMP– patient group, NLR levels of those with neuropathic pain according to the DN4 scale were found to be significantly higher than of those without neuropathic pain. In line with these findings, we think that in this patient group determined as DMP– as a result of EMG examination, thin fibre neuropathy and related neuropathic pain may be present, and that NLR value can be used as a marker in the diagnosis of early diabetic polyneuropathy in DM patients.

When the VAS score and DN4 score of DMP+ patients in the patient group were examined, it was seen that they had significantly higher scores when compared to DMP– patients. In addition, the VAS and DN4 scores of both patient groups were statistically correlated, supporting each other.

Conclusion

In our study, statistically significant findings were obtained which support many other studies suggesting the factors of HbA_{1c}, CRP, sedimentation increases, and length of disease duration as risk factors for the development of diabetic polyneuropathy. In addition, statistically significant findings were found showing that new inflammatory markers, NLR, PLR and MPV levels, which were the focus of our study, could be markers for the development of DPN. In terms of neuropathic pain, a significant correlation was found between NLR level and DN4 score. This leads us to think that the combination of NLR level and DN4 score may be a good marker for the development of diabetic polyneuropathy.

The systemic complications of diabetes are still major public health problems. Diabetic neuropathy is one of the important complications that negatively affect the quality of life of people with diabetes. Therefore, there is a need for inexpensive and easy-to-access markers that we can use to diagnose neuropathy at an early stage.

There is no study in the literature that reveals the relationship between diabetic neuropathy, neuropathic pain and NLR, PLR and MPV. In this respect, our study is unique. However, the small number of patients in our study is a disadvantageous aspect. Therefore, its reliability in diagnosing patients with diabetic polyneuropathy should be further examined with studies with larger patient and control groups.

DATA AVAILABILITY – Data supporting the findings of this study are available from the corresponding author on request.

DECLARATIONS – The ethics committee of Harran University approved the study.

CONFLICT OF INTEREST – The authors declare no competing interests.

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EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Spinal anesthesia efficiency in thoracolumbar stabilizations

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| English | https://doi.org/10.18071/isz.76.0415 | www.elitmed.hu

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Érkezett:
2023. január 6.
Elfogadva:
2023. február 27.

Background and purpose – Spinal surgery has an important place in neurosurgery practice. Surgical procedures on the lumbar spine include stabilization, discectomy, foraminotomy and decompression. Lumbar and lower thoracic spinal surgery can be safely performed under spinal anesthesia (SA). However, there are not many studies on the safety and efficacy of spinal anesthesia in patients who have undergone long segment stabilization surgery.
Methods – Patients who underwent lumbar and lower thoracic spinal instrumentation operations with general anesthesia (GA) or spinal anesthesia were included in the study. Demographic characteristics and American Society of Anesthesiologists (ASA) physical status of the patients were all recorded. Visual analog scale and quality of life scores were obtained before and after the operation.
Results – 572 patients with SA and 598 patients with GA were included in the study, 352 / 347 had only-lumbar region and 220 / 251 had thoracolumbar region operations, respectively. All patients underwent short/long segment stabilization. Mean operating time was 106.1 / 156.7 minutes. Average blood loss was 375 / 390 mL. All patients were mobilized 16-24 / 24-36 hours after surgery. In our patient group, there were both high-risk and normal-risk subgroups in terms of ASA physical status. During the clinical follow-up, a statistically significant improvement was found for VAS and quality of life scores for both groups ($p<0.05$).
Conclusions – Spinal anesthesia appears to be a very effective method in lumbar and thoracolumbar surgery. Along with careful patient selection, using this highly effective

A spinalis anesztézia hatékonysága thoracolumbalis stabilizációban
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Háttér és cél – A gerincsebészet fontos helyet foglal el az idegsebészeti gyakorlatban. Az ágyéki gerinc sebészeti eljárásai közé tartozik a stabilizáció, a discectomia, a foraminotomia és a dekompresszió. Az ágyéki és alsó mellkasi gerincműtétek biztonságosan végezhetők spinalis anesztéziában (SA). A gerincvelői érzéstelenítés biztonságosságáról és hatékonyságáról azonban nem sok tanulmány áll rendelkezésre a hosszúszegmentum-stabilizációs műtéten átesett betegek esetében.
Módszerek – A vizsgálatba olyan betegeket vontunk be, akik lumbalis vagy alsó mellkasi gerincműtéten estek át általános érzéstelenítésben (GA) vagy spinalis érzéstelenítésben. A betegek demográfiai jellemzőit és az Amerikai Aneszteziológustársaság (American Society of Anesthesiologists, ASA) által előírt fizikai státuszt rögzítettük. A műtét előtt és után vizuális analóg skálán fájdalompontszámokat és életminőségi pontszámokat mértünk.
Eredmények – A vizsgálatba 572 SA-s és 598 GA-s beteget vontunk be, 352 / 347 esetben csak a lumbalis régióban, illetve 220 / 251 esetben a thoracolumbalis régióban végeztünk műtétet. Minden betegnél rövid/hosszú szegmensstabilizációt végeztünk. Az átlagos műtéti idő 106,1 / 156,7 perc volt. Az átlagos vérveszteség 375 / 390 ml volt. Minden beteget 16–24 / 24–36 órával a műtét után mobilizáltunk. Betegcsoportunkban az ASA fizikai státusz szempontjából magas és normálkockázatú alcsoport egyaránt volt. A klinikai utánkövetés során mindkét csoportban statisztikailag szignifikáns javulást tapasztaltunk a VAS- és életminőség-pontszámok tekintetében ($p < 0,05$).
Következtetés – A spinalis érzéstelenítés nagyon hatékony módszernek tűnik az

method provides a comfortable space for the surgeon.

Keywords: thoracolumbar, lumbar, stabilization, spinal, anesthesia

ágyéki és thoracolumbalis gerincműtéteknél. Gondos betegkiválasztás mellett ennek a rendkívül hatékony módszernek az alkalmazása kényelmes teret biztosít a sebész számára.

Kulcsszavak: thoracolumbalis, lumbalis, stabilizáció, spinalis, anesztézia

Spinal surgery has an important place in neurosurgery practice. Considering the high number of patients with low back and accompanying radicular pain, it is very important to minimize the complications associated with general anesthesia. Perioperative cardio-pulmonary stability is critical because of the increasing proportion of elderly patients and their comorbidities. So, the perioperative risk profile must have been modified[1, 2].

Surgical procedures on the lumbar spine include stabilization, discectomy, foraminotomy and decompression. Lumbar and lower thoracic spinal surgery can be safely performed under general endotracheal anesthesia (GA) or spinal anesthesia (SA)[3, 4]. Patients typically receive GA for these procedures[5].

Although it has been stated that SA can be used safely in operations such as simple discectomy and single-level decompression, and even in high-risk patients[6, 7], there are not many studies about the results in high-risk patients undergoing long segment stabilization. Thanks to SA, pulmonary and cardiovascular complications, hemorrhage and hypoxia are reduced. Especially in traumatic patients, it is very important to provide better postoperative pain and perioperative neural control. These complications can be seen after GA[8].

There are various studies in the literature in terms of postoperative nausea, postoperative pain, operation time, time spent in the post-anesthesia care unit and cost-effectiveness. In these studies, the effect of GA and SA on lumbar surgery was compared[9]. However, there are not many studies on the safety and efficacy of SA in patients who have undergone long segment stabilization surgery. In this study, we aimed to demonstrate that effective and beneficial results that can be obtained in patients undergoing thoracolumbar stabilization with spinal anesthesia.

Materials and methods

This study was performed in accordance with the Declaration of Helsinki. Patients or their legal caregivers, in cases of patients with intellectual disability, gave their informed signed consent and permitted their information to be used for scientific purposes.

We retrospectively analyzed the medical charts of all patients undergoing lumbar spine surgery in the period January 2014 – December 2020. 1170 patients who underwent lumbar and lower thoracic spinal instrumentation operations were included in the study. Patients aged 18 to 75 years with multilevel spinal involvement, patients with pain resistant to conservative treatment (at least 6 weeks), and patients with progressive neurological deficit were included in the study. Only cases operated on the lower thoracic region and thoracolumbar junction were included in the study. Patients with additional comorbidities such as cardiovascular, neuromuscular, renal, hepatic or metabolic disease, obesity, bleeding abnormalities and patients with cauda equina syndrome were not included in the study.

All surgical procedures were carried out by the same surgeons and same anesthesiologists with similar surgical and anesthetic techniques. No preemptive analgesia application was performed in our patients. SA was achieved with a heavy spinal dose of bupivacaine of 3-3.5 mL. Preloading was performed with normal saline (8 mL/kg) over 13 minutes. The patients were placed in a sitting position. Local anesthesia was achieved by local infiltration of 2-3 mL of 2% prilocaine. L1 level was determined as the upper point for SA. In the upper levels, local anesthetic and sedative agents were supported. The sensory level of the block was assessed by pinprick test. When the patient became anxious, midazolam 1-2 mg was given intravenously. After surgery, the patients remained in the PACU until they regained the adequate motor function of their lower extremities.

In the GA group, technically, total intravenous anesthesia (TIVA) was used. In the TIVA technique, when intravenous analgesic agents are titrated and administered, a fast, easy and reliable anesthesia is provided, while the total amount of anesthetic drug administered is reduced. Anesthesia induction was performed with 2 mg/kg iv propofol and 1 mcg/kg iv remifentanil. For endotracheal intubation, 0.1 mg/kg iv vecuronium was administered. After the prone position was placed, anesthesia was maintained with 50% O_2 and air together with 0.1 mcg/kg×min remifentanil and propofol infusion. Propofol infusion was administered for 20-30 minutes, respectively, as 12, 9 and 6 mg/kg×h.

Patient-Controlled Analgesia (PCA) treatment was applied to the patients in both groups in the postoperative period. Opioids and local anesthetics are generally preferred in PCA. Among them, opioids are widely used. Morphine is often used because it is cheap and effective. If morphine-related side effects develop, fentanyl or oxycodone is also preferred.

Demographic characteristics and American Society of Anesthesiologists (ASA)[10] physical status of the patients were all recorded. The clinical outcome was determined by the presence of postoperative pain, the absence of anesthesia-related complications, and the overall postoperative recovery. Intra- and postoperative variables including duration of operation, blood loss, complications, and patient satisfaction rate were documented. The patients were diagnosed with detailed neurological and radiological imaging examinations. Visual analog scale (VAS)[11] and quality of life scores were obtained before and after the operation. The VAS is a validated, subjective measure for acute and chronic pain. Quality of life was assessed using the SF-36 Health Survey[12]. At the time of discharge, usually two or three days after surgery for SA and four or five days for GA, postoperative clinical assessments were performed and patients were requested to complete the questionnaire again. In addition, the same procedures were repeated at the post-op third and 12th months. The groups were compared both within themselves and with each other.

Table 1. *Summarized data of patients*

Variables	Patients with SA (n = 572)	Patients with GA (n = 598)
Age, years	45.23±18.52	49.13±19.67
Male/Female	264/308	283/315
Operation site (%)		
Thoracolumbar	220 (38.4%)	251 (41.9%)
Lumbar	352 (61.6%)	347 (58.1%)
Mean weight (kg)	75.3	81.2
Mean Operating Time (min)	106.1	156.7
Average blood loss (mL)	375	390
Average hospital stay (day)	3-4	5-6
Mobilization time (hour)	16-24	24-36
ASA physical status		
I	49 (8.5%)	47 (7.8%)
II	192 (33.6%)	200 (33.4%)
III	217 (38%)	221 (37%)
IV	114 (19.9%)	130 (21.8%)
PACU VAS score	1.5±0.8	3.1±0.8
VAS 24h score	1.7±0.9	2.7±0.9

ASA: American Society of Anesthesiologists; PACU: post anesthesia care unit; VAS: visual analogue scale (0–10).
SA: spinal anesthesia; GA: general anesthesia

Statistical analysis

All statistical analyses were performed using IBM SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). The data are reported as the mean ± SD for normally distributed continuous variables and as the number and percentage for dichotomous variables. Data were compared between groups using the chi-square test for categorical data and the t-test for continuous data. A two-tailed $p < 0.05$ was considered to indicate statistically significant differences.

Results

Of the 1170 patients who were included in the study, 699 had only lumbar region operations and 471 had thoracolumbar region operations. The patients consisted of 547 (46.8%) males and 623 (53.2%) females with a mean age of 47.18 ± 19.09 years (range 19–75 years) and mean weight 78.25 kg (range, 54-108 kg) at initial symptom onset. The characteristic data and the surgical procedure for these patients and their pathologies are detailed in **Table 1** and **2**. Surgery was successfully completed in all cases.

In our patient group, there were both high-risk and normal-risk subgroups in terms of ASA physical status. In addition, there was no obvious difference in proportion **(Table 1)**. All patients underwent short (<2 level) / long (>2 level) segment stabilization operation **(Table 2)**. Mean operating time was 106.1 minutes (range, 82-158

Table 2. *Surgical procedure and preoperative diagnosis*

Procedure and diagnosis	Lumbar (n = 699)	Thoracolumbar (n = 471)
Short segment stabilization	341 (29.1%)	165 (14.1%)
Long segment stabilization	363 (31.1%)	301 (25.7%)
Recurrent disc herniation	152 (12.9%)	73 (6.2%)
Multilevel spinal stenosis	215 (18.4%)	147 (12.6%)
Vertebrae fracture	107 (9.1%)	112 (9,6%)
Spondylolisthesis	92 (7,9%)	64 (5.5%)
Revision of ınstrumentation	86 (7.4%)	122 (10.4%)

Table 3. *Complications*

Complications	Patients with SA (n = 572)	Patients with GA (n = 598)
Cardiac	6 (1%)	6 (1%)
Dural tear	5 (1%)	6 (1%)
Nausea-vomiting	17 (2.9%)	20(3.3%)
Bleeding	5 (1%)	7 (1.1%)
CSF-fistula	3 (0.5%)	5 (0.8%)
Headache	3 (0.5%)	1(0.1%)
Convert from SA to GA	12 (2.1%)	–
Allergy	4 (0.6%)	3 (0.5%)

Cardiac: rhythm disturbance, atrial fibrillation, bradycardia, hypotension; GA: general anesthesia; SA: spinal anesthesia; CSF: cerebrospinal fluid

minutes). Average blood loss was 375 mL (range, 190-875 mL), and no blood transfusion was required for the members of the SA group. On the other hand, mean operating time was 156.7 minutes (range, 95-218 minutes), and average blood loss was 390 mL (range, 205-1175 mL) for the GA group. No patient died in this series. For SA group, all patients were mobilized 16-24 hours after surgery and for GA group they were mobilized 24-36 hours after surgery. The average duration of hospital stay was 2-3 days for the SA group and 4-5 days for the GA group, respectively.

Cardiac complications (rhythm disturbance and atrial fibrillation) developed in two patients, and bradycardia and hypotension developed in four patients due to increased anesthesia level. Thereupon, the patients were placed in the supine position during the perioperative period and after the necessary medications were taken, they were placed in the prone position again and their operations were completed without any problems. In addition, primary suturation was performed due to dural tear development in five patients during surgery in the SA group. When the complication rates were compared between the two groups, no significant difference was observed.

In the SA group, 12 patients had to be converted to GA before starting the operation. In 10 of these patients, adequate anesthetic effect was not observed in the desired dermatome in the control examination, while problems occurred during lumbar puncture in 2 of them. The operations of the patients were completed without any problems. The postoperative complications are shown in detail in **Table 3**. In addition, patients' pain conditions during their early stay in the PACU were also noted **(Table 1)**.

Table 4 and **5** shows the changes in VAS scores after the intervention. Detailed quality of life scoring for the groups are shown in **Table 6** and **7**. When the VAS and quality of life scores of the patients were evaluated, statistically significant improvement was found in the early post-op period; no significant difference was found in the early post-op period and the last clinical follow-up. When the two groups were compared with each other, no statistically significant difference was found. However, VAS-PACU and VAS-24h scores were found to be lower in the SA group and a statistically significant difference was obtained ($p<0,05$).

Table 4. *VAS scores and clinical follow-up (with SA patients)*

	Lumbar (n = 352)	Thoracolumbar (n = 220)	p-value
Pre VAS score	7.8 ± 2.86	7.2 ± 2.14	
Post VAS score, months (3rd /12 th)	2.2 ± 0.41 / 3.1 ± 0.64	2.1 ± 0.61 / 3.0 ± 0.34	<0.05
Early clinical follow-up (Improve/Stable)	325 / 27	192 / 28	<0.05
Last clinical follow-up (Improve/Stable)	310 /42	173 / 47	<0.05

VAS: visual analogue scale (0–10); SA: spinal anesthesia

Table 5. *VAS scores and clinical follow-up (with GA patients)*

	Lumbar (n = 347)	Thoracolumbar (n = 251)	p-value
Pre VAS score	7.6 ± 2.27	7.4 ± 2.21	
Post VAS score, months (3rd /12 th)	2.0 ± 0.37 / 3.0 ± 0.68	2.2 ± 0.58 / 2.9 ± 0.29	<0.05
Early clinical follow-up (Improve/Stable)	317 / 30	221 / 30	<0.05
Last clinical follow-up (Improve/Stable)	307 /40	193 / 58	<0.05

VAS: visual analogue scale (0–10); GA: spinal anesthesia

Discussion

Our aim with this retrospective study conducted with a large cohort was to determine whether spinal anesthesia is safe in patients undergoing long/short segment stabilization surgery. In addition, we think that our study makes a significant contribution to the literature with the high number of patients with high-risk ASA physical status. Posterior lumbar stabilization can be per-

formed under SA without mortality and with very low morbidity[13].

It has been reported in the literature that SA can be used effectively in the lower thoracic and lumbosacral regions[14]. It has also been shown that SA and GA are reasonable anesthetic approaches, especially in the lumbar region, and do not outweigh each other in terms of mortality or morbidity[15]. The fact that GA is a widely accepted method for lumbar region operations has been associated with the comfort level of the anesthetists and the preference of the surgeon[16].

SA has become increasingly popular in recent years. Moreover, high-risk patients may not tolerate GA owing to complications or side effects[17]. Atelectasis and pulmonary aspiration, cardiovascular imbalance, respiratory collapse and nerve injury are several perioperative complications and can be associated with GA[18, 19]. It is known that the risk of spinal degenerative diseases increases with age. With the increase of risky patient rates in the elderly population, it is very important to reduce anesthetic complications as much as possible[20]. In our study, when we compared the two groups with different complication rates, similar results were obtained. Due to the high number of high-risk patients in our study, we think that SA can be used safely in this group as well.

Table 6. *Detailed Quality of Life Score (with SA patients)*

Mean scores for SF-36	Thoracolumbar	Lumbar	p-values
Physical functioning	81.32/92.08/	80.24/92.91/	<0.05
(Pre/3rd/12th)	91.17	91.77	
Role limitation caused by physical health	75.27/90.85/	76.29/91.34/	<0.05
(Pre/3rd/12th)	89.87	90.27	
Body pain	55.49/81.92/	55.72/81.99/	<0.05
(Pre/3rd/12th)	80.78	81.57	
General health	66.79/78.53/	65.79/79.32/	<0.05
(Pre/3rd/12th)	77.63	78.23	
Vitality (energy/fatigue)	56.87/64.21/	55.89/64.61/	<0.05
(Pre/3rd/12th)	63.88	64.28	
Social functioning	81.55/90.46/	81.78/91.13/	<0.05
(Pre/3rd/12th)	89.25	89.67	
Role limitation caused by emotional problems	91.31/95.56/	90.91/95.87/	<0.05
(Pre/3rd/12th)	94.63	94.42	
Emotional well-being	67.39/74.84/	68.01/75.27/	<0.05
(Pre/3rd/12th)	73.78	74.51	
Physical component score (PCS)	44.53/50.32/	45.17/51.02/	<0.05
(Pre/3rd/12th)	49.87	49.95	
Mental component score (MCS)	53.67/56.88/	53.52/56.71/	<0.05
(Pre/3rd/12th)	55.76	55.61	

The fact that patients did not complain about pain in the first few hours after the operation with SA was attributed to the inhibition of nociceptive pathways by this form of anesthesia. Thus, the reduction of sensorial block lasts longer than motor block. Moreover, acute pain scores were found to be lower in SA than in GA patients. Although postoperative VAS scores were significantly lower in SA patients in the first three hours, first analgesic requirement times were similar[21, 22]. The need for analgesic medication of our patients manifested itself between the third and fifth hours after the operation. In our study and in correlation with this, VAS-PACU and VAS-24h scores were found to be lower in the SA group and a statistically significant difference was obtained. The quality of life of the patients, which has not been mentioned in the literature before, was also evaluated in our study. We found no statistically significant difference between the two groups in long-term results in both quality of life and VAS scores. It was noteworthy that both groups achieved quite satisfactory results.

In spine surgery, operation times can be extended. When the discomfort felt due to the prone position of the patients is added to this, there may be problems in the tolerance of the patients from time to time. Of course, this problem can be solved with certain medical treatments. Although the lack of tolerance sometimes causes distress to both the surgeon and the patient during surgery, SA is the preferred method due to low post-op PACU-pain scores and low complication rates. It should be kept in mind that the agents for sedation may cause airway obstruction requiring intervention[23, 24]. In addition, older patients demonstrate delayed recovery of psychomotor function after sedation. Although we had to give additional sedation in 25.6% of our cases, we did not encounter any complications.

The reported frequencies of serious complications are low and mainly due to the spread of anesthesia leading to circulatory and respiratory insufficiency. In the literature, it has been shown that cardiac parameters, heart rate and blood pressure are lower in patients undergoing SA. Thus, the findings that SA has short-term benefits were supported[7, 21]. In addition, different studies comparing SA and GA reported no significant difference in morbidity

Table 7. *Detailed Quality of Life Score (with GA patients)*

Mean scores for SF-36	Thoracolumbar	Lumbar	p-values
Physical functioning	79.27/91.12/	81.71/81.9/	<0.05
(Pre/3rd/24th)	90.42	80.08	
Role limitation caused by physical health	73.12/89.66/	75.63/75.9/	<0.05
(Pre/3rd/24th)	88.15	74.85	
Body pain	54.79/80.97/	55.98/56.1/	<0.05
(Pre/3rd/24th)	80.05	55.74	
General health	64.53/77.86/	67.03/67.3/	<0.05
(Pre/3rd/24th)	76.93	66.95	
Vitality (energy/fatigue)	55.21/63.80/	56.92/57.1/	<0.05
(Pre/3rd/24th)	62.45	56.84	
Social functioning	80.42/90.12/	82.56/82.6/	<0.05
(Pre/3rd/24th)	89.03	82.01	
Role limitation caused by emotional problems	89.67/95.47/	91.82/92.2/	<0.05
(Pre/3rd/24th)	94.17	92.11	
Emotional well-being	66.24/73.68/	67.91/68.2/	<0.05
(Pre/3rd/24th)	72.57	68.30	
Physical component score (PCS)	43.43/51.17/	44.88/44.9/	<0.05
(Pre/3rd/24th)	49.67	44.81	
Mental component score (MCS)	52.97/55.82/	53.44/53.6/	<0.05
(Pre/3rd/24th)	54.73	53.51	

and mortality[25]. Reductions in hospital stay, nausea and vomiting, and PACU pain scores were found in patients undergoing SA, and it provided additional benefits such as better perioperative hemodynamics and shorter anesthesia time[26]. There are also studies in the literature showing that no particular difference can be found between the two methods[3, 4]. Consistent with the literature data, we found no statistically significant difference in terms of operation time, amount of bleeding, mobilization time and hospital stay between the groups. However, it was noted that the SA group was better in all data. We attributed the shortening of the operation time to the decrease in the time spent in the PACU and the rapid recovery of the patients from the anesthesia effect.

The risk of hospital-acquired infections, pressure ulcers, and other adverse events increase with the length of hospital stays. Thus, increased hospital costs, and further prolonging hospital stay are seen. Shorter operative time and anesthesia time suggest a faster turnover rate and more efficient use of the operation room. Taken together, SA may be the more cost-effective method of anesthesia[27, 28]. However, before drawing any such conclusions, it is important to consider comparative postoperative complications[29]. As we have seen, in some patients, the desired dermatomal level of anesthetic effect may not be achieved. In addition, a successful lumbar puncture cannot be achieved in some patients. For this reason, proper patient selection and the surgeon's habits should always be kept in the foreground.

Limitations

The limitations of our study are the retrospective study design, and the selection of all patients from a single center.

Conclusion

Both general and spinal anesthesia have been previously reported to be effective techniques for use in 1-2 levels of lumbar laminectomy or disc surgery. However, spinal anesthesia appears to be a very effective method in lumbar and thoracolumbar surgery where long segment stabilization will be performed, including high-risk patients. Improvements in the quality of life of patients with low complication rates are pleasing. Along with careful patient selection, using this highly effective method provides a comfortable space for the surgeon.

DECLARATION OF CONFLICTING INTERESTS – The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
FUNDING – The authors received no financial support for the research, authorship, and/or publication of this article.

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ESETISMERTETÉS

CASE REPORT

Pembrolizumab-induced peripheral nervous system damage: A combination of myositis/ myasthenia overlap syndrome and motor axonal polyneuropathy

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PRINT | English | https://doi.org/10.18071/isz.76.0422 | www.elitmed.hu

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Érkezett:
2023. március 9.
Elfogadva:
2023. április 8.

Introduction – Immune-checkpoint inhibitors (ICI) are effective drugs in cancer treatment that block immune checkpoints and stimulate an attack on cancer cells. However, various side effects were reported with ICIs. Peripheral nervous system (PNS) side effects are three times more frequent than those in the central nervous system.
Case report – A 63-year-old male patient was admitted to our department with a 10-day history of dyspnea, diplopia, and generalized weakness. He had a diagnosis of non-small cell lung cancer, which was treated with pembrolizumab. His neurological symptoms appeared one week after the second course of pembrolizumab, and gradually worsened. His neurological examination showed nasal speech, bilateral ptosis, tongue and neck flexor weakness, prominent asymmetrical upper limb weakness, and mild lower limb weakness. Deep tendon reflexes and sensory examination were normal. He had an elevated creatine kinase level (4430 U/L). Needle electromyography (EMG) showed a myopathic pattern, and single fiber EMG demonstrated an increased jitter in the right frontal muscle. Pembrolizumab treatment was discontinued, and intravenous methylprednisolone followed by intravenous immunoglobulin (IVIg) were initiated. His symptoms gradually improved. However, his weakness began to worsen after a month, and repeated nerve conduction studies

Pembrolizumab által kiváltott perifériás idegrendszeri károsodás: A myositis / myasthenia overlap szindróma és a motoros axonalis polyneuropathia kombinációja

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Bevezetés – Az immunellenőrző pontokat blokkoló immunellenőrzőpont-gátlók (ICI-k) hatékony gyógyszerek a rák kezelésében, mivel segítik a rákos sejtek elleni támadás beindulását. Mindazonáltal, az ICI-kkel kapcsolatban számos különböző mellékhatásról számoltak be. A perifériás idegrendszeri (PNS) mellékhatások háromszor gyakoribbak, mint a központi idegrendszeri mellékhatások.
Esetismertetés – Egy 63 éves férfi beteget 10 napja fennálló nehézlégzéssel, diplopiával és generalizált gyengeséggel vettek fel osztályunkra. Korábban nem kissejtes tüdőrákot diagnosztizáltak nála, amit pembrolizumabbal kezeltek. Neurológiai tünetei egy héttel a második pembrolizumabciklus után jelentek meg, és fokozatosan romlottak. Neurológiai vizsgálata orrhangú beszédet, kétoldali ptosist, a nyelv- és a nyakhajlító izmok gyengeségét, markáns aszimmetrikus felső végtagi gyengeséget és enyhe alsó végtagi gyengeséget mutatott. A mély ínreflexek és az érzékszervi vizsgálat normális volt. A kreatinkináz szintje emelkedett volt (4430 E/l). A tűelektromiográfia (EMG) myopathiás mintázatot mutatott, és az egyszálas EMG fokozott remegést mutatott a jobb frontális izomban. A pembrolizumabkezelést abbahagyták, és intravénás metilprednizolon, majd intravénás immunglobulin (IVIg) adását kezdeményezték. A beteg tünetei fokozatosan javultak. A gyengesége azonban egy hónap múlva súlyosbodni kezdett, és az ismételt idegvezetési vizs-

showed a predominantly motor axonal polyneuropathy. Thereafter, the patient was treated with IVIg infusions (0.4 g/every two weeks) to maintain his motor function.
Conclusion – Our case showed that ICIs could simultaneously or sequentially cause damage in multiple domains of the PNS. Early recognition of these adverse events is essential since the outcome is favorable with rapid cessation of the causative ICI and administration of immune-modulator treatment.

Keywords: immune checkpoint inhibitor, polyneuropathy, myasthenia gravis, myocarditis, intravenous immunoglobulin

gálatok túlnyomórészt motoros axonalis polyneuropathiát mutattak ki. Ezt követően a beteget IVIg-infúziókkal (0,4 g/kétheten-te) kezelték a motoros funkció fenntartása érdekében.
Következtetés – Betegünk esete azt mutatja, hogy az ICI-k egyidejűleg vagy szekvenciálisan károsodást okozhatnak a PNS több területén. E mellékhatások korai felismerése alapvető fontosságú, mivel a kiváltó ICI-kezelés gyors abbahagyásával és immunmoduláns kezeléssel kedvező a kimenetel.

Kulcsszavak: immunellenőrzőpont-gátló, polyneuropathia, myasthenia gravis, myocarditis, intravénás immunglobulin

Immune-checkpoint inhibitors (ICI) recently emerged as a state-of-art therapy for numerous cancer types. By blocking immune checkpoints, which are down-regulators of the immune system to induce tolerance for self-cells, they stimulate an attack on cancer cells. Owing to their high efficacy, the number of ICIs is rapidly expanding. The primary target of the ICIs includes T-lymphocyte-associated antigen 4, programmed cell death protein-1, and its ligand[1]. Although they are highly effective in cancer treatment, various side effects, primarily related to over-activation of the immune system, were reported with ICIs. In a large meta-analysis, the most frequent immune-mediated adverse events included hypothyroidism, vitiligo, hepatitis, pneumonitis, colitis, and hypophysitis[2]. Overall, neurological side effects occur in 1% of the patients. Among them, peripheral nervous system (PNS) involvement, including myasthenic syndrome, myositis, Guillain-Barré syndrome and other peripheral neuropathies, is three times more frequent than central nervous system (CNS) involvement[3]. ICI-related myasthenic syndrome (IrMG) and myositis (IrMyositis) typically manifest with peculiar symptoms and occur separately or in combination, suggesting a distinct myositis/myasthenia overlap syndrome. On the other hand, co-occurence of myositis/myasthenia overlap syndrome, and ICI-related peripheral neuropathy (IrPN) was only reported in a single case report[4]. Here, we describe a patient with non-small cell lung cancer who had a sequential occurrence of myositis/myasthenia overlap syndrome and axonal polyneuropathy.

Case description

A 63-year-old male patient was admitted to our department with a 10-day history of fatigable dyspnea, diplopia, and generalized weakness. Five days before his admittance, he was diagnosed with myasthenia gravis and prescribed prednisolone 80 mg/day and pyridostigmine 60 mg, four times a day, but his symptoms continued worsening. His past medical history was significant for non-small cell lung cancer which was initially treated with cisplatin and pemetrexed. After two cycles, pembrolizumab was added. Although a therapeutic response was achieved with this treatment, one week after the second course of pembrolizumab his neurological symptoms appeared and gradually worsened. He was also using amiodarone 200 mg/day for inducible ventricular fibrillation. His family history was unremarkable.

His neurological examination showed nasal speech, asymmetrical bilateral ptosis, bilateral limitation of lateral gaze, tongue weakness, neck flexor weakness, asymmetrical proximal and distal weakness in the upper, and symmetrical weakness in proximal lower limb muscles. Deep tendon reflexes and sensory examination were normal. Blood biochemistry analysis revealed elevated creatine kinase (4430 U/L) and troponin T (942 pg/mL) levels. Needle EMG showed myogenic motor unit potentials in all examined muscles **(Figure 1A)** accompanied by positive sharp waves. Repetitive nerve stimulation test from the right trapezius muscle was normal. However, an increased jitter was observed in the right frontal muscle

(Figure 1B). Nerve conduction studies were normal **(Figure 2A, 2B)**. Acetylcholine receptor antibodies (Anti-AchR), muscle-specific kinase antibodies (Anti-MuSK), and the paraneoplastic antibody panel were negative (Anti-Hu, anti-Yo, Anti-Ri, Anti-amfifizin, Anti-NMDAR, Anti-VGKC). Anti-titin antibodies were positive in the myositis-associated antibody panel. Pulmonary function tests and arterial blood gas analysis revealed a restrictive ventilatory impairment, and non-invasive mechanical ventilation was initiated.

With these findings, a diagnosis of myositis/myasthenia overlap syndrome was made and pembrolizumab treatment was immediately discontinued. Intravenous methylprednisolone 1000 mg/day for five days followed by intravenous immunoglobulin (IVIg) 2 g/kg were initiated and pyridostigmine was stopped due to a lack of meaningful clinical response. After one week, his symptoms gradually improved with only a residual mild weakness bilaterally in finger extensors, and iliopsoas. Electrocardiograph, echocardiography, and cardiac MRI were negative for accompanying myocarditis. He was discharged from the hospital with oral prednisolone 60 mg/day and monthly infusions of IVIg 0,4 g/kg. However, after a month, his weakness began to worsen, predominantly in the upper extremities. In addition to muscle weakness, deep tendon reflexes were absent, except for bilateral hypoactive triceps reflex and he had hypoesthesia and hypoalgesia in the distal parts of the lower limbs. Therefore, nerve conduction studies were repeated which showed a predominantly motor axonal polyneuropathy **(Figure 2C, 2D)**. CK level was normal (61 U/L), and troponin T level decreased to 180 pg/mL. A slightly elevated protein level (49 mg/dl) without pleocytosis was observed in cerebrospinal fluid (CSF) analysis. Hence, another course of IVIg 2 g/kg was initiated for the possibility of IrPN. Progression of weakness stopped with this treatment, and he was discharged with prednisolone 40 mg/day. Follow-up scans were compatible with remission in his underlying malignancy. Therefore, cisplatin and pemetrexed were also stopped. Three weeks after, his symptoms relapsed with increased weakness, more pronounced in the upper limbs. Repeated NCS showed a decrease in the motor amplitudes in the upper limb nerves. CK level was normal. Thus, a repeated dose of IVIg 0,4 g/kg was initiated. However, his symptoms continued to worsen in the following week, and another loading dose of IVIg (2 g/kg) was given. His symptoms stopped worsening with this treatment. However, the remission period lasted for two weeks, a repeated IVIg (1 g/kg) infusion was required. Thereafter, the patient was treated with IVIg infusions (0,4 g/every two weeks) to maintain his motor function and he was put on a steroid tapering scheme. According to Naranjo's adverse drug reaction assessment score of 6, IrMyositis, IrMG, combined with IrPN were probably caused by pembrolizumab.

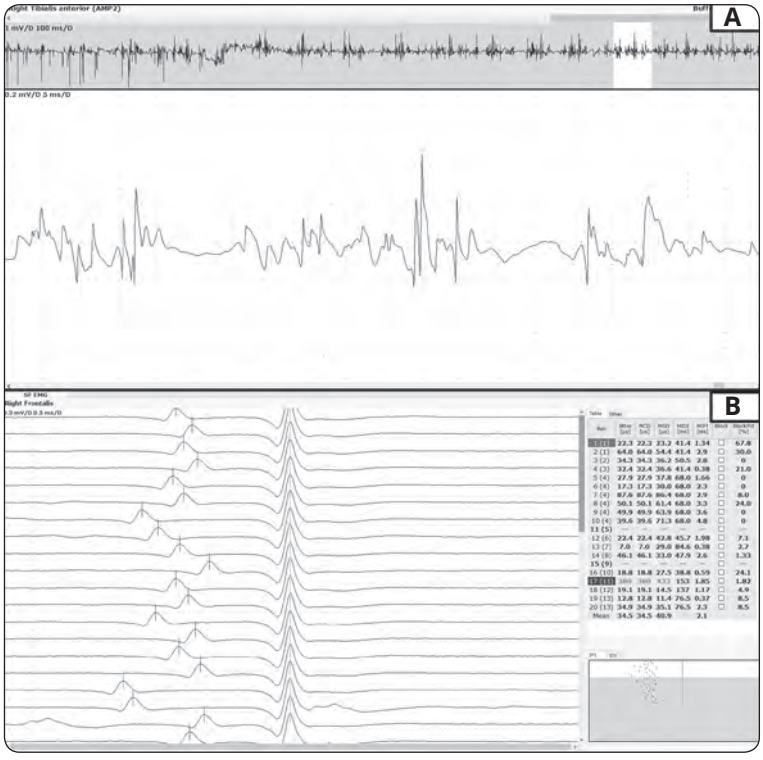

Figure 1. *Needle electromyography* **(1A)** *of the right tibialis anterior muscle demonstrated myogenic motor unit potentials and single fiber electromyography* **(1B)** *showed an increased jitter in the right frontal muscle*

Discussion

Here, we report a patient exhibiting a combination of myositis/myasthenia overlap syndrome, and polyneuropathy after pembrolizumab treatment. Although ICI-related neuromuscular system damage is rare, it can be life-threatening. The most frequent neuromuscular syndromes associated with ICIs are myositis, myasthenic syndrome, demyelinating polyradiculoneuropathy, and overlaps of these conditions[5]. Presentation and disease course of ICI-related neuromuscular conditions differ from the typical forms of these disorders.

Like in the case of our patient, IrMyositis typically occurs in the first three months of ICI treatment and progresses to a peak in 1-30 days[5]. Initially, our patient had proximal and distal weakness in the upper limbs accom-

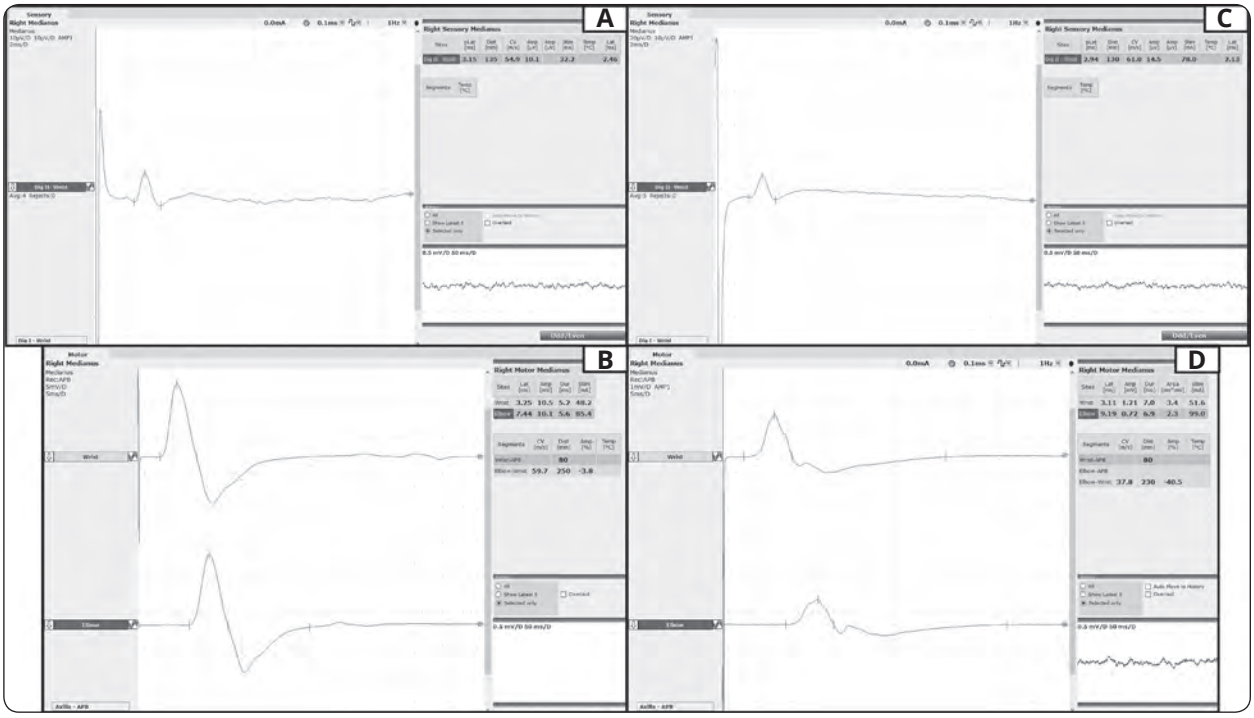

Figure 2. *In nerve conduction studies, median sensory nerve action potential (SNAP) and median motor compound motor action potential (CMAP) were normal in the initial test* **(2A and 2B)**. *On the other hand, median motor CMAP amplitude was markedly decreased in the repeated test, whereas median SNAP remained normal* **(2C and 2D)**

panied by proximal weakness in the lower limbs. Along with this, oculo-bulbar muscle involvement was prominent. Likewise, the typical presentation of the previously published cases includes axial and limb-girdle weakness accompanied by oculomotor and bulbar involvement. In addition, 20% of patients with IrMyositis need non-invasive or invasive ventilatory support like our patient[6]. The diagnosis of myositis was straightforward in our patient due to a subacute muscle weakness and hyperCKemia with typical EMG findings. Therefore, we did not perform a muscle biopsy.

Around 30% of IrMyositis overlap with IrMG, which can present with a severe disease course and have fatal outcome[5]. On the other hand, approximately 20% of the patients only exhibit mild ocular symptoms. The impact of the myasthenic component in IrMyositis is a matter of debate since ocular involvement can also be observed in IrMyositis. Meanwhile, like in the case of our patient, a clear benefit from cholinesterase inhibitors may not be evident in patients with a myositis/myasthenia overlap syndrome[7]. Anti-AChR antibodies can be observed in about half of the patients, whereas Anti-MuSK was found only in a single patient previously[8]. Both antibodies were absent in our patient. On the other hand, anti-titin antibody test was positive. Interestingly, it was previously reported in patients with a combination of idiopathic inflammatory myopathy and myasthenia gravis without ICI use[9, 10]. Although this suggests the possibility of a mechanistic role of anti-titin in the combination of these disorders, future studies are necessary to conclude its function in myositis/myasthenia overlap syndrome. The reported incidence of ICI-related myocarditis is up to 1.14%. It is more frequent with an accompanying IrMG or IrMyositis[6]. Although cardiac MRI was normal, highly elevated troponin-T could suggest at least a minor cardiac involvement in our patient.

IrPN occurs in 1-3% of patients in previous case series and tends to present after a median of 3-3.5 doses of ICIs, later than the typical onset of myositis/myasthenia overlap syndrome[11]. The most common presentation is acute or chronic inflammatory demyelinating neuropathy. Other reported neuropathy types were cranial, small fiber neuropathies, ANCA-associated mononeuritis multiplex, sensory neuronopathy, length-dependent sensorimotor axonal polyneuropathy, and neuralgic amyotrophy[12]. Our patient had an acute onset pure motor axonal neuropathy, mimicking an acute motor axonal neuropathy (AMAN). However, course of the neuropathy was progressive. Although it is difficult to attribute axonal changes only to ICIs, since our patient also underwent a cytotoxic chemotherapy in addition to pembrolizumab, the acute-onset with therapeutic response to IVIg and an albumino-cytologic dissociation suggested inflammatory mechanism. For the treatment of IrPN, the immediate discontinuation

of ICIs is uncontroversial. Corticosteroids are not recommended for the treatment of AMAN or typical Guillain-Barré syndrome (GBS). On the other hand, in ICI-related GBS, steroids are considered as first-line treatment option in the guidelines of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)[13, 14]. We hesitated to use high-dose steroids in our patient because that could lead to a potential exacerbation which was described in the motor forms of chronic immune-mediated neuropathies such as multifocal motor neuropathy and motor chronic inflammatory demyelinating neuropathy[15]. Typically, the outcome is described to be favorable with steroids and discontinuation of ICIs in IrPN and maintenance therapy are usually not required[12]. However, our patient significantly deteriorated between IVIg doses, and showed an IVIg-dependent clinical course.

Conclusion

Although ICIs revolutionized cancer treatment, adverse events can be life-threatening. Our case showed that ICIs could simultaneously or sequentially cause damage in multiple domains of the peripheral nervous system. Early recognition of these adverse events is of the utmost importance since the outcome is favorable with rapid cessation of the causative ICI and administration of immune-modulator treatment.

DECLARATIONS – Informed consent to publish the case report was obtained from the patient.
CONFLICTS OF INTEREST AND SOURCE OF FUNDING – None declared.

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ESETISMERTETÉS

CASE REPORT

Minimal invasive transnasal endoscopic removal of intracranial foreign body after airbag deployment

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PRINT | English | https://doi.org/10.18071/isz.76.0427 | www.elitmed.hu

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Érkezett:
2022. június 8.
Elfogadva:
2022. november 27.

Airbag induced injuries such as skull and cervical spine fractures, epidural and subdural hematomas, atlantooccipital dislocations or brainstem lacerations are already documented in published literature, however, no previous case have been published about a penetrating foreign body of the skull base following airbag deployment. Removal of an intracranial foreign body is very dangerous and difficult, or even if it possible and necessary, requires open surgery in most of the cases. In this article we present the minimal invasive, transnasal removal of a coin from the intracranial, frontobasal region using high-resolution endoscopy combined with image-guided navigation.

We report the case of a 59-year-old male who was brought to the emergency department after a car accident. He suffered a penetrating injury by a coin that was placed on the car's airbag at the moment of the accident. Upon the airbag being deployed the foreign body entered the skin through the right lower eyelid, crossing the orbital cavity, ethmoid cells, sphenoid sinus and the anterior part of the planum sphenoidale at an equal distance of 2mm from the two internal carotid arteries, extending into the intracranial space, without injuring the pituitary stalk and the chiasm. We proceeded to remove the coin endoscopically using a transnasal transseptal transsphenoidal approach under general anesthesia. The dura was closed with a multilayer skull base reconstruction technique using two layers of abdominal

Kinyíló légzsák okozta intracranialisan penetráló idegentest minimálinvazív transnasalis endoszkópos eltávolítása

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Légzsák okozta koponya- és nyakigerincsérülések, epiduralis és subduralis haematomák, atlantooccipitalis ficamok vagy agytörzsi sérülések dokumentáltak a szakirodalomban, azonban kinyíló légzsák utáni, intracranialisan penetráló, koponyabázist elérő idegentest esete eddig nem került közlésre. Amennyiben szükség van rá, és technikailag lehetséges, az intracranialis idegentest-eltávolítás igen veszélyes és körülményes feladat, és az esetek nagy részében nyílt műtéti feltárást igényel. Ezen esetismertetésben egy minimálisan invazív, transnasalis műtéti technikát mutatunk be, mely során nagy felbontású sebészeti mikroszkópot, endoszkópot és neuronavigációt használtunk az idegentest eltávolításához.

Egy 59 éves férfi került beszállításra a sürgősségi osztályra autóbaleset után. A baleset során a légzsákon elhelyezett pénzérme okozott intracranialisan penetráló sérülést. A légzsák kinyílását követően a rajta elhelyezett pénzérme az alsó szemhéjon, majd a szemüregen, ethmoidalis sejteken, sinus és planum sphenoidalén keresztül jutott az intracranialis térbe, ahol egyenlő távolságra állt meg a két arteria carotis interna között, azoktól 2 mm-re, anélkül, hogy ezen érképleteket, a hypophysis nyelét vagy a chiasma opticumot megsértette volna. Eltávolítását általános érzéstelenítésben, transnasalis transseptalis megközelítés során endoszkóppal végeztük. A kemény agyhártyán levő szövethiányt több rétegű zárási technikával láttuk el, ami két réteg hasi zsírszövetből és

free fat and nasal septal mucoperiosteal flap. There were no postoperative complications, nor CSF rhinorrhea. The patient was discharged 10 days after the operation.

To our knowledge, this is the first published case of a penetrating foreign body of the skull base, extending into the intracranial cavity following airbag deployment. In some dedicated cases, a minimal invasive endoscopic approach should be considered as an alternative to anterior craniotomy if access is possible when foreign bodies from the skull base area need to be removed. This procedure is efficient, safe and minimally invasive.

Keywords: intracranial foreign body, coin, airbag induced injury, endoscopic approach, skull base reconstruction

orrnyálkahártya-lebenyből állt. Posztoperatív rhinorrhoea, illetve egyéb szövődmény nem jelentkezett. A beteget 10 nappal a beavatkozás után emittáltuk.

Ismereteink alapján ez az első intracranialisan penetráló idegentest okozta sérülés esete az irodalomban, ami légzsák kinyílása következtében jött létre. Hasonló, dedikált esetekben a koponyabázist is érintő idegentestek eltávolítása érdekében minimálisan invazív, endoszkópos megközelítés mérlegelendő az anterior craniotomiás feltárással szemben.

Kulcsszavak: intracranialis idegentest, pénzérme, légzsák okozta sérülés, endoszkópos megközelítés, koponyaalap-rekonstrukció

Airbags act as an energy-absorbing medium between a vehicle's occupants and steering wheel, headliner and windshield. They became widespread in the 1990s and ever since then they are an essential part of an automobile. Modern vehicles may feature up to 12 airbag modules in various locations. Although these security measures decrease the severity of injuries related to motor vehicle accidents, published literature demonstrates that they can lead to serious eye and head injuries[1–4].

Penetrating foreign bodies of the skull base and paranasal sinuses, especially of the ethmoidal and sphenoidal sinuses, are very rare[5–7] and may pose complications due to the potential major vessel and nerve injury, intracranial hemorrhage, cerebral contusion, consequential edema, focal neurological deficits, infections and hydrocephalus[8]. Surgical removal is associated with an increased risk due to the surrounding anatomical structures such as the internal carotid artery, which makes sphenoidal sinus injures a potentially life-threatening occurrence[9 10]. Because of this most of the foreign bodies penetrating the anterior fossa and skull base are removed via anterior craniotomy, which carries a significantly higher perioperative risk. Endoscopic removal of foreign bodies from the nose and paranasal sinuses has been previously performed, however, the endoscopic approach has rarely been used in case of intracranial foreign bodies[11, 12].

In our institute, we have been using a neuroendoscope procedure for around thirty years. At the beginning only III. ventricle fenestration and tumor biopsy was performed, but as our experience has grown, we have supplemented our repertoire with endonasal transsphenoidal pituitary surgery, and finally we have transplanted the endoscopic approach for the management of the larger and more complex tumors invading the sinonasal area and the skull base during the last 10 years[13–15]. With the aim of minimizing the invasivity, the potential complications and the unsatisfactory cosmetic outcomes, we took the courage to remove the intracranial foreign body endoscopically.

Based on this, the authors hereby present the successful transnasal endoscopic removal of a foreign body which was impacted in the skull base, "decapitating" the sphenoid sinus following airbag deployment during a car accident. The multidisciplinary surgical management was carried out using high-resolution endoscopy and image-guided navigation by a team consisting of neurosurgeons and otorhinolaryngologists.

Case report

Patient history

A 59-year-old male was brought to the emergency department by ambulance after being involved in a car accident. Respecting the polytrauma protocol, the patient immediately underwent a whole-body CT scan, which revealed a circular shaped foreign body (28 × 30 × 2 mm) impacted in the medial, frontobasal area above the planum sphenoidale, extending into the intracranial space. The scan also revealed right periorbital swelling, free air and blood in the right orbit, fracture of the medial and inferior wall of the right orbit and ethmoidal labyrinth. Intracranial free air was observed frontally on the right side **(Figure 1)**.

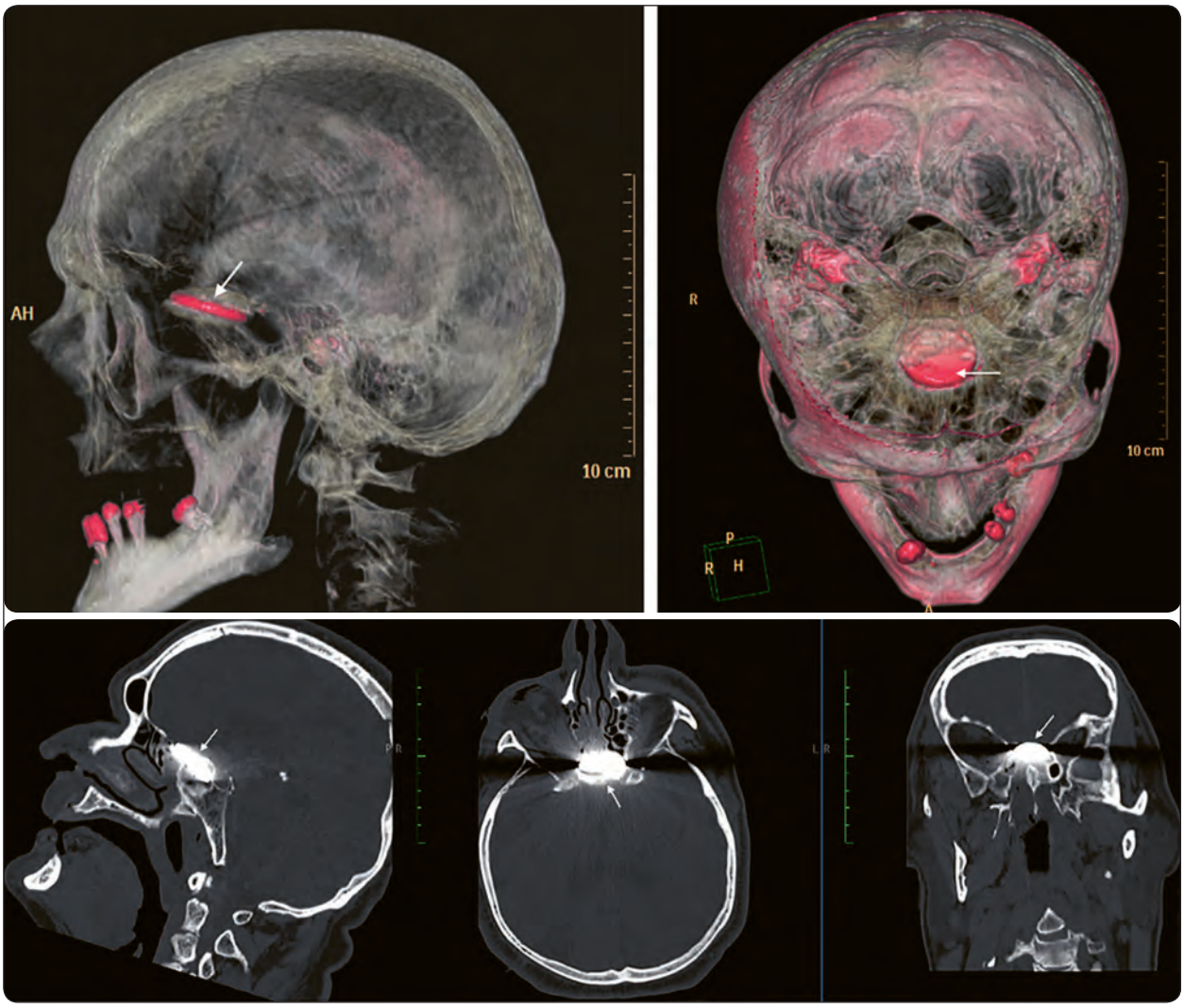

Figure 1. *3D reconstruction of the axial CT scan, showing a coin-shaped foreign body (marked with arrow) in medial, frontobasal area above the planum sphenoidale extended into intracranial space. Three plane reconstruction (axial, coronal and sagittal) show a probably metallic foreign body (marked with arrow)*

Based on the reconstruction given by the CT images, a metal foreign body might have entered through the skin via the lower eyelid, crossing the eyeball, orbit, the sphenoid sinus and the planum sphenoidale. There was no sign of vascular, brain and meningeal injury.

The patient was under the influence of alcohol, with a Glasgow Coma Scale of 14/15.

During the physical examination, a right periorbital suffusion, 2-cm laceration on the lower eyelid, massive subconjunctival hemorrhage and severe perforating ocular injury could be detected **(Figure 2)**. On slit lamp examination, structures of the anterior segment couldn't be recognized due to the severe, destructing perforating trauma. Haemophtalmus could also be diagnosed with the partial collapse of the globe. The visual acuity was decreased to no light perception and the eye movements were limited to supraduction and adduction. There was no impairment of visual acuity of the left eye, direct pupillary light reflex was normal and eye movements were without limitations on that side. The rest of the cranial nerve functions were intact. No external bleeding or liquor leakage was observed during the evaluation of the patient.

After excluding all other possible traumatic injuries, the patient was admitted to the Neurosurgery department for further treatment. Prophylactic antibiotic therapy was started with ceftriaxone. Considering the entry wound in the right infraorbital region and the close contact with the internal carotid arteries, optic nerves and sphenoid sinus, a multidisciplinary team meeting, composed of neurosurgery specialists, otorhinolaryngologists, ophthalmologists, and the radiologist was essential to provide with the best possible surgical treatment.

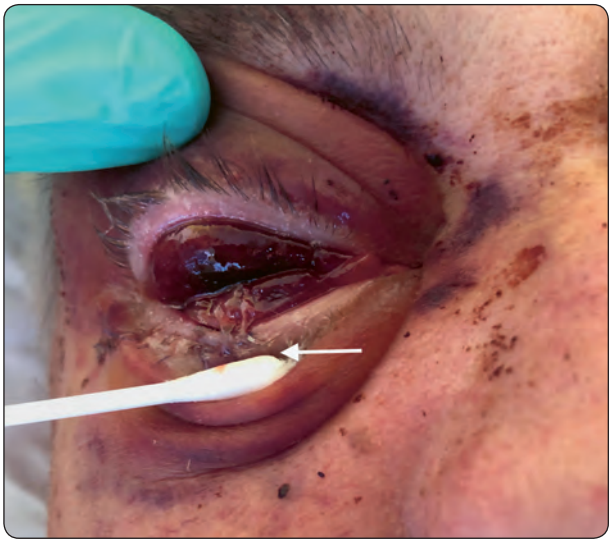

Figure 2. *Preoperative photograph of the patient demonstrating right periorbital ecchymosis, conjunctival hemorrhage, suffusion and a 2 cm laceration of the lower eyelid*

A CT scan was performed using an ultrafast 256-slice Philips Brilliance iCT, the slice thickness was 1mm with a total of 220 slices. Images were exported as DICOM files to a Medtronic Stealth Station S8 navigation system. Access to the target was visualized in multiplanar image reconstruction.

Endoscopic procedure

The sphenoid sinus exploration was performed via a transnasal, transseptal endoscopic (30 degrees, 4mm, 170mm, Storz) approach. Following Xylometazoline surface anaemization (topical instillation), the posterior third of the septum was infiltrated with 2% Lidocaine + adrenaline, and the mucoperiosteum was raised. On the right side, a vertical incision was made at the height of the anterior pole of the middle turbinate, the mucoperiosteum was elevated from the vomer below, and the lamina perpendicular above. The bony septum was pierced and both sphenoidal ostia were identified. The sphenoidal rostrum was removed to give a broad view of the sphenoidal plain.

With suction and with a tough rasparatorium, keeping the mucoperiosteum in sight, the horizontal (coin) foreign body was exposed **(Figure 3)**. Exploration was made slowly and cautiously not to injure the frontobasal anatomical structures, especially the internal carotid artery, the circle of Willis and the optic nerves or the optic chiasm. To do so, we avoided fast movements in cranial and posterior directions. With Rosen's curette, the front edge of the coin was tilted and removed with a Weil handle.

Although the planum sphenoidale and the dura were extensively destroyed, and even the damaged frontobasal brain surface was visible, no cerebrospinal liquor (CSF) leakage was detected. The suspected CSF leak pathway was closed by local edema. Laceration, i.e., the absence of free and removable wound edges made the reconstruction of the skull base difficult. Therefore the defect was closed with just abdominal fat tissue in two layers (intracranial giant-bath plug and overlay extracranial intrasphenoidal support) **(Figure 4)** and overlaid with the nasal mucoperiosteum in septal line as a third layer. No fibrin glue was used. Moistened, gel-coated, balloon inflated nasal tampons were introduced in both nostrils to compress the mucosal flap against the defect, for 7 days. However, this last step isn't necessary for small defects. Due to overlay closure, ceftriaxone, vancomycin and a spinal drain was applied for 7 days to prevent nasal li-

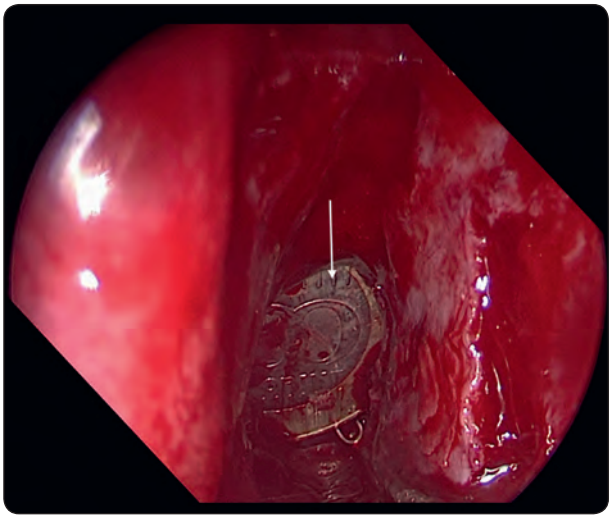

Figure 3. *Intraoperative endoscope image of the foreign body (Hungarian 200 Forint coin) (marked with arrow)*

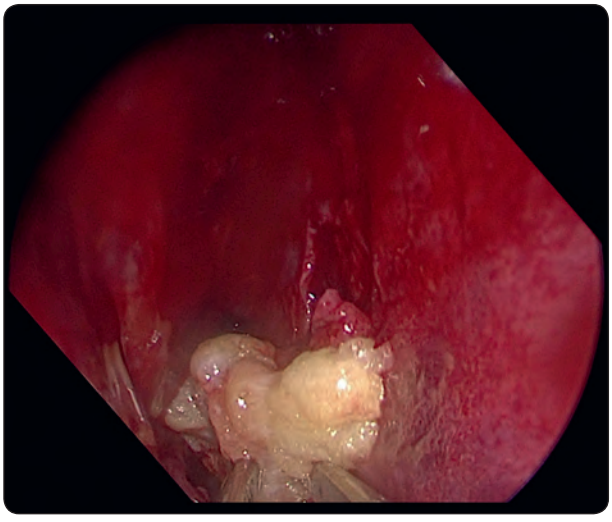

Figure 4. *Giant bath-plug technique using free abdominal fat*

quorrhea and consequential meningitis. After removal of the tampons the endoscopic control examination revealed good wound healing and no SCF leakage. The patient was discharged 10 days after the operation without any postoperative complication.

Discussion

Intracranial metallic foreign bodies occur as a result of accidents, self-harm or iatrogenic incidents and may have significant potential morbidity and mortality[10, 16]. Removal of the foreign body is indicated to prevent further complications, such as central nervous system infection, CSF leakage, injuries to the nerves and vessels[8, 11]. Traditionally these foreign bodies were removed via craniotomy, however, this approach increases the risk for perioperative complications. Foreign bodies close to the base of the skull can be considered for endoscopic removal, depending on the experience of the surgeon and most importantly on the availability of a collaborative multidisciplinary team[11]. Given that our institute had these endowments, in contrast with the traditional approach, we opted for an endoscopic procedure and successfully removed the coin using the transnasal transseptal transsphenoidal endoscopic technique. As a result of the minimally invasive intervention, which was relatively short and uncomplicated, the patient was able to leave the hospital quickly.

Endoscopic surgery has the benefits of decreased morbidity, decreased length of hospitalization, less blood loss, no remaining visible scars and has been used to treat lesions of the anterior skull base[6].

After the foreign body is removed, the bony defect needs to be closed endoscopically to prevent meningitis and CSF leakage. In the case of multilayer dura closure when intracranial intradural and extradural layers are used, it is not recommended to reduce the liquor pressure because it leads to slippage of the layers. In the case of inlay or overlay, however, it is the increased liquor pressure that can push the graft away from the CSF leaks. Nota bene reducing liquor pressure increases the risk of ascending infection.

However, due to the indication of unusual endoscopic surgery and the significantly damaged and presumably infected wound, we faced significant difficulty with the closure of the frontobasal defect. Traditionally the skull base is reconstructed with a multilayer technique using fascia lata and abdominal free fat, however in our case due to the mechanism of the injury which resulted in brain contusion, the lack of intact dura and bone edges made the closing more difficult[17]. Normally, abdominal free fat is another feasible option for grafting material during endoscopic skull base reconstruction[18]. Because the widely accepted multilayer technique requires larger access in order to be spread out over the intracranial surface, and we did not want to cause more damage and complications, we decided to use only bath-plug technique supplemented with nasal mucoperiosteal flap[19]. With the help of the two-layer abdominal fat tissue (intracranial giant bath plug and overlay extracranial intrasphenoidal support) and the mobilized nasal mucoperiosteum from caudally, we finally achieved our goal of the multiple layer wound closure. This latter was also supported with gel-coated, balloon inflated tampons intranasally, but this is usually not necessary. To promote wound cleansing and to avoid the formation of local abscess no fibrin glue was used. After the patient was healed, with no complication, we believe that closure of the anterior skull base using giant bath-plug together with nasal mucoperiosteal flap is an easy-to-use and also reliable skull base reconstruction technique especially in contaminated, traumatic skull base injuries.

Periorbital trauma may result in orbital hemorrhage with the risk of developing the sight threatening orbital compartment syndrome. The increased orbital pressure can damage the optic nerve by direct compression, or by causing ocular ischemia via decreased perfusion from compromised vascular flow. Immediate lowering of the intraorbital pressure can be reached by acute canthotomy and cantholysis. It should be noted, however, that the procedure is contraindicated in case of open globe injury since it can aggravate the damage of the eye by enhancing the prolapse of the intraocular content. Taken together, although without decompression, irreversible vision loss may occur due to the increased orbital pressure and early recognition and prompt treatment is essential to prevent vision loss, careful ophthalmological examination is indispensable in order to exclude open globe injury.

In our case, unfortunately, the destruction of the eye was so extensive that it made it impossible to attempt the restoration of the anatomical integrity of the eyeball.

Conclusion

In this paper we presented a successful endoscopic transnasal removal of a coin pierced into the sphenoidal sinus that extended into the intracranial space. Due to the potential life-threatening complications, foreign bodies in the sphenoid sinus and skull base should be treated. Recently, with the raising popularity of endoscope, alternative approaches to craniotomy should be considered if access is possible, as it is an efficient, safe and minimally invasive procedure. However, closure of the anterior skull base in these cases might be difficult, using giant bath-plug together with nasal mucoperiosteal flap is an easy to use and also reliable skull base reconstruction technique especially in contaminated, traumatic skull base injuries.

DISCLOSURE OF INTEREST – The authors declare that they have no competing interest.

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