CLINICAL NEUROSCIENCE

75. ÉVFOLYAM 7–8. SZÁM • 2022. JÚLIUS 30.

IDEGGYÓGYÁSZATI SZEMLE

L M

CLINICAL NEUROSCIENCE

75. ÉVFOLYAM 7–8. SZÁM • 2022. JÚLIUS 30.

IDEGGYÓGYÁSZATI SZEMLE

OFFICIAL JOURNAL
of the
Hungarian Neurological Society,
Hungarian Neurosurgical Society,
Hungarian Society of Clinical Neurophysiology,
Hungarian Society of Child Neurology,
Hungarian Society of Neuroradiology,
Hungarian Epilepsy League,
Horányi Béla Clinical Neuroscience Society,
Hungarian Stroke Society
and Hungarian Neuroscience Society

•

A Magyar Neurológiai Társaság,
a Magyar Idegsebészeti Társaság,
a Magyar Klinikai Neurofiziológiai Társaság,
Magyar Gyermekneurológiai Társaság,
a Magyar Neuroradiológiai Társaság,
a Magyar Epilepszia Liga,
a Horányi Béla Klinikai Idegtudományi Társaság,
a Magyar Stroke Társaság
és a Magyar Idegtudományi Társaság
HIVATALOS LAPJA

L M

Ideggyógyászati Szemle/Clinical Neuroscience
havonta megjelenő szakfolyóirat
Impakt faktor: 0,708 (2021)

ISSN 0019-1442

Mailing address • A szerkesztőség postacíme
H-1083 Budapest, Balassa u. 6.
Dr. Kovács Tibor/Tibor Kovács MD
Semmelweis Egyetem Neurológiai Klinika/Department of Neurology, Semmelweis University
Telefon: (36-1) 210-0337; fax: (36-1) 210-1368;
e-mail: clinical.neuroscience@med.semmelweis-univ.hu, kovacs.tibor@med.semmelweis-univ.hu

Előfizetési díja egyéni előfizetők részére: 7900 Ft/év
Intézmények részére: 12 000 Ft + áfa/év
Támogatói előfizetés, amely akár intézmény, akár magánszemély által történhet, és a lap fejlesztését szolgálja: minimum 15 000 Ft + áfa/év
Csak online előfizetés:
Intézményi 9000 Ft + áfa/év
Egyéni bruttó 6000 Ft/év
A lap egy példánya bruttó 2000 Ft
Kérjük, banki átutalással a 10404089-40810913 számú bankszámlára utalja át az előfizetési díjat.

Kiadja és terjeszti:
több mint 30 éve az orvostudomány szolgálatában
LITERATURA MEDICA
a LifeTime Media egészségügyi divíziója

1021 Budapest, Hűvösvölgyi út 75/A
Postacím: 1539 Budapest, Pf. 603
Telefon: (36-1) 316-4556, e-mail: litmed@lam.hu
Felelős vezető: Cserni Tímea ügyvezető igazgató

A kiadó munkatársai:
Kiadói szerkesztő: Dr. Kazai Anita
Korrektor: Kulcsár Gabriella
Tervező: Stache Éva
Tördelőszerkesztő: Boldog Dániel Zoltán

Nyomdai munkák: Vareg Hungary Kft.
Felelős vezető: Egyed Márton ügyvezető igazgató
Előfizetésben kézbesíti a Magyar Posta Zrt. (1900 Budapest).
Kézbesítéssel kapcsolatos információk:
(36-1) 767-8262.

www.eLitMed.hu

TARTALOM CONTENTS

EREDETI KÖZLEMÉNYEK

ESETISMERTETÉSEK

ORIGINAL ARTICLES

CASE REPORTS

eLitMed.hu
A GYÓGYÍTÁS MŰVÉSZETE
A folyóirat tartalma a www.eLitMed.hu portálon érhető el.

A kiadvány a Magyar Tudományos Akadémia támogatásával készült.

A folyóiratot az MTMT indexeli és a REAL archiválja.
A folyóirat a következő adatbázisokban szerepel/journal indexed and abstracted in:
Science Citation Index Expanded (SciSearch®), Neuroscience Citation Index®, Journal Citation Report/Science Edition, ISI Web of Science, MEDLINE, Index Copernicus, SCOPUS, Scirus, Google Scholar, EBSCO

COMPARISON OF OREXIN-A AND NEUROFILAMENT LIGHT CHAIN LEVELS IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS: A PILOT STUDY

Ercan SARUHAN[1], Muammer KORKMAZ[2], Basak ALTIPARMAK[3], Kursad TOSUN[4], Gulnihal KUTLU[5]

[1]Department of Medical Biochemistry, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey
[2]Department of Neurology, Mugla Research and Training Hospital, Mugla, Turkey
[3]Department of Anesthesiology and Reanimation, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey
[4]School of Science, Siena College, Loudonville, NY, USA
[5]Department of Neurology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey

English | https://doi.org/10.18071/isz.75.0223 | www.elitmed.hu

Background and purpose – Multiple sclerosis is an autoimmune disease of the central nervous system, with myelin degeneration and Relapsing-Remitting Multiple Sclerosis (RRMS) as the most common type. The aim of this study was to determine the levels of Neurofilament Light Chain (NFL) and Orexin-A (OXA) in patients with RRMS and compare it with healthy control subjects' data.
Methods – In this case-control study of 61 subjects, serum and cerebrospinal fluid samples were collected from 23 RRMS patients and 38 healthy control subjects. NFL and OXA levels were determined in cerebrospinal fluid and serum samples using enzyme-linked immunosorbent assay kits. Self-reported questionnaires were also administered to evaluate fatigue severity and impact. Receiver operating characteristic curve analysis was used to determine the optimal cut-off value of NFL and OXA.
Results – The NFL and OXA concentrations in cerebrospinal fluid of RRMS patients were significantly higher than those of the control group ($p < 0.001$), but no significant difference was found in the serum concentrations ($p = 0.842$, $p = 0.597$, respectively). The cut-off values were found to be 1.194 ng/ml for NFL and 77.81 pg/ml for OXA in cerebrospinal fluid. A positive correlation was found between the Expanded Disability Status Scale and Epworth Sleepiness Scale in RRMS patients ($\rho = 0.49$, $p = 0.045$).
Conclusion – These results suggest that increased levels of both NFL and OXA in cerebrospinal fluid reflect neu-

OREXIN-A- ÉS NEUROFILAMENTUM-KÖNNYŰLÁNC FEHÉRJESZINTEK RELAPSZÁLÓ-REMITTÁLÓ SCLEROSIS MULTIPLEXBEN SZENVEDŐKNÉL: PILOT VIZSGÁLAT

Saruhan E, MD; Korkmaz M, MD; Altiparmak B, MD; Tosun K, MD; Kutlu G, PhD
Ideggyogy Sz 2022;75(7–8):223–230.

Háttér és cél – A sclerosis multiplex (SM) a központi idegrendszer autoimmun betegsége, aminek leggyakoribb típusa a relapszáló-remittáló forma (RRSM). A tanulmány célja az volt, hogy meghatározza a neurofilamentum-könnyűlánc- (NFL-) és az orexin-A- (OXA-) fehérjeszinteket RRSM-betegekben, és összehasonlítsa azokat egészséges kontrollszemélyek adataival.
Módszerek – Ebben az eset-kontroll vizsgálatban összesen 61 személytől (23 RRSM-beteg és 38 egészséges kontroll) gyűjtöttünk szérum- és cerebrospinalisfolyadék-mintákat. A szérum- és cerebrospinalisfolyadék-minták NFL- és OXA-szintjeit enzimkapcsolt immunszorbens esszékkel határoztuk meg. A vizsgálati alanyok fáradtságszintjük és annak életminőségre kifejtett hatásának meghatározása céljából kérdőíveket is kitöltöttek. Az NFL- és OXA-szintek optimális határértékének meghatározása érdekében ROC-görbe-analízist végeztünk.
Eredmények – A kontrollszemélyekkel összehasonlítva, az RRSM-betegek cerebrospinalis folyadékmintáiban szignifikánsan magasabbak voltak az NFL- és az OXA-koncentrációk ($p < 0,001$), de a szérumkoncentrációk között nem találtunk szignifikáns különbséget ($p = 0,842$, $p = 0,597$). A cerebrospinalis folyadékminták NFL- és OXA-szintjének optimális határértékei a következők voltak: 1,194 ng/ml (NFL) és 77,81 pg/ml (OXA). Az RRSM-betegek esetében pozitív korrelációt találtunk a kiterjesztett rokkantsági skála (EDSS) és az Epworth-féle álmosságskála pontszámai között ($\rho = 0,49$, $p = 0,045$).

Correspondent: Dr. Ercan SARUHAN, Department of Medical Biochemistry, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey. Telephone: +905336643392, fax: +902522115249, e-mail: ercansaruhan@mu.edu.tr
https://www.orcid.org/0000-0001-6416-1442

Érkezett: 2021. július 14. Elfogadva: 2021. augusztus 5.

ronal destruction in RRMS. Further research of neurodegeneration should focus on neuropeptides to determine the possible roles in RRMS pathogenesis.

Keywords: *fatigue, multiple sclerosis, neurofilament light chain, orexin*

Következtetés – Eredményeink alapján a cerebrospinalis folyadék megemelkedett NFL- és OXA-szintjei egyaránt arra utalnak, hogy az RRSM-betegekben neuronalis destrukció zajlik. A neurodegenerációval kapcsolatos további vizsgálatoknak arra kell fókuszálniuk, hogy meghatározzák a neuropeptidek szerepét az RRSM patogenezisében.

Kulcsszavak: *fáradtság, sclerosis multiplex, neurofilamentum-könnyűlánc, orexin*

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), in which myelin degeneration and axonal damage are seen, caused by several inflammatory molecules activated by the autoimmune response[1]. Of the different types of MS based on the course of the disease, Relapsing-Remitting Multiple Sclerosis (RRMS) is the most common, characterized by attacks of neurological symptoms and periods of remission. Although symptoms vary among patients, fatigue is the most frequent symptom in MS patients and can be underdiagnosed[2, 3].

It has been previously shown that peptides can play a role in the pathogenesis of fatigue in patients with MS[4]. Orexin-A (hypocretin-1, OXA) is one of these peptides and the role of OXA has been reported in some studies in literature[5]. OXA is a hypothalamic neuropeptide that regulates energy homeostasis, feeding behavior, sleep-wake cycle; a deficiency of OXA causes narcolepsy[6–8]. *Papuc* et al. found a positive correlation between OXA level and fatigue level[5]. Orexins also have neuroprotective and immune-modulatory properties[9].

Neurofilaments are the structural parts of neurons, which are subdivided into light, medium, and heavy chain ones according to protein size[10]. Neurofilament Light Chain (NFL) is an important neurodegeneration marker and predictor of MS and higher levels in cerebrospinal fluid (CSF) have been found to correlate with disease progression[11–13].

These data suggest that NFL and OXA are good predictors of neurodegeneration and can be used to understand the pathogenesis of MS. While fatigue is a common symptom in MS, the mechanisms of this symptom are not well understood. Therefore, it was hypothesized that RRMS patients with fatigue could have lower OXA and higher NFL levels compared to control subjects. The aim of this study was to determine the relationship of these biomarkers with fatigue and sleepiness, which are the most common symptoms of RRMS. In addition, cut-off values were determined for NFL and OXA parameters in the diagnosis of RRMS, and correlations were examined of serum and CSF concentrations to ascertain if serum levels could be used as non-invasive diagnostic markers instead of CSF levels. These parameters could help to achieve better understanding of the neurochemical mechanisms of fatigue and the pathogenesis of RRMS.

Methods

STUDY DESIGN

A total of 61 subjects were enrolled in the study: 23 treatment-naive patients diagnosed with RRMS according to the 2017 revisions of the McDonald criteria[14] and 38 control subjects with no neurological diseases. All neurological examinations, cranial and spinal magnetic resonance imaging (MRI), and detection of the oligoclonal band in CSF were conducted for a definitive diagnosis of MS. The control group included elective cases who had no systemic or neurological diseases and were scheduled for surgery under spinal anesthesia. Patients were excluded if they had a previous diagnosis of MS, a history of cardiovascular disease, diabetes mellitus, hypertension, sleep disorder, or a body mass index (BMI) > 35 kg/m^2, or were aged under 18 or over 65 years.

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Mugla Sitki Kocman University (28/06/2018-10/III). This study was conducted in accordance with the ethical standards as laid down in the Helsinki declaration and its later amendments. Informed consent was obtained from all participants included in the study.

ASSESSMENTS

Disability in patients with RRMS was measured using the Expanded Disability Status Scale (EDSS) score[15]. The total EDSS score ranges from 0 to 10 and higher scores represent greater disability in RRMS. Fatigue and sleepiness of participants were assessed using validated questionnaires[16–18]. To evaluate excessive daytime sleepiness, the Epworth Sleepiness Scale (ESS) was applied. This is an 8-item questionnaire, with a possible maximum score ranging from 0 to 24. An ESS score of > 16 indicates greater sleepiness during daily activities[19]. Fatigue in participants was evaluated by using the well-validated scales of the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS). FSS measures the severity of fatigue and was developed especially for use in neurological disorders. Each of the nine items in the scale is scored from 1 to 7 and the FSS score is calculated by using the arithmetic mean. A score of > 4.6 is indicative of severe fatigue[20]. The MFIS is a modified questionnaire of the Fatigue Impact Scale, indicating how fatigue affects the daily life of the patient[21]. The 21 items of the MFIS assess the impact of fatigue in respect of physical, cognitive, and psychosocial functioning.

BIOCHEMICAL ANALYSIS

All patients in the control group received standard monitoring with electrocardiography, non-invasive blood pressure, and peripheral oxygen saturation measuring in the operating room. A sedation protocol with 2 mg intravenous midazolam was applied before the spinal anesthesia. Under aseptic conditions, an anesthesiologist performed a lumbar puncture with a 25-gauge spinal needle and 2 ml of CSF were collected into polypropylene tubes. CSF samples of patients with RRMS were collected into 2 ml polypropylene tubes by lumbar puncture with a 25-gauge spinal needle by a neurologist. CSF samples were centrifuged in 1 hour at 1000 x g for 10 minutes. Venous blood samples were collected into blood tubes by venipuncture simultaneously with CSF samples. The blood tubes were centrifuged at 2000 x g for 15 minutes to separate serum. CSF and serum samples were transported to the freezer in one hour and stored at -86 °C until analysis.

CSF protein concentrations were determined by the turbidimetric method on a COBAS c702 analyzer (Roche Diagnostics GmbH; Mannheim, Germany). Neurofilament Light Chain (Cat# E4467Hu) and Orexin-A (Cat# E1296Hu) concentrations were measured in serum and in CSF using human-specific enzyme-linked immunosorbent assays (ELISA) (BT-laboratory, Shanghai, China) according to the instructions of the manufacturer. NFL assay sensitivity was 0.054 ng/mL with inter-assay and intra-assay coefficients of variation less than 10% and 8%, respectively. OXA assay sensitivity was 2.53 pg/mL with inter-assay and intra-assay coefficients of variation less than 10% and 8%, respectively.

STATISTICAL ANALYSIS

To determine whether there was a significant difference between patients and controls in terms of serum and CSF biochemical values, Wilcoxon-Mann-Whitney test was used. Summary statistics were expressed as minimum, maximum, median, first and third quartiles, and mean ± standard deviation. The correlation between variables was explored by using Spearman's correlation analysis. P-values less than 0.05 were considered statistically significant. All data analysis was performed by statistical software R (R Core Team, 2016). Receiver Operating Characteristic (ROC) curve analysis was used to determine the ability of the NFL and OXA in CSF to predict the demyelinating disease. We also used the same analysis to determine the optimal cut-off value based on Youden index. The area under the ROC curve (AUC) was used to determine the accuracy of these biomarkers. Higher AUC values indicate better test performance. A biomarker with AUC value is equal to 1 discriminates individuals perfectly as diseased or healthy. We used DeLong's method to estimate the AUC and its 95% confidence interval (CI). The 95% CIs were computed with 2000 stratified bootstrap replicates for sensitivities and specificities. Post hoc power calculation was performed using GPower 3.1 software.

Results

SUBJECTS

A total of 61 subjects (28 female, 33 male) were included in this study. The mean age of RRMS patients was 36.7 ± 9.7 years (range 22-55 years), while the mean age of the control group was 48.2 ± 14.5 years (range 20-65 years). Post hoc power calculations were applied and the sample size was seen to provide 0.982 power and 1.118 effect size for OXA at α error probability level of 0.05.

Table 1. *Comparison of CSF and serum parameters between RRMS patients and controls*

	Controls (n=38)	RRMS (n=23)	p-value
NFL_{CSF} (ng/mL)	0.78 ± 0.54	1.55 ± 0.40	
	0.72 (0.49, 0.92)	1.53 (1.24, 1.85)	*<0.001**
OXA_{CSF} (pg/mL)	62.68 ± 38.80	105.99 ± 38.64	
	59.79 (42.61, 72.35)	97.7 (76.5, 123.20)	*<0.001**
NFL_{SER} (ng/mL)	5.84 ± 10.68	7.57 ± 12.67	
	1.26 (1.04, 2.20)	1.46 (0.92, 2.77)	0.842
OXA_{SER} (pg/mL)	304.57 ± 488.62	369.18 ± 595.05	
	81.83 (55.64, 226.8)	79.61 (49.05, 385.5)	0.597
$Protein_{CSF}$ (mg/dL)	35.68 ± 13.89	31.98 ± 12.13	
	31.20 (27.55, 41.85)	27.60 (24.95, 37.70)	0.227

RRMS: relapsing and remitting multiple sclerosis, NFL: neurofilament light chain, OXA: orexin-A, CSF: cerebrospinal fluid, SER: serum
Data are presented as mean ± SD, median, and quartiles (25th–75th percentiles).
p-values were obtained from Wilcoxon-Mann-Whitney test.
* An italic p-value indicates a statistically significant difference between groups.

COMPARISON OF BIOMARKERS BETWEEN PATIENTS AND CONTROLS

The NFL and OXA concentrations in the CSF of RRMS patients were significantly higher than those of the control group ($p < 0.001$ for both, Wilcoxon-Mann-Whitney test, **Table 1**, **Figure 1** and **2**), but no significant difference was found in serum concentrations ($p = 0.842$, $p = 0.597$, respectively). No correlation was determined between serum and CSF biomarkers (all p-values > 0.05, Spearman's correlation). There was no evidence to suggest a significant difference in CSF protein concentrations between the groups ($p = 0.227$, Wilcoxon-Mann-Whitney test, **Table 1**).

CUT-OFF VALUES FOR RRMS DIAGNOSIS

ROC analysis was used to measure the diagnostic ability of NFL and OXA in CSF and to define the cut-off values for these biomarkers in predicting RRMS disease. The AUCs were 0.91 and 0.86 respectively for NFL and OXA in CSF. Three cut-off values based on local maxima of the ROC curves were determined for each biomarker to classify the condition. The cut-off values for NFL in CSF in predicting RRMS were 1.034 (sensitivity = 0.96, specificity = 0.79), 1.119 (sensitivity = 0.87, specificity = 0.84), and 1.194 (sensitivity = 0.83, specificity = 0.92). For OXA in CSF, the cut-off values were 72.76 (sensitivity = 0.78, specificity = 0.76), and 77.81 (sensitivity = 0.74, specificity = 0.84). The cut-off values giving the highest Youden Index, or equivalently, the highest Sensitivity + Specificity were 1.194 ng/mL for NFL in CSF and 77.81 pg/mL for OXA in CSF **(Table 2, Figure 3** and **4)**.

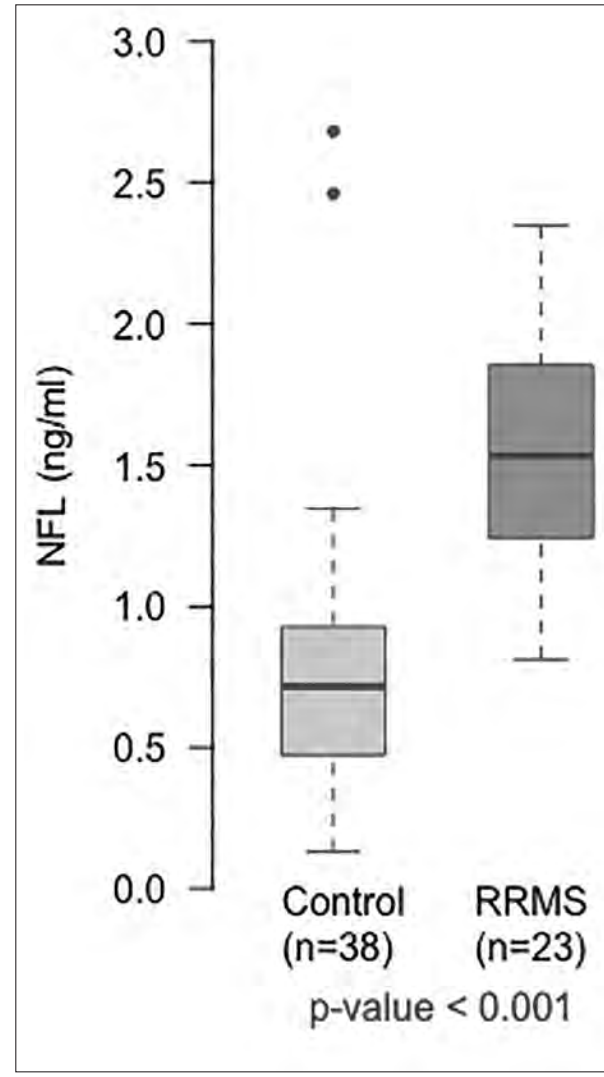


Figure 1. *Comparison of NFL levels in CSF between groups*

Table 2. *Optimal cut-off values that can be used to diagnose RRMS and their corresponding sensitivity and specificity values*

	AUC 95% CI	Cut-off	Sensitivity 95% CI	Specificity 95% CI
NFL (ng/mL)	0.91	1.03	0.96	0.79
	0.83 – 0.99		0.87 – 1.00	0.66 – 0.92
		1.12	0.87	0.84
			0.74 – 1.00	0.71 – 0.95
		1.19*	0.83	0.92
			0.65 – 0.96	0.82 – 1.00
OXA (pg/mL)	0.86	72.76	0.78	0.76
	0.77 – 0.95		0.61 – 0.91	0.61 – 0.89
		77.81*	0.74	0.84
			0.57 – 0.91	0.71 – 0.95

* The cut-off values giving the highest Youden Index, or equivalently, the highest Sensitivity and Specificity.

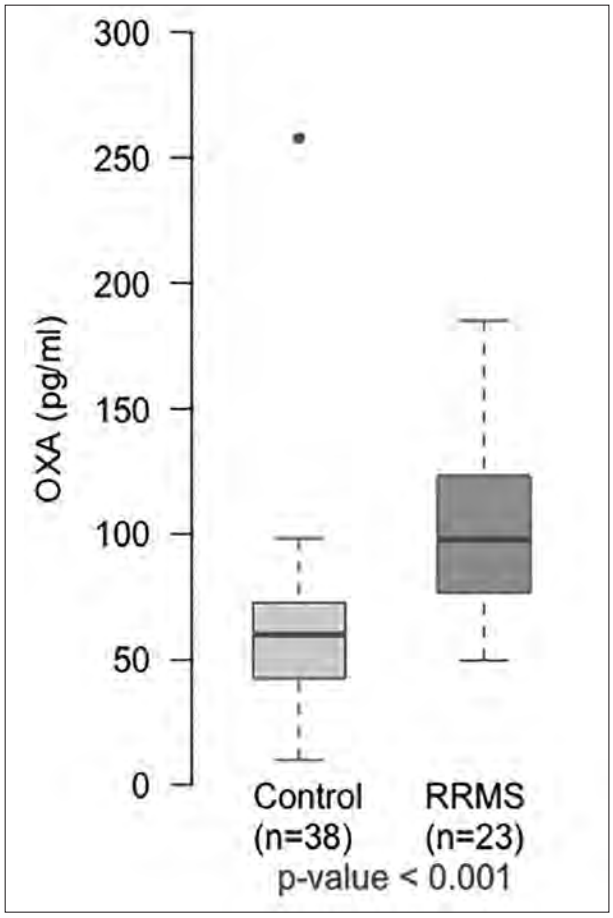


Figure 2. *Comparison of OXA levels in CSF between groups*

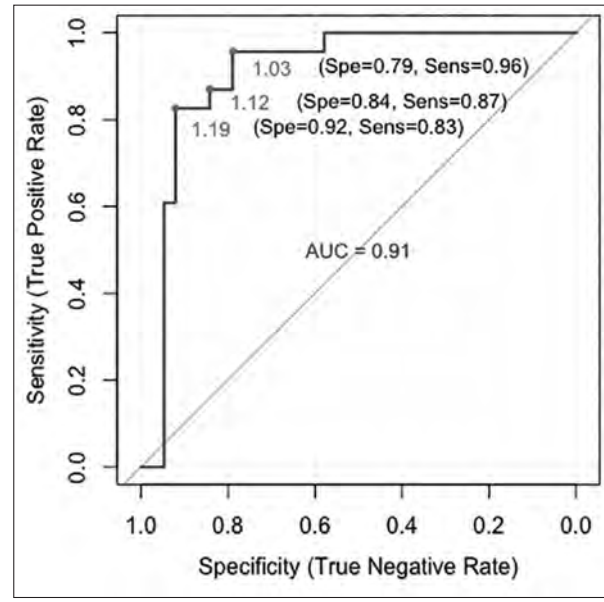


Figure 3. *The ROC plot of the NFL in CSF. Three best cut-off values for the NFL in CSF in predicting RRMS are marked on the graph; 1.034 (sensitivity = 0.96, specificity = 0.79), 1.119 (sensitivity = 0.87, specificity = 0.84), and 1.194 (sensitivity = 0.83, specificity = 0.92)*

FATIGUE AND SLEEPINESS SCALES

A positive correlation was determined between the EDSS and ESS scores in RRMS patients (rho = 0.49, p = 0.045, Spearman's correlation). No correlation was observed between the EDSS and other scales (MFIS and FSS). MFIS, FSSS, and ESS of 17 RRMS patients were determined. Fatigue was seen in 6 of the patients. There was no significant difference between RRMS patients with fatigue and those without, in terms of NFL and OXA concentrations.

MAGNETIC RESONANCE IMAGING

The McDonald criteria for demonstration of dissemination in space on MRI examination were fulfilled by 23 RRMS patients. Dissemination in space is defined as one or more lesions showing hyperin-

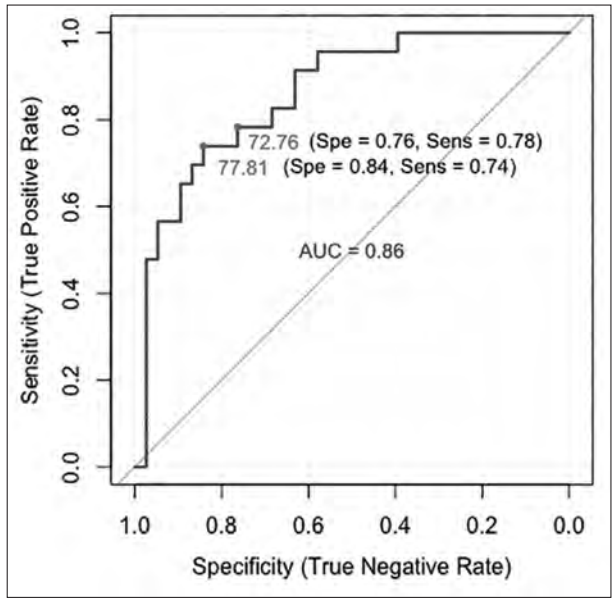


Figure 4. *The ROC plot of the OXA in CSF. Two best cut-off values for the OXA in CSF in predicting RRMS are marked on the graph; 72.76 (sensitivity = 0.78, specificity = 0.76), and 77.81 (sensitivity = 0.74, specificity = 0.84)*

tensity on T2-weighted images, which are characteristic of MS in two or more of four areas of the CNS: periventricular, cortical, or juxtacortical, and infratentorial brain regions, and in the spinal cord. No hypothalamic MS lesions were detected on the T2-weighted images of any patient.

Discussion

In this study, the neurochemical mechanisms of RRMS were evaluated by measuring OXA and NFL concentrations in CSF and serum. The most significant finding of the study was that the levels of both OXA and NFL in CSF were higher in the RRMS patients than in the control group. Axonal degeneration might increase NFL and OXA levels in CSF. No significant difference was found in serum levels. The trace levels of released NFL and OXA in CSF after axonal damage might not affect serum concentrations. Therefore, the use of serum biomarkers is of little value in the diagnosis of RRMS. The CSF levels of NFL and OXA can predict RRMS better than serum biomarkers, and cut-off values were determined in this study as 1.194 ng/ml for NFL and 77.81 pg/ml for OXA in CSF to diagnose RRMS. The low sensitivity of NFL and OXA cut-off values makes them difficult to use as reliable diagnostic markers. NFL and OXA levels have been studied separately in previous studies, but these biomarkers have not been evaluated together before. Further studies on neurodegeneration biomarkers should focus on the correlation of these peptides' levels in serum and CSF to be able to use the serum as a non-invasive diagnostic marker and more reliable cut-off values are needed for RRMS diagnosis.

NFL is considered a relevant biomarker of CNS degeneration and it increases in different neurological diseases such as stroke, dementia, and MS. The increase can be determined not only in the CSF but also in the serum, especially in progressive MS[22], but also in RRMS[23]. NFL levels in CSF and serum may be a good predictor of MS as described in previous studies[24–26]. These studies found that serum and CSF NFL levels correlated with disease severity and activity but serum NFL has been found to be less sensitive. In the current study, the higher NFL levels in CSF were in line with previous studies but no significant differences could be determined in serum NFL levels. This discordance could be attributed to the small sample size of this study and to the ELISA method. *Kuhle* et al. found that correlations between CSF and serum NFL levels were strongest for Simoa method and weaker for ELISA method[27]. In addition to neurodegeneration, metabolic alterations in the turnover of NFL may play a role. A significant correlation was found between serum NFL levels and age in previous studies[23, 28]. Cut-off values determined for the prediction of RRMS in the current study were similar to those reported by *Bhan* et al.[29].

Previous studies have demonstrated a correlation between CSF OXA levels and disease activity. *Gencer* et al. found decreased CSF OXA levels in MS patients compared to a healthy control group, and CSF OXA levels were negatively correlated with the progression index in RRMS[30]. The results of the current study were not in line with those findings. Gencer et al. did not compare RRMS with healthy control subjects and *Knudsen* et al. compared the attack and remission groups of RRMS and found no difference in CSF OXA levels[31]. These conflicting results of the current study and the literature may be attributed to the comparison of healthy control subjects and RRMS patients in the current study. It can be considered that OXA is another product of axonal degeneration which is prominent in the early phase of RRMS, and therefore, higher levels of CSF OXA could be a good predictor of neurodegeneration in RRMS.

OXA regulates the sleep-wake cycle and the association with fatigue in RRMS has been investigated in other studies. Papuc et al. found no difference between MS patients with fatigue and healthy control subjects, but a positive correlation was determined between CSF OXA levels and fatigue

severity in MS patients[5]. Another study of MS patients by *Constantinescu* et al. showed no correlation between fatigue and OXA levels in CSF[32]. In the current study, there was also found to be no difference in CSF OXA levels between fatigued and non-fatigued RRMS patients, but higher levels were found in RRMS patients compared to the healthy control subjects. These findings showed that OXA levels in RRMS patients were not associated with fatigue but could be used as a good predictor of neurodegeneration. Nevertheless, the relationship between OXA and fatigue remains uncertain.

In respect of the correlation of fatigue scores and NFL levels in RRMS, *Hakansson* et al. found no association between fatigue scores and NFL concentrations[33]. In the current study, there was also found to be no correlation between NFL, OXA, and fatigue scores. These results indicated that fatigue in RRMS had different mechanisms beyond the scope of these biomarkers. Further studies should focus on new biomarkers for the pathogenesis of fatigue in RRMS.

The main strength of this study was the well-designed comparison of a healthy control group with treatment-naive RRMS patients. However, there were some limitations to the study, primarily that fatigue and sleepiness were evaluated from the self-reported subjective scales of MFIS, FISS, and ESS in patients, and not in the control group. That fatigue may have been potentially under-reported by the patients may have caused bias in the study. A second limitation that could have affected the results was the relatively small sample size. Especially the number of RRMS patients with fatigue (n = 6) was not sufficient to be able to make a reliable statistical analysis of the biomarkers. Further prospective cohort studies with a larger number of patients are required to investigate the role of NFL and OXA in MS-related fatigue. Third, this was a cross-sectional study, which cannot describe the cause and effect relationship between biomarkers and clinical outcomes. Nevertheless, despite these limitations, this study can be considered of value in respect of the determination of cut-off values and differences between OXA and NFL in a comparison of RRMS patients and healthy control subjects.

Conclusion

Despite neuropeptides having been investigated in many clinical trials, the research on the subject of neurodegeneration in RRMS is still at an early stage. The results of this study demonstrated that increased levels of both NFL and OXA in CSF may reflect axonal degeneration in RRMS. However, NFL and OXA cannot be used as diagnostic markers, because of the low sensitivity of the cut-off values. In addition, relatively little is known about the turnover of these peptides in humans, limiting their potential use as a biomarker. These are markers of neuronal degeneration and certainly cannot be considered as diagnostic biomarkers, especially in a disorder such as MS where plenty of clinical and laboratory data are utilized for the diagnosis, such as clinical history, neurophysiological studies, MRI, and the presence of CSF oligoclonal bands. Further research of neurodegeneration should focus on neuropeptides to determine the possible roles of them in RRMS pathogenesis. These biomarkers may have also therapeutic potential in RRMS. The effect of treatment on these parameters should also be studied to be able to establish new treatment modalities based on these neuropeptides.

DECLARATION OF COMPETING INTEREST
The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. *Compston A, Coles A*. Multiple sclerosis. Lancet 2008;372: 1502-17. https://doi.org/10.1016/S0140-6736(08)61620-7
2. *Krupp L.* Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Multiple sclerosis (Houndmills, Basingstoke, England) 2006;12:367-8. https://doi.org/10.1191/135248506ms1373ed.
3. *Braga DM, Prado GF, Bichueti DB, Oliveira EM*. Positive correlation between functional disability, excessive daytime sleepiness, and fatigue in relapsing-remitting multiple sclerosis. Arq Neuropsiquiatr 2016;74:433-8. https://doi.org/10.1590/0004-282x20160069
4. *Ayache SS, Chalah MA*. Fatigue in multiple sclerosis - Insights into evaluation and management. Neurophysiol Clin 2017;47:139-71. https://doi.org/10.1016/j.neucli.2017.02.004
5. *Papuc E, Stelmasiak Z, Grieb P, Pawel G, Rejdak K*. CSF hypocretin-1 concentrations correlate with the level of fatigue in multiple sclerosis patients. Neurosci Lett 2010; 474:9-12. https://doi.org/10.1016/j.neulet.2010.02.062
6. *Mieda M.* The roles of orexins in sleep/wake regulation. Neurosci Res 2017;118:56-65. https://doi.org/10.1016/j.neures.2017.03.015
7. *Jørgen Jennum P, Østergaard Pedersen L, Czarna Bahl JM, Modvig S, Fog K, Holm A, et al.* Cerebrospinal fluid

biomarkers of neurodegeneration are decreased or normal in narcolepsy. Sleep 2016;40. https://doi.org/10.1093/sleep/zsw006
8. *de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al*. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998;95:322-7. https://doi.org/10.1073/pnas.95.1.322
9. *Couvineau A, Voisin T, Nicole P, Gratio V, Abad C, Tan YV*. Orexins as novel therapeutic targets in inflammatory and neurodegenerative diseases. Front Endocrinol (Lausanne) 2019;10:709. https://doi.org/10.3389/fendo.2019.00709
10. *Gaiottino J, Norgren N, Dobson R, Topping J, Nissim A, Malaspina A, et al*. Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. Plos One 2013;8. https://doi.org/10.1371/journal.pone.0075091
11. *Kuhle J, Kropshofer H, Haering DA, Kundu U, Meinert R, Barro C, et al*. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 2019;92:e1007-e15. https://doi.org/10.1212/WNL.0000000000007032
12. *Arrambide G, Espejo C, Eixarch H, Villar LM, Alvarez-Cermeno JC, Picon C, et al.* Neurofilament light chain level is a weak risk factor for the development of MS. Neurology 2016;87:1076-84. https://doi.org/10.1212/WNL.0000000000003085
13. *Barro C, Benkert P, Disanto G, Tsagkas C, Amann M, Naegelin Y, et al*. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. Brain 2018;141:2382-91. https://doi.org/10.1093/brain/awy154
14. *Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17: 162-73. https://doi.org/10.1016/S1474-4422(17)30470-2
15. *Kurtzke JF*. Rating neurologic impairment in multiple sclerosis. An expanded disability status scale (EDSS). 1983;33: 1444. https://doi.org/10.1212/WNL.33.11.1444
16. *Armutlu K, Keser I, Korkmaz N, Akbiyik DI, Sümbüloğlu V, Güney Z, et al.* Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. J Neurol Sci 2007;255:64-8. https://doi.org/10.1016/j.jns.2007.01.073
17. *Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al*. The validity and reliability of the fatigue severity scale in Turkish multiple sclerosis patients. Int J Rehabil Res 2007;30:81-5. https://doi.org/10.1097/MRR.0b013e3280146ec4
18. *Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I.* Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath 2008;12:161-8. https://doi.org/10.1007/s11325-007-0145-7
19. *Johns MW*. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5. https://doi.org/10.1093/sleep/14.6.540
20. *Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD*. The Fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology 1989;46:1121-3. https://doi.org/10.1001/archneur.1989.00520460115022
21. *Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF*. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18 Suppl 1:S79-83. https://doi.org/10.1093/clinids/18.Supplement_1.S79
22. *Kapoor R, Smith KE, Allegretta M, Arnold DL, Carroll W, Comabella M, et al*. Serum neurofilament light as a biomarker in progressive multiple sclerosis. Neurology 2020; 95:436-44. https://doi.org/10.1212/WNL.0000000000010346
23. *Disanto G, Barro C, Benkert P, Naegelin Y, Schädelin S, Giardiello A, et al*. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. Ann Neurol 2017;81:857-70. https://doi.org/10.1002/ana.24954
24. *de Flon P, Laurell K, Sundstrom P, Blennow K, Soderstrom L, Zetterberg H, et al*. Comparison of plasma and cerebrospinal fluid neurofilament light in a multiple sclerosis trial. Acta Neurol Scand 2019;139:462-8. https://doi.org/10.1111/ane.13078
25. *Hakansson I, Tisell A, Cassel P, Blennow K, Zetterberg H, Lundberg P, et al*. Neurofilament levels, disease activity and brain volume during follow-up in multiple sclerosis. J Neuroinflammation 2018;15:209. https://doi.org/10.1186/s12974-018-1249-7
26. *Kuhle J, Barro C, Disanto G, Mathias A, Soneson C, Bonnier G, et al.* Serum neurofilament light chain in early relapsing remitting MS is increased and correlates with CSF levels and with MRI measures of disease severity. Mult Scler 2016;22:1550-9. https://doi.org/10.1177/1352458515623365
27. *Kuhle J, Barro C, Andreasson U, Derfuss T, Lindberg R, Sandelius Å, et al*. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa. Clinical Chemistry and Laboratory Medicine (CCLM) 2016;54:1655-61. https://doi.org/10.1515/cclm-2015-1195
28. *Mattsson N, Andreasson U, Zetterberg H, Blennow K*. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol 2017;74:557-66. https://doi.org/10.1001/jamaneurol.2016.6117
29. *Bhan A, Jacobsen C, Myhr KM, Dalen I, Lode K, Farbu E.* Neurofilaments and 10-year follow-up in multiple sclerosis. Mult Scler 2018;24:1301-7. https://doi.org/10.1177/1352458518782005
30. *Gencer M, Akbayir E, Sen M, Arsoy E, Yilmaz V, Bulut N, et al.* Serum orexin-A levels are associated with disease progression and motor impairment in multiple sclerosis. Neurol Sci 2019;40:1067-70. https://doi.org/10.1007/s10072-019-3708-z
31. *Knudsen S, Jennum PJ, Korsholm K, Sheikh SP, Gammeltoft S, Frederiksen JL*. Normal levels of cerebrospinal fluid hypocretin-1 and daytime sleepiness during attacks of relapsing-remitting multiple sclerosis and monosymptomatic optic neuritis. Mult Scler 2008;14:734-8. https://doi.org/10.1177/1352458508088939
32. *Constantinescu CS, Niepel G, Patterson M, Judd A, Braitch M, Fahey AJ, et al*. Orexin A (hypocretin-1) levels are not reduced while cocaine/amphetamine regulated transcript levels are increased in the cerebrospinal fluid of patients with multiple sclerosis: no correlation with fatigue and sleepiness. J Neurol Sci 2011;307:127-31. https://doi.org/10.1016/j.jns.2011.04.024
33. *Hakansson I, Johansson L, Dahle C, Vrethem M, Ernerudh J.* Fatigue scores correlate with other self-assessment data, but not with clinical and biomarker parameters, in CIS and RRMS. Mult Scler Relat Disord 2019;36:101424. https://doi.org/10.1016/j.msard.2019.101424

EARLY AND LATE PREDICTORS OF POSTOPERATIVE NEUROCOGNITIVE DYSFUNCTION IN CARDIAC SURGERY

Yusuf Salim URCUN[1], Yasar ALTUN[2], Arda Aybars PALA[3]

[1]Department of Cardiovascular Surgery, Adiyaman Training and Research Hospital, Adiyaman, Turkey
[2]Department of Neurology, Adiyaman Training and Research Hospital, Adiyaman, Turkey
[3]Department of Cardiovascular Surgery, Adiyaman Training and Research Hospital, Adiyaman, Turkey

PRINT | English | https://doi.org/10.18071/isz.75.0231 | www.elitmed.hu

Background and purpose – Postoperative cognitive dysfunction (POCD) is a multifactorial image characterized by insufficiency in features such as the ability to perform tasks requiring high brain functions. Cognitive dysfunction such as memory loss and decreased concentration, confusion, and delirium are common conditions in some patients in the early period after major surgical interventions such as cardiac surgery. POCD causes delays in postoperative recovery, long return-to-work times, and decreased quality of life. This study aims to demonstrate POCD in early and late stages in patients undergoing cardiac surgery through the Montreal Cognitive Assessment (MoCA) and the Mini Mental Test (MMT). In addition, we aim to determine predictive factors with these neurocognitive tests.
Methods – MMT and MoCA tests were applied to the patients included in the study before cardiac surgery, on the sixth postoperative day and third month. Neurocognitive dysfunction detected on the sixth postoperative day was accepted as an early period, its detection in the postoperative third month was accepted as a late period.
Results – 127 patients without neurocognitive dysfunction in the preoperative period were included in the study. For early neurocognitive impairment, age, mean platelet volume (MPV), New York Heart Association (NYHA) classification, x-clamp time, cardio-pulmonary bypass (CPB) time, postoperative intensive care and hospital stay duration, and an event of acute myocardial infarction (AMI) in the preoperative period were determined as predictive factors. In addition, in late-period of neurocognitive dysfunction age, MPV, NYHA classification, x-clamp duration, CPB time, postoperative intensive care and hospital stay duration were shown as predictors of neurocognitive dysfunction.

A POSZTOPERATÍV NEUROKOGNITÍV DISZFUNKCIÓ KORAI ÉS KÉSŐI PREDIKTORAI SZÍVSEBÉSZETI BEAVATKOZÁS UTÁN
Urcun YS, MD; Altun Y, MD, Associate Prof.; Pala AA, MD
Ideggyogy Sz 2022;75(7–8):231–240.

Háttér és cél – A posztoperatív kognitív diszfunkció (POCD) számos elemből összeálló állapot, amit a magasabb agyi funkciókat igénylő feladatok végrehajtásában jelentkező zavar jellemez. A nagy sebészeti beavatkozások, így például a szívsebészeti beavatkozások utáni korai időszakban gyakran jelenik meg memóriazavarral, csökkent koncentrációs készséggel, zavartsággal vagy delíriummal jellemezhető kognitív diszfunkció. A POCD következtében elhúzódik a posztoperatív gyógyulás, megnő a munkába való visszatéréshez szükséges időtartam és csökken a beteg életminősége. Vizsgálatunk célja az volt, hogy a Montreal Kognitív Felmérés (MoCA) és a Mini Mentális Teszt (MMT) segítségével felmérjük, milyen mértékben fordul elő POCD a szívsebészeti beavatkozások utáni korai és késői időszakban. Célunk volt továbbá annak megállapítása, hogy e neurokognitív tesztek a POCD milyen prediktív faktorait képesek kiszűrni.
Módszerek – A vizsgálatba bevont betegekkel a szívsebészeti beavatkozás előtt, a hatodik posztoperatív napon és a harmadik posztoperatív hónapban végeztük el a két tesztet. A hatodik posztoperatív napon detektált neurokognitív diszfunkciót korai, míg a harmadik posztoperatív hónapban detektált neurokognitív diszfunkciót késői POCD-nek számítottuk.
Eredmények – A vizsgálatba 127 olyan beteget vontunk be, akik a preoperatív periódusban nem rendelkeztek neurokognitív diszfunkcióval. A korai neurokognitív diszfunkciót a következő tényezők jelezték előre: életkor, átlagos vérlemezke-térfogat (MPV), New York Heart Association (NYHA-) osztályozás pontszáma, x-clamp-idő, cardiopulmonalis bypass (CPB) időtartama, a posztoperatív intenzív terápiás és kórházi ápolás időtartama, akut myocardialis infarktus (AMI) előfordulása a preoperatív periódusban.

Correspondent: Yusuf Salim URCUN, MD, Adiyaman Training and Research Hospital, Department of Cardiovascular Surgery, Yunus Emre, 1164. Street, postal zip code: 02200 Adiyaman, Turkey.
Tel: +90 546 470 98 05, fax: +90 416 214 53 99. E-mail: ys_urcun@hotmail.com
https://orcid.org/0000-0002-1061-1900

Érkezett: 2021. január 14. Elfogadva: 2021. április 30.

Conclusion – The results of our study support the literature findings showing that delirium is associated with a decline in cognitive functions three months after cardiac surgery. As a result, the lack of agreed diagnostic tests in the definition of POCD makes it difficult to standardize and interpret the research in this area. Therefore, a consensus to be reached in the diagnosis of POCD will ensure the use and correct interpretation of neurophysiological tests. In our study, advanced age and long hospital and intensive care stays were shown as predictive factors for both early and late neurocognitive dysfunctions. Furthermore, smoking was shown as a predictive factor only for late neurocognitive dysfunction.

Keywords: *cardiac surgery, neurocognitive disfunction, Montreal cognitive assesment, Mini Mental test*

A késői neurokognitív diszfunkciót a következő tényezők jelezték előre: életkor, MPV, NYHA-klasszifikáció, x-clamp-idő, CPB-időtartam, a posztoperatív intenzív terápiás és kórházi ápolás időtartama.
Következtetés – Eredményeink alátámasztják azt a szakirodalmi megállapítást, miszerint a delírium a szívsebészeti beavatkozások utáni harmadik hónapban a kognitív funkciók hanyatlásával jár együtt. Ebből az következik, hogy a POCD definiálásához használható standard diagnosztikai tesztek hiánya megnehezíti a kutatási eredmények interpretálását ezen a szakterületen. A neurofiziológiai teszteket csak akkor lehet majd megfelelő módon használni és interpretálni, ha kialakul a konszenzus a POCD diagnózisa kapcsán. Eredményeink szerint az előrehaladott életkor, valamint a hosszú posztoperatív intenzív terápiás és kórházi ápolási idő előre jelzi mind a korai, mind a késői neurokognitív diszfunkciót; a dohányzás csak a késői neurokognitív diszfunkció kockázati tényezője.

Kulcsszavak: *szívsebészet, neurokognitív diszfunkció, Montreal Kognitív Felmérés, Mini Mentális Teszt*

Postoperative cognitive dysfunction (POCD) is a multifactorial image characterized by insufficiency in features such as the ability to perform tasks requiring high brain functions. Symptoms and severity vary in each patient. Cognitive changes are usually temporary, but in some cases, they may last for weeks after anesthesia, or even be permanent and may be a precursor to further disorders. Cognitive function is defined as a person's functions to use perception, memory, and information[1]. Cognitive dysfunction such as memory loss and decreased concentration, confusion, and delirium are common conditions in some patients in the early period after major surgical interventions such as cardiac surgery[2]. Although the etiology of postoperative cognitive dysfunction is not fully known, it is thought to be multifactorial. Popular opinions today are that the answer to POCD formation is a systemic inflammatory response triggered by the joint effect of stress response during surgery, the type of surgery and anesthesia[3]. Although developments in surgical and anesthesia techniques in recent years have significantly decreased the frequency of all kinds of serious complications after major surgery, POCD is still frequently encountered, especially in elderly patients. Although different rates are reported depending on the type and length of anesthesia and surgery, evaluation methods, and definitions, a frequency varying between 20-80% is reported[4]. POCD has been shown to have negative effects on clinical results by prospective clinical studies[5, 6]. POCD causes delays in postoperative recovery, long return-to-work times, and decreased quality of life[7].

Since a weak correlation has been shown between self-definition of cognitive symptoms and objective tests, pre- and post-operative neuropsychological tests are used for the diagnosis of POCD[8]. The Montreal Cognitive Assessment (MoCA) and the Mini Mental Test (MMT) are commonly used tests in many centers in the diagnosis of cognitive dysfunction. MMT is a bedside test that can be applied by healthcare professionals in a short time. MoCA[9], which has higher sensitivity and specificity compared to MMT in the evaluation of neurocognitive dysfunctions, has excellent sensitivity to define mild cognitive impairment (90%) and very good specificity (87%), and it also has good test-retest reliability ($r=0.92$, $p=0.001$)[10]. MoCA is used to differentiate cognitive weakness in vascular cognitive dysfunctions, vascular dementia, and cardiovascular diseases[11]. A test that can be defined as the "gold standard" for postoperative cognitive dysfunction has not yet been developed. MMT, which is one of the neurological examination and neurophysiological tests in a clinic, is frequently preferred for its ease of application. However, there are no studies showing that the more sensitive MoCA test is used in the postoperative period in PCOD patients.

In this study, we aim to investigate the predictive factors of POCD and their effect on postoperative clinical results and to contribute to the literature on the management of the disease.

Materials and methods

The study was approved by the Adiyaman University ethics committee with the approval number of 2020/6-39. All patients who underwent cardiac surgery in our hospital over a period of 3 months were included in the study after obtaining their written consent. Patients with preoperative neurocognitive dysfunction (MoCA<21 / MMT <26), education level below secondary education, a neurological and psychiatric disease, an alcohol and substance addiction, a chronic renal failure, not providing consent to the study, with clinical conditions that may lead to cerebral ischemia during the study (cerebral embolism, long-term hypotension, cardiac arrest, or respiratory arrest), and patients with cerebral hemorrhage were not included in the study.

Anesthesia premedication was provided in all patients by administering Diazepam 5 mg per os the night before the operation, and Morphine sulfate 10 mg im. 30 minutes before the operation. After the patient was taken to the operating room they were monitored, and ECG electrodes, venous tracts and a radial artery catheter for full arterial monitoring were placed, and the anesthesia induction was performed with fentanyl 30-50 μg/kg. Succinyl Choline 1 mg/kg was used, and pancuronium 0.1 mg/kg was used as a muscle relaxant. 3 μg/kg/min fentanyl infusion and isoflurane inhalation were used for the maintenance treatment. Intubated patients were ventilated with 100% O_2. A Foley catheter was used to monitor urine output during the operation. Under general anesthesia, median sternotomy was performed, left internal mammarian artery and saphenous vein grafts were used. A centrifugal bypass pump and a membrane oxygenator were used and moderate hypothermia was applied. All cases were heparinized and the activated clotting time (ACT) was kept above 400 seconds. The pump flow rate was adjusted to 2.4 L/min/m^2 according to the body surface area of the patients. Cold blood cardioplegia was applied. Patients who were taken to the intensive care unit were extubated when appropriate alertness was observed and there was no problem in blood gas and chest tube drainage. Patients who were followed up in the intensive care unit on the first and second days after the operation were taken to the ward on the second postoperative day if there was no additional problem. Patients who did not have any problem during follow-up in the ward were discharged on the sixth postoperative day.

MMT and MoCA were applied to all patients on the morning of the operation, after the operation, on the sixth postoperative day and on the third postoperative month, which provides the data for this study. The tests used in the study were determined by a neurologist and scored by the same neurologist (Y.A). In the questionnaires used in the study, orientation, recording memory, attention, calculating, language, concentration, memory, executive function, abstract thinking, and orientation tests were used. A score of 21 for the MoCA test and under 26 for the MMT was considered to be a neurocognitive dysfunction. Care was taken to ensure that the test conditions applied were the same for each patient. The tests were administered at the same time of day, in the same room, and by the same person each time. Detection of a neurocognitive dysfunction on the sixth postoperative day was defined as an early neurocognitive dysfunction, and the continuation of the condition in the third postoperative month as a late neurocognitive dysfunction.

Preoperative analysis and examination results were compared with the preoperative data of the patients, including age, gender, body mass index, NYHA functional class, smoking status, comorbid diseases (diabetes mellitus, hypertension, and chronic obstructive pulmonary disease). The x-clamp and cardiopulmonary bypass times from the operative data of the patients, the duration of stay in the intensive care unit, hospital stay, mechanical ventilation time from the postoperative parameters, and the postoperative blood tests and ejection fraction results were compared.

STATISTICAL ANALYSIS

The SPSS 11.5 program was used for data analysis. As descriptors, mean±standard deviation and median (minimum-maximum) were used for the quantitative variables and the number of patients (percentage) for the qualitative variables. Whether there is a difference between the categories of the qualitative variable with two categories in terms of quantitative variables were examined using the Student's t-test if normal distribution assumptions were provided, and the Mann-Whitney U test if not. When the relationship between the two qualitative variables was analyzed, the Chi-square test was used. Univariate and Multivariate Logistic Regression analyzes were used to determine the risk factors affecting neurocognitive dysfunction. The statistical significance level was taken as 0.05.

Table 1. *Demographic Data for Early Neurocognitive Disorder-1*

Variables	Early neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
Age	54.55±8.81	55.50 (34.00-70.00)	66.16±7.39	66.00 (53.00-83.00)	*<0.001*[a]
BMI	27.30±3.82	27.35 (19.10-37.30)	27.94±4.50	27.50 (18.60-40.00)	0.390[a]
AST	24.74±11.13	22.00 (12.00-64.00)	26.36±11.92	24.00 (10.00-64.00)	0.434[b]
ALT	24.29±11.96	21.50 (10.00-70.00)	26.20±17.11	22.00 (7.00-111.00)	0.799[b]
Albumin	4.10±0.27	4.10 (3.60-4.59)	4.03±0.43	4.00 (2.80-4.82)	0.493[b]
Urea	40.81±12.74	39.00 (21.00-71.00)	38.07±14.98	37.00 (20.00-123.00)	0.202[b]
Creatine	0.90±0.19	0.92 (0.44-1.49)	0.89±0.17	0.87 (0.60-1.60)	0.176[b]
MPV	8.13±0.94	8.20 (6.29-10.60)	8.93±1.16	8.78 (6.36-11.20)	*<0.001*[a]
Hemoglobin	14.36±1.62	14.35 (9.80-16.90)	13.88±1.75	13.70 (9.60-18.00)	0.076[b]
NYHA	1.84±0.64	2.00 (1.00-3.00)	2.26±0.66	2.00 (1.00-4.00)	*0.001*[b]
Ejection fraction	50.67±8.65	53.50 (30.00-63.00)	49.71±7.62	50.00 (30.00-65.00)	0.234[b]
MoCA on the preoperative-postoperative 6th day	2.38±1.45	2.00 (0.00-7.00)	8.49±4.85	8.00 (2.00-19.00)	*<0.001*[b]
MMT on the preoperative-postoperative 6th day	2.29±1.58	2.00 (0.00-6.00)	7.16±3.22	7.00 (1.00-17.00)	*<0.001*[b]

SD: standard deviation, Min.: minimum, Max.: maximum, a: Student-t test, b: Mann-Whitney U test, BMI: body mass index, AST: aspartate amino transferase, ALT: alanine amino transferase, MPV: mean platelet volume, NYHA: New York Heart Association, MoCA: Montreal Cognitive Assessment, MMT: Mini Mental test

Results

127 patients without preoperative neurocognitive dysfunction were included in the study. While a neurocognitive dysfunction was observed in 69 (54.3%) patients in the early period, it was observed that such a condition continued in the late period in 25 (19.6%) patients. When the demographic characteristics of patients with early neurocognitive dysfunction were examined, age, mean platelet volume (MPV), New York Heart Association (NYHA) classification and acute myocardial infarction (AMI) were found to be statistically more significant in the group with a neurocognitive dysfunction ($p<0.05$) **(Tables 1** and **2)**. The x-clamp time, cardio-pulmonary bypass (CPB) time, duration of stay in the intensive care unit and in the hospital were found to be statistically more significant in patients with an early neurocognitive dysfunction ($p<0.001$) **(Table 3)**. Compared to preoperative values, the MoCA and MMT scores were found to be statistically less significant on the 6th postoperative day **(Table 1)**.

Age, MPV, NYHA classification, x-clamp time, CPB time, postoperative length of intensive care unit and inpatient hospital stays, and occurrence of AMI in the preoperative period, were found to be significant as a result of the analysis in **Tables 1, 2** and **3**. Factors thought to have an effect on early neurocognitive dysfunction were included in the regression analysis **(Table 4)**. Considering the results of the univariate logistic regression analysis in Table 4, all variables were found to be significant risk factors and were included in the multivariate logistic regression analysis. According to the multivariate logistic regression results, the variables of age, MPV, postoperative intensive care duration (days), hospital stay (days) and preoperative AMI all combined were found to be significant in the model. The risk of early neurocognitive dysfunction increased by 1.235 times for every single unit of increase in age factor, by 2.615 times for each single unit of increase in MPV, by 1.095 times per unit of increase in postoperative intensive care duration (day) and by a multiple of 2.072 for every single unit of increase in hospital stay (day). AMI, on the other hand, increases the risk of early neurocognitive dysfunction by 5.733 times **(Table 4)**.

When the demographic characteristics of the patients with late-stage neurocognitive impairment were examined, age, MPV and high NYHA classi-

Table 2. *Demographic Data for Early Neurocognitive Disorder-2*

Variables		Early neurocognitive dysfunction				
		No		Yes		
		N	%	N	%	p-value
Gender	Male	44	75.9	50	72.5	0.664
	Female	14	24.1	19	27.5	
Smoking Status	No	18	31.0	22	31.9	0.918
	Yes	40	69.0	47	68.1	
DM	No	24	41.4	28	40.6	0.927
	Yes	34	58.6	41	59.4	
COPD	No	48	82.8	49	71.0	0.121
	Yes	10	17.2	20	29.0	
TFT Disorder	No	48	82.8	58	84.1	0.844
	Yes	10	17.2	11	15.9	
HT	No	26	44.8	28	40.6	0.630
	Yes	32	55.2	41	59.4	
AMI	No	42	72.4	36	52.2	*0.020*
	Yes	16	27.6	33	47.8	

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, TFT: thyroid function test, HT: hypertension, AMI: acute myocardial infarction

Table 3. *Operative and postoperative data for early neurocognitive impairment*

Variables	Early neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
X-Clamp time	64.76±12.91	64.50 (35.00-96.00)	78.07±17.60	76.00 (48.00-143.00)	*<0.001*[b]
CPB time	87.64±13.36	89.50 (60.00-110.00)	114.39±24.89	110.00 (75.00-194.00)	*<0.001*[b]
Postoperative intensive care time (days)	31.14±12.78	26.00 (23.00-72.00)	63.70±37.35	48.00 (21.00-268.00)	*<0.001*[b]
Hospital stay (days)	5.78±1.43	5.00 (4.00-12.00)	9.12±5.76	8.00 (6.00-48.00)	*<0.001*[b]
Postoperative Ventilation Time (hours)	8.73±2.46	8.00 (5.00-18.00)	11.81±14.73	8.00 (4.00-124.00)	0.554[b]

CPB: cardiopulmonary bypass

Table 4. *Univariate logistic regression analysis results for early neurocognitive dysfunction*

Variables (Reference)	β	S.E.	p-value	OR	95% CI for OR	
					Lower limit	Upper limit
Age	0.183	0.034	*<0.001*	1.201	1.124	1.283
Mean Platelet Volume	0.705	0.188	*<0.001*	2.024	1.400	2.925
NYHA	0.989	0.300	*0.001*	2.688	1.494	4.836
X-Clamp time	0.066	0.016	*<0.001*	1.068	1.035	1.102
CPB time	0.093	0.018	*<0.001*	1.097	1.059	1.138
Postoperative intensive care time (days)	0.089	0.016	*<0.001*	1.093	1.059	1.129
Hospital stay (days)	1.192	0.219	*<0.001*	3.295	2.144	5.063
AMI	0.878	0.380	*0.021*	2.406	1.143	5.067

β: Beta coefficient, S.E.: standard error of mean, OR: odds ratio, CI.: confidence interval, NYHA: New York Heart Association, CPB: cardiopulmonary bypass, AMI: acute myocardial infarction

Table 5. *Demographic Data for Late Neurocognitive Dysfunction-1*

Variables	Late neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
Age	59.29±9.66	60.00 (34.00-81.00)	67.24±8.40	66.00 (54.00-83.00)	*<0.001*[a]
BMI	27.74±4.23	27.70 (18.60-37.80)	27.30±4.14	27.00 (20.20-40.00)	0.644[a]
AST	26.01±11.47	24.00 (12.00-64.00)	24.04±11.97	24.00 (10.00-64.00)	0.345[b]
ALT	25.90±15.89	22.00 (8.00-111.00)	23.00±10.23	21.00 (7.00-48.00)	0.748[b]
Albumin	4.06±0.35	4.10 (2.80-4.82)	4.09±0.44	4.10 (2.90-4.70)	0.438[b]
Urea	39.31±14.29	37.50 (20.00-123.00)	39.36±13.12	38.00 (21.00-87.00)	0.713[b]
Creatine	0.90±0.17	0.90 (0.44-1.49)	0.87±0.22	0.81 (0.60-1.60)	0.178[b]
MPV	8.46±1.08	8.50 (6.29-11.20)	9.01±1.28	9.15 (6.77-11.20)	*0.028*[a]
Hemoglobin	14.12±1.69	14.20 (9.60-16.90)	14.03±1.81	13.64 (10.50-18.00)	0.544[b]
NYHA	2.01±0.71	2.00 (1.00-4.00)	2.32±0.48	2.00 (2.00-3.00)	*0.037*[b]
Ejection Fraction	50.43±7.70	50.00 (30.00-65.00)	49.00±9.57	50.00 (30.00-65.00)	0.453[b]
MoCA on preoperative-postoperative 3rd month	2.05±1.86	1.00 (0.00-8.00)	9.08±5.62	7.00 (2.00-19.00)	*<0.001*[b]
MMT on preoperative-postoperative 3rd month	2.20±1.71	2.00 (0.00-9.00)	6.64±3.49	6.00 (1.00-16.00)	*<0.001*[b]

SD: standard deviation, Min.: minimum, Max.: maximum, a: Student-t test, b: Mann-Whitney U test, BMI: body mass index, MPV: mean platelet volume, AST: aspartate amino transferase, ALT: alanine amino transferase, NYHA: New York Heart Association, MoCA: Montreal Cognitive Assessment, MMT: Mini Mental test

Table 6. *Demographic Data for Late Neurocognitive Dysfunction-2*

Variables		Late neurocognitive dysfunction				
		No		Yes		
		N	%	N	%	p-value
Gender	Male	77	75.5	17	68.0	0.444
	Female	25	24.5	8	32.0	
Smoking Status	No	27	26.5	13	52.0	*0.014*
	Yes	75	73.5	12	48.0	
DM	No	42	41.2	10	40.0	0.915
	Yes	60	58.8	15	60.0	
COPD	No	79	77.5	18	72.0	0.565
	Yes	23	22.5	7	28.0	
TFT Disorder	No	84	82.4	22	88.0	0.496
	Yes	18	17.6	3	12.0	
HT	No	47	46.1	7	28.0	0.101
	Yes	55	53.9	18	72.0	
AMI	No	63	61.8	15	60.0	0.871
	Yes	39	38.2	10	40.0	

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, TFT: thyroid function test, HT: hypertension, AMI: acute myocardial infarction

fication variables were found to be statistically more significant in the group with a neurocognitive dysfunction ($p < 0.05$) **(Table 5)**. There was no difference between the groups in terms of having AMI ($p=0.871$). Smoking was found to be statistically more significant in the group with a late neurocognitive dysfunction ($p=0.014$) **(Table 6)**. X-clamp time, CPB time, ICU and hospital stay times were statistically significantly higher in patients with an early neurocognitive dysfunction ($p<0.001$) **(Table 7)**. When compared with their preoperative values, MoCA and MMT scores were found to be statisti-

Table 7. *Operative and Postoperative Data for Late Neurocognitive Dysfunction*

Variables	Late neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
X-Clamp time	67.62±12.54	68.00 (35.00-96.00)	89.84±20.77	82.00 (60.00-143.00)	*<0.001*[b]
CPB time	92.96±14.08	95.00 (60.00-129.00)	139.76±21.26	137.00 (113.00-194.00)	*<0.001*[a]
Postoperative intensive care time (days)	41.06±31.18	28.00 (21.00-268.00)	80.52±18.39	72.00 (48.00-120.00)	*<0.001*[b]
Hospital stay (days)	6.90±2.60	6.00 (4.00-24.00)	10.40±8.65	8.00 (6.00-48.00)	*<0.001*[b]
Postoperative Ventilation Time (hours)	10.37±12.06	8.00 (4.00-124.00)	10.56±5.44	9.00 (4.00-23.00)	0.341[b]

CPB: cardiopulmonary bypass

Table 8. *Univariate logistic regression analysis results for late neurocognitive dysfunction*

Variables (Reference)	β	S.E.	p-value	OR	95% CI for OR	
					Lower limit	Upper limit
Age	0.097	0.029	*0.001*	1.102	1.042	1.165
Mean Platelet Volume	0.433	0.201	*0.032*	1.542	1.039	2.287
NYHA	0.693	0.344	*0.044*	2.000	1.019	3.928
X-Clamp time	0.102	0.024	*<0.001*	1.108	1.057	1.160
CPB Time	0.289	0.076	*<0.001*	1.336	1.151	1.550
Postoperative intensive care time (days)	0.043	0.010	*<0.001*	1.044	1.024	1.066
Hospital stay (days)	0.183	0.074	*0.013*	1.200	1.039	1.386

β: Beta coefficient, S.E.: standard error of mean, OR: odds ratio, CI.: confidence interval, NYHA: New York Association, CPB: cardiopulmonary bypass

cally significantly lower in the postoperative 3rd month **(Table 5)**.

Age, MPV, NYHA classification, x-clamp time, CPB time, and postoperative intensive care and hospital stay times, which were found to be significant as a result of the analyzes in **Tables 5**, **6** and **7** and also thought to affect late neurocognitive dysfunction, were included in the univariate logistic regression analysis **(Table 8)**. Considering the results of the univariate logistic regression analysis in **Table 8**, all variables were found to be significant risk factors and were included in the multivariate logistic regression analysis. According to the multivariate logistic regression results, x-clamp times and postoperative intensive care times (days) both were found to be significant together in the model. A one unit increase in the x-clamp time was found to increase the risk of late-stage neurocognitive dysfunction by 1.112-fold and a one unit increase in the postoperative intensive care time (day), by 1.032-fold **(Table 8)**.

Discussion

In this study, POCD was shown with low MoCA values in the early period affecting 54.3% of patients, and in the late period 19.6% of patients. POCD in cardiac surgery has been the subject of research and discussion for many years. In a study conducted on patients who underwent coronary artery surgery, it was shown that 40-80% of the patients had a decrease in mental abilities such as concentration, attention, and memory[12]. POCD is the most common neurological disorder after cardiac surgery. It is a problem that affects not only patients, but also their relatives and may cause additional costs in the health systems in both the long and short-terms[13]. Many factors in the preoperative, operative and postoperative phases can lead to POCD. Although the incidence of POCD after coronary artery bypass graft operation is found to be high in the early period, the majority of patients can return to their preoperative basal neurocogni-

tive values[14]. Therefore, POCD can be said to be time-dependent. Most dysfunctions are observed at the time of discharge. While neurocognitive dysfunction is observed at a rate of 50-80% at the time of discharge, it is observed with a rate of 20-50% in the 6th week and 10-30% in the 6th month[15]. *Newman* et al. observed a decrease in cognitive function in 53% of the patients at the time of discharge, in 36% after 6 months and in 42% after 5 years, and thought that the most important predictor of late-stage cognitive dysfunction was early cognitive dysfunction[12]. *Johnson* et al. in a study involving patients aged 68 and over, found that 26% of the patients had PCOD in the first postoperative week after non-cardiac surgery, while only 10% of patients had a cognitive dysfunction in the third postoperative month[16]. Similar to previous studies, it was observed in our study that the neurocognitive disorders in the early period did not persist in the third postoperative month in most patients. While the incidence of neurocognitive dysfunction was 54.3% of patients in the early postoperative period, it was found that the situation continued in 19.6% of the patients in the late period. This may be due to the unstable performance of the patients in the early period. It may also be due to the use of MMT as a neuropsychological test battery in other studies and the use of the more-sensitive MoCA in our study.

Cognitive dysfunctions are more common in the elderly. The increase in the mean age in the patient group that will undergo cardiac surgery has brought concerns about POCD. Cognitive functions are very important in this patient group in order to overcome post-operative physical difficulties. Therefore, POCD formation can lead to a failure in the postoperative period. The associated increased delirium risk also affects the postoperative results[17]. Advanced age is one of the risk factors for the occurrence of POCD. Brain blood flow and brain mass decrease in elderly patients, neuronal loss and changes in neurotransmitter concentrations increase the possibility of postoperative cognitive dysfunction[3]. In our study, advanced age was observed as a predictive factor in univariate analysis for early and late neurocognitive dysfunction. In the multivariate analyzes, it was shown to be an independent predictor of early neurocognitive dysfunction. In the study conducted by *Selnes* et al., the effect of age on cognitive dysfunctions was attributed to the higher prevalence of other risk factors, such as diabetes mellitus and kidney failure in the elderly population[15]. However, the fact that there was no difference in the incidence of comorbidities between the groups in our study has shown that the age factor alone is a predictor of neurocognitive dysfunction. *Sauër* et al. showed that advanced age prolonged the duration of POCD[18]. The fact that age was found to be one of the predictors of late-stage neurocognitive dysfunction in our study supports the findings of this study. In a study in which postoperative delirium was evaluated with the Confusion Assessment Method (CAM), postoperative delirium was independently associated with cognitive decline one month after surgery[19]. In our study, MoCA and MMT scores were found to be statistically significantly lower at the third postoperative month compared to the preoperative values.

In our study, chronic smoking was found to be a predictor of late-stage neurocognitive dysfunction in the univariate analyzes. The effect of smoking on neurocognitive performance is divided into two as acute and chronic. It increases cognitive performance through nicotine in the acute effect, while in chronic use it is associated with poor cognitive function due to the vascular damage it causes[20]. There are studies indicating that factors predisposing to vascular diseases such as hypertension, hypercholesterolemia, and smoking cause cognitive dysfunction[21]. These factors are also associated with postoperative delirium[22,23]. *Pérez Belmonte* et al. have shown that smoking is one of the POCD factors[24]. *Heffernan* et al. have associated chronic smoking with short and long-term memory problems[25]. However, in a study by *Djaiani* et al., age, cognitive function, years of education, and impaired left ventricular function were shown as predictive factors of neurocognitive decline in the 6th week after CABG, while the preventive or causative effect of smoking could not be demonstrated[26]. The fact that patients had a preoperative AMI triggers both an acute inflammation and prolongs hospital stay. In our study, having preoperative AMI and preoperative MPV were shown as independent predictors of early POCD. While MPV was also observed as a predictor of late POCD in univariate analyzes, the effect of AMI was not observed in chronic POCD. MPV is one of the indicators of the inflammatory process and shows the platelet size. In our study, the inflammatory process caused by AMI may have triggered the early period neurocognitive dysfunction and the increase in MPV. By *Beeri* et al. inflammation was shown as a common factor in coronary artery disease and cognitive disorders[27]. The decrease in inflammation due to AMI over time may explain that it is not a factor in late neurocognitive dysfunction.

NYHA classes are among the indicators of cardiac symptoms, cardiac status and functional capacity[28]. There are studies in the literature that associate low functional capacity and high NYHA

classes with neurocognitive dysfunction[29]. In our study, low functional capacity was detected as one of the indicators of early and late neurocognitive dysfunction in univariate analyzes. This can be attributed to the long recovery times and the long time to return to normal activities of patients with low functional capacity.

In our study, x-clamp and CPB times were shown as predictors of early and late neurocognitive dysfunction in univariate analyzes. The cases that require a long x-clamp time also lead to an increase in CPB times. *Kilo* et al., in their study on CABG patients, also showed CPB as the only predictor of neurocognitive dysfunction after CABG[30]. Again, *Xu* et al. and *Boodhwani* et al. demonstrated cardiopulmonary bypass times as predictors of POCD[31, 32]. The action mechanisms of cardiopulmonary bypass and x-clamp times are not yet fully understood. As it is known, body blood flow in the x-clamp process is provided by a completely artificial system. Debates continue about how optimal cerebral perfusion should be in this process. It is known that low cerebral perfusion and high cerebral perfusion under an X-clamp affects cognitive functions severely[33]. Inappropriate cerebral perfusion pressure combined with prolonged CPB and x-clamp times may have caused POCD. Moreover, particle or gas micro-embolisms and inflammatory mediators that occur as a result of blood contact with foreign surfaces may be the cause of this situation[34].

In our study, long hospital and intensive care stays were shown as predictors of both early and late neurocognitive dysfunctions. Similarly in the literature, it was found that in case of elective patients with a preoperative MoCA score lower than 26 who underwent open-heart surgery, the cost of mechanical ventilation, the duration of stay in the intensive care unit and in hospital were significantly increased, but postoperative cognitive involvement was not mentioned[35]. In addition, *Wilson* et al. and *Steinmetz* et al. showed in their large-scale studies that long hospital and intensive care stays lead to neurocognitive dysfunctions[36, 37]. The most important consequence of postoperative cognitive dysfunction is that patients lose their functional independence. In the postoperative period, this situation causes prolongation of the intensive care stays. According to our study, long intensive care stays may be a result of both postoperative dysfunction and a cause of early and late neurocognitive dysfunction.

The results of our study support the literature findings showing that delirium is associated with a decline in cognitive functions three months after cardiac surgery. As a result, the lack of agreed diagnostic tests in the definition of POCD makes it difficult to standardize and interpret the research in this area. Therefore, a consensus to be reached in the diagnosis of POCD will ensure the use and correct interpretation of neurophysiological tests. Large-scale studies are needed to precisely determine how MoCA, a new generation test, is affected by cardiopulmonary bypass and anesthetics in patients undergoing CABG surgery. Thus, it will be possible to determine whether MoCA will be included in the routine postoperative evaluation.

FINANCIAL SUPPORT: None.
CONFLICT OF INTEREST: None.

REFERENCES

1. *Hanning CD*. Postoperative cognitive dysfunction. Br J Anaesth 2005;95(1):82-7. https://doi.org/10.1093/bja/aei062
2. *Moller JT, Cluitmans P, Rasmussen LS, et al*. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction [published correction appears in Lancet 1998;351(9117):1742]. Lancet 1998;351(9106):857-61. https://doi.org/10.1016/S0140-6736(97)07382-0
3. *Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G*. Postoperative cognitive dysfunction after cardiac surgery. Chest 2005;128(5):3664-70. https://doi.org/10.1378/chest.128.5.3664
4. *Funder KS, Steinmetz J, Rasmussen LS*. Cognitive dysfunction after cardiovascular surgery. Minerva Anestesiol 2009; 75(5):329-32.
5. *Fick DM, Steis MR, Waller JL, Inouye SK*. Delirium superimposed on dementia is associated with prolonged length of stay and poor outcomes in hospitalized older adults. J Hosp Med 2013;8(9):500-5. https://doi.org/10.1002/jhm.2077
6. *Partridge JS, Dhesi JK, Cross JD, et al*. The prevalence and impact of undiagnosed cognitive impairment in older vascular surgical patients. J Vasc Surg 2014;60(4):1002-11.e3. https://doi.org/10.1016/j.jvs.2014.04.041
7. *McKhann GM, Goldsborough MA, Borowicz LM Jr, et al*. Cognitive outcome after coronary artery bypass: a one-year prospective study. Ann Thorac Surg 1997;63(2):510-5. https://doi.org/10.1016/S0003-4975(96)01057-0
8. *Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT; ISPOCD group.* The International Study of Postoperative Cognitive Dysfunction. The assessment of

postoperative cognitive function. Acta Anaesthesiol Scand 2001;45(3):275-89. https://doi.org/10.1034/j.1399-6576.2001.045003275.x
9. *Folstein MF, Folstein SE, McHugh PR*. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98.
10. *Nasreddine ZS, Phillips NA, Bédirian V, et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment [published correction appears in J Am Geriatr Soc 2019;67(9):1991]. J Am Geriatr Soc 2005;53(4):695-9. https://doi.org/10.1111/j.1532-5415.2005.53221.x
11. *McLennan SN, Mathias JL, Brennan LC, Stewart S*. Validity of the Montreal cognitive assessment (MoCA) as a screening test for mild cognitive impairment (MCI) in a cardiovascular population. J Geriatr Psychiatry Neurol 2011;24(1):33-8. https://doi.org/10.1177/0891988710390813
12. *Newman MF, Kirchner JL, Phillips-Bute B, et al.* Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery [published correction appears in N Engl J Med 2001;344(24):1876]. N Engl J Med 2001; 344(6):395-402. https://doi.org/10.1056/NEJM200102083440601
13. *Weintraub WS, Jones EL, Craver J, Guyton R, Cohen C*. Determinants of prolonged length of hospital stay after coronary bypass surgery. Circulation 1989;80(2):276-84. https://doi.org/10.1161/01.CIR.80.2.276
14. *Stygall J, Newman SP, Fitzgerald G, et al*. Cognitive change 5 years after coronary artery bypass surgery. Health Psychol 2003;22(6):579-86. https://doi.org/10.1037/0278-6133.22.6.579
15. *Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM*. Neurobehavioural sequelae of cardiopulmonary bypass. Lancet 1999;353(9164):1601-6. https://doi.org/10.1016/S0140-6736(98)07576-X
16. *Johnson T, Monk T, Rasmussen LS, et al*. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 2002;96(6):1351-7. https://doi.org/10.1097/00000542-200206000-00014
17. *Ansaloni L, Catena F, Chattat R, et al*. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. Br J Surg 2010;97(2):273-80. https://doi.org/10.1002/bjs.6843
18. *Sauër AM, Kalkman C, van Dijk D.* Postoperative cognitive decline. J Anesth 2009;23(2):256-9. https://doi.org/10.1007/s00540-009-0744-5
19. *Sauër AC, Veldhuijzen DS, Ottens TH, Slooter AJC, Kalkman CJ, van Dijk D*. Association between delirium and cognitive change after cardiac surgery. Br J Anaesth 2017; 119(2):308-15. https://doi.org/10.1093/bja/aex053
20. *Cervilla JA, Prince M, Mann A*. Smoking, drinking, and incident cognitive impairment: a cohort community based study included in the Gospel Oak project. J Neurol Neurosurg Psychiatry 2000;68(5):622-6. https://doi.org/10.1136/jnnp.68.5.622
21. *Black SE*. Vascular cognitive impairment: epidemiology, subtypes, diagnosis and management. J R Coll Physicians Edinb 2011;41(1):49-56. https://doi.org/10.4997/JRCPE.2011.121
22. *Rudolph JL, Marcantonio ER*. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011;112(5):1202-11. https://doi.org/10.1213/ANE.0b013e3182147f6d
23. *Balasundaram B, Holmes J*. Delirium in vascular surgery. Eur J Vasc Endovasc Surg 2007;34(2):131-4. https://doi.org/10.1016/j.ejvs.2007.02.016
24. *Pérez-Belmonte LM, Florido-Santiago M, Millán-Gómez M, Barbancho MA, Gómez-Huelgas R, Lara JP*. Research long-term cognitive ımpairment after off-pump versus on-pump cardiac surgery: Involved risk factors. J Am Med Dir Assoc 2018;19(7):639-640.e1. https://doi.org/10.1016/j.jamda.2018.02.012
25. *Heffernan TM, Ling J, Parrott AC, Buchanan T, Scholey AB, Rodgers J.* Self-rated everyday and prospective memory abilities of cigarette smokers and non-smokers: a web-based study. Drug Alcohol Depend 2005;78(3):235-41. https://doi.org/10.1016/j.drugalcdep.2004.11.008
26. *Djaiani GN, Phillips-Bute B, Blumenthal JA, Newman MF; Neurologic Outcome Research Group; CARE Investigators of the Duke Heart Center.* Chronic exposure to nicotine does not prevent neurocognitive decline after cardiac surgery. J Cardiothorac Vasc Anesth 2003;17(3):341-5. https://doi.org/10.1016/S1053-0770(03)00047-8
27. *Beeri MS, Ravona-Springer R, Silverman JM, Haroutunian V*. The effects of cardiovascular risk factors on cognitive compromise. Dialogues Clin Neurosci 2009;11(2):201-12. https://doi.org/10.31887/DCNS.2009.11.2/msbeeri
28. *Jessup M, Abraham WT, Casey DE, et al*. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119 (14):1977-2016. https://doi.org/10.1161/CIRCULATIONAHA.109.192064
29. *Demers C, McKelvie RS, Negassa A, Yusuf S; RESOLVD Pilot Study Investigators*. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. Am Heart J 2001;142(4):698-703. https://doi.org/10.1067/mhj.2001.118468
30. *Kilo J, Czerny M, Gorlitzer M, et al*. Cardiopulmonary bypass affects cognitive brain function after coronary artery bypass grafting. Ann Thorac Surg 2001;72(6):1926-32. https://doi.org/10.1016/S0003-4975(01)03199-X
31. *Xu T, Bo L, Wang J, et al.* Risk factors for early postoperative cognitive dysfunction after non-coronary bypass surgery in Chinese population. J Cardiothorac Surg 2013;8:204. https://doi.org/10.1186/1749-8090-8-204
32. *Boodhwani M, Rubens FD, Wozny D, et al*. Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery. Circulation 2006;114(1 Suppl):I461-6. https://doi.org/10.1161/CIRCULATIONAHA.105.001354
33. *Kellermann K, Jungwirth B.* Avoiding Stroke During Cardiac Surgery. Semin Cardiothorac Vasc Anesth 2010;14: 95-101. https://doi.org/10.1177/1089253210370902
34. *Moody DM, Brown WR, Challa VR, Stump DA, Reboussin DM, Legault C*. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. Ann Thorac Surg 1995;59(5):1304-7. https://doi.org/10.1016/0003-4975(95)00057-R
35. *Vimuktanandana A, Chiravanich W, Urusopone P, Sirilaksanamanon P, Indrambarya T*. Effect of preoperative cognitive dysfunction on postoperative outcomes in cardiac surgery. Chula Med J 2019; 63:9-12.
36. *Wilson RS, Hebert LE, Scherr PA, Dong X, Leurgens SE, Evans DA*. Cognitive decline after hospitalization in a community population of older persons. Neurology 2012;78 (13):950-6. https://doi.org/10.1212/WNL.0b013e31824d5894
37. *Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS; ISPOCD Group*. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009;110(3): 548-55. https://doi.org/10.1097/ALN.0b013e318195b569

AN ENDOSCOPE-ASSISTED CRANIOMETRIC CADAVERIC STUDY FOR THE BRAIN STEM AND THE CISTERNAL SEGMENT OF THE TROCHLEAR NERVE

Ahmet Tulgar BAŞAK[1], Nazlı ÇAKICI[2]

[1]Neurosurgery Department, VKV American Hospital, Nişantaşı, İstanbul, Turkey
[2]Neurosurgery Department, Medicana Internatıonal Hospital, Beylikdüzü, İstanbul, Turkey

PRINT | English | https://doi.org/10.18071/isz.75.0241 | www.elitmed.hu

Background and purpose – This study analyzed the relationship of trochlear nerve with neurovascular structures using craniometric measurements. The study was aimed to understand the course of trochlear nerve and minimize the risk of injury during surgical procedures.
Methods – Twenty trochlear nerves of 10 fresh cadavers were studied bilaterally using endoscopic assistance through the view afforded by the lateral infratentorial-supracerebellar, and the combined presigmoid-subtemporal transtentorial approaches. Trochlear nerves were exposed bilaterally taking seven parameters into consideration: the distance between the cisternal segment of trochlear nerve and vascular structures (superior cerebellar artery/SCA; posterior cerebral artery/PCA), the origin of the trochlear nerve in the brain stem, the angle in the level of tentorial junction, length, diameter, and length of nerve in the cisternal segment.
Results – We identified the brain stem and cisternal segments of the trochlear nerve. The lateral infratentorial supracerebellar approach allowed the exposure of the cisternal segments (crural and ambient cisterns), including the origin of the nerve in the brain stem. The combined presigmoid-subtemporal transtentorial approaches provided visualization of the cisternal segment of the nerve and the free edge of the tentorium. In this study, the mean length and width of the trochlear nerve in the cisternal segment were 30.3 and 0.74 mm, respectively. Length of the trochlear nerve from its origin to its dural entrance was 37.2 mm, tentorial dural entrance angle of the trochlear nerve and exit angle of the trochlear nerve from the brain stem were 127.0 degrees and 54 degrees, PCA to trochlear nerve in mid ambient cistern and SCA to

A TROCHLEARIS IDEG AGYTÖRZSI ÉS CISTERNALIS SZEGMENSÉNEK ENDOSZKÓPASSZISZTÁLT CRANIOMETRICUS CADAVERVIZSGÁLATA
Başak AM, MD; Çakıcı N, MD
Ideggyogy Sz 2022;75(7–8):241–246.

Háttér és cél – Vizsgálatunk célja a trochlearis ideg és a neurovascularis struktúrák kapcsolatának feltárása volt craniometriás mérések segítségével. Célunk volt a trochlearis ideg lefutásának megértése és ezáltal az ideg sérülésének minimalizálása a sebészi beavatkozások során.
Módszerek – Tíz friss cadaver húsz trochlearis idegét tanulmányoztuk bilateralisan endoszkópos segítséggel, lateralis infratentorialis-supracerebellaris és kombinált praesigmoidalis-subtemporalis transtentorialis megközelítésekből. A trochlearis idegeket mindkét oldalon feltártuk, és megmértük a következő hét paraméterüket: a trochlearis ideg cisternalis szegmense és az érstruktúrák (arteria cerebellaris superior és arteria cerebellaris posterior) közötti távolság; a trochlearis ideg eredete az agytörzsben; a tentorialis junctio szintjén mért szög; hossz; átmérő; a trochlearis ideg hossza a cisternalis szegmensben.
Eredmények – Azonosítottuk az agytörzset és a trochlearis ideg cisternalis szegmensét. A lateralis infratentorialis-supracerebellaris megközelítés lehetővé tette a cisternalis szegmens (cruralis és ambiens cisternák) feltárását, ezen belül az ideg agytörzsi eredetének feltárását. A kombinált praesigmoidalis-subtemporalis transtentorialis megközelítés lehetővé tette az ideg cisternalis szegmensének és a tentorium szabad szélének vizualizálását. Mérésünk szerint a trochlearis ideg cisternalis szegmensének átlagos hossza és átmérője 30,3 és 0,74 mm volt. A trochlearis ideg hossza az eredetétől a durába lépéséig 37,2 mm volt. A trochlearis ideg tentorialis durába lépési szöge és az agytörzsből való kilépési szöge 127,0 fok, illetve 54 fok volt. A trochlearis ideg és az arteria cerebellaris posterior közötti távolság az ambiens cisterna közepén 7,3 mm volt.

Correspondent: Nazlı ÇAKICI MD, Medicana International Hospital;
Beylikdüzü Caddesi No:3, 34100, Beylikdüzü, İstanbul, Turkey.
Telephone number: +90 530575 9556. E-mail: drnazlicakici@yahoo.com
https//:orcid.org/0000-0003-1480-6235

Érkezett: 2021. január 26. Elfogadva: 2021. június 12.

trochlear nerve in mid ambient cistern were 7.3 mm and 6.8mm.
Conclusion – Trochlear nerve is vulnerable to injury during the surgical procedures. Therefore, it is necessary to have a sufficient knowledge of the anatomy of cisternal segment and its relationship with adjacent neurovascular structures. The anatomical and craniometric data can be helpful in middle and posterior fossa surgery in minimizing the potential injury of the trochlear nerve.

Keywords: *anatomy, craniometry, Surgimap, trochlear nerve, trochlear nerve injury*

A trochlearis ideg és az arteria cerebellaris anterior közötti távolság az ambiens cisterna közepén 6,8 mm volt.
Következtetés – A trochlearis ideg gyakran megsérül a sebészeti beavatkozások során. Ezt megelőzendő, fontos cisternalis szegmense anatómiájának pontos ismerete és az ideg neurovascularis struktúrákkal való kapcsolatának feltárása. A trochlearis ideg sérülésének minimalizálása érdekében a középső és a hátulsó koponyaalap műtétei során hasznos az ideg anatómiai és craniometriás adatainak ismerete.

Kulcsszavak: *anatómia, craniometria, Surgimap, trochlearis ideg, trochlearisideg-sérülés*

The trochlear nerve is the cranial nerve with the longest intracranial course (approximately 60 mm), but also the thinnest (0.75–1 mm)[1]. The trochlear nerves arise from the inferolateral part of the inferior colliculus in the dorsal midbrain[2]. Nerve fibers decussate in the superior medullary velum and innervate contralateral superior oblique muscles. The superior oblique muscle rotates the eye inward and downward. The trochlear nerve is a somatic efferent nerve that courses in basal cisterns. After entering the tentorial incisura, it courses interdural[3]. This nerve has been described in literature with brain stem, cisternal, tentorial, cavernous, and orbital segments[2, 4–6]. Because of its thin structure and concealed location in the inferior part of the tentorium, it is very vulnerable to injury – especially the cisternal segment – during surgical procedures. In this study, we examined the angle of the nerve from the dorsal midbrain, its relationship with the other neurovascular structures in the ambient cistern, and its relation with the tentorial incisura. Endoscopic assistance and craniometric measurements used in this study were done based on the anatomical landmarks. We hope these measurements will assist surgeons in preoperative planning with the intraoperative anatomy-based navigation information and thereby minimize the risk of morbidity.

Materials and methods

In this study, we used ten fresh cadaveric heads. The cadavers were obtained from Medipol University Anatomy Department and the study was carried out in the Anatomy laboratory of Medipol University. Cadavers without any identified intracranial pathology were included in the study. Six of the cadavers were male, and four were female. The age of cadavers was varying between 52 and 85 years. The average age was 69.1 years.

In order to reveal the brain stem and the cisternal segments of the nerve, subtemporal and supracerebellar infratentorial approaches were performed with endoscopic assistance. The heads were positioned with a three-pin skull clamp (Doro QR3, USA) in vertical position. Initially, a standard supracerebellar infratentorial approach was used to expose the origin of both trochlear nerves at the midbrain. Tentorial leaves were lateralized by using 2.0 sutures. Retractors were placed in vertical position, and arachnoid adhesions were carefully dissected. Endoscopic assistance and measurements used to expose the cisternal segment of the nerve were done according to the identified landmarks. Later on, subtemporal approach was performed, and the temporal lobe was retracted carefully. The cisternal segment of the trochlear nerve was visualized in the ambient and crural cisterns. Anatomical position of the nerve was preserved as much as possible (in cadaveric specimens the positions of anatomical structures may be altered few millimeters after aspiration of the cerebrospinal fluid) and craniometric measurements were done using calipers (**Figures 1–6**). The nerve was followed and visualized up to the free edge of the tentorium. Endoscopic procedures were performed by using rigid endoscopes (Karl Storz GmbH.Co, Tuttlingen, Germany) and 0, 30, and 45° lenses. Angle measurements were calibrated with Surgimap (New York, USA) software program.

Results

The following seven parameters were determined for nerve protection during surgery: 1. Distance

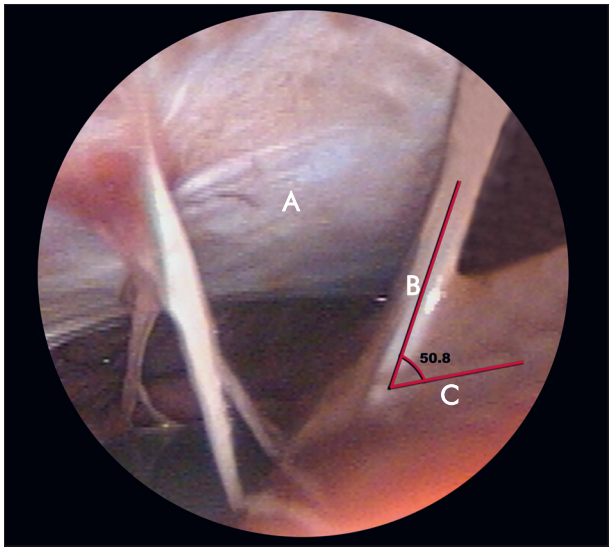


Figure 1. *The angle of exit of the 4th nerve from the brain stem (left side, infratentorial supracerebellar approach, 30° endoscopic view):* **A.** *tentorium,* **B**. *4th nerve,* **C.** *brain stem*

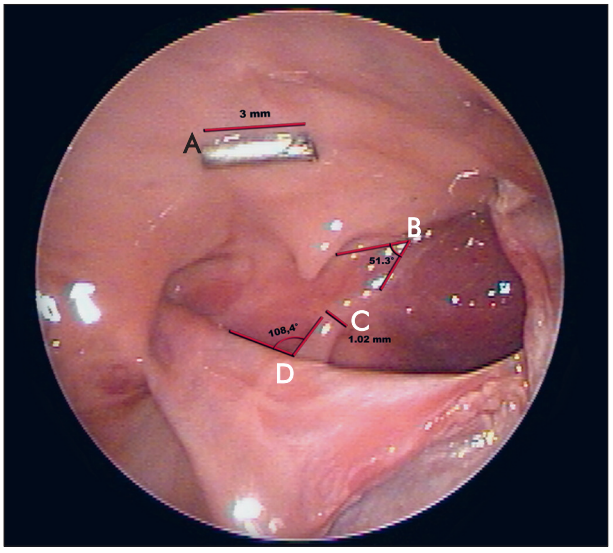


Figure 2. *The angle of exit of the 4th nerve from the brain stem, angle of participation in the tentorium and the thickness of the 4th nerve (left subtemporal approach, 0° endoscopic view):* **A**. *scale,* **B**. *angle of exit from the brain stem,* **C**. *the thickness of the nerve,* **D**. *participation angle in the tentorium*

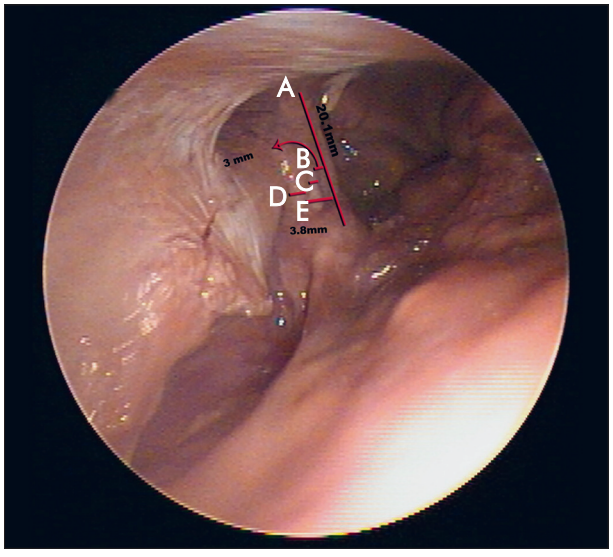


Figure 3. *The length of the 4th nerve in the cistern and its relationship with SCA, PCA (right subtemporal view with 45° endoscopic view):* **A.** *the length of the 4th nerve,* **B.** *the distance between the SCA and the 4th nerve,* **C.** *SCA,* **D**. *PCA,* **E.** *the distance between the 4th nerve and the PCA*

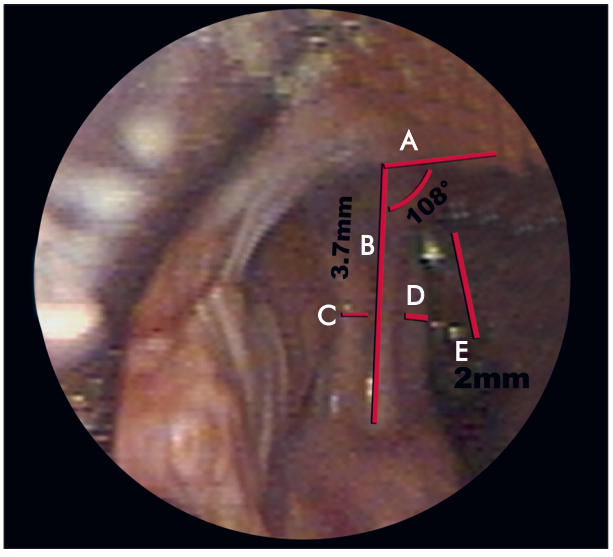


Figure 4. *The length of the 4th nerve in the cistern and the relationship of the SCA with the PCA and the angle of participation in the tentorium (right subtemporal view with 45° endoscopic view):* **A**. *the participation angle,* **B**. *the length of the 4th nerve,* **C**. *SCA,* **D**. *PCA,* **E**. *scale*

between the trochlear nerve and the superior cerebellar artery; 2. Distance between the trochlear nerve and the posterior cerebral artery; 3. Arising angle of the nerve from the brain stem; 4. Angle between the tentorium and the nerve; 5. Length of the nerve; 6. Diameter of the nerve; 7. Length of the nerve in ambient cistern. **Table 1** shows the results of the craniometric measurements.

The median infratentorial supracerebellar approach allowed exposure of the cisternal seg-

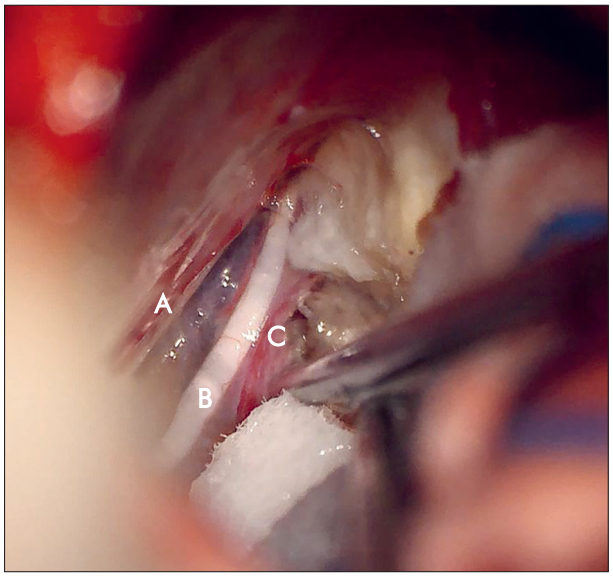


Figure 5. *Intraoperative relationship of the 4th nerve with cisternal PCA and SCA:* **A**. *SCA,* **B**. *4th nerve,* **C**. *PCA*

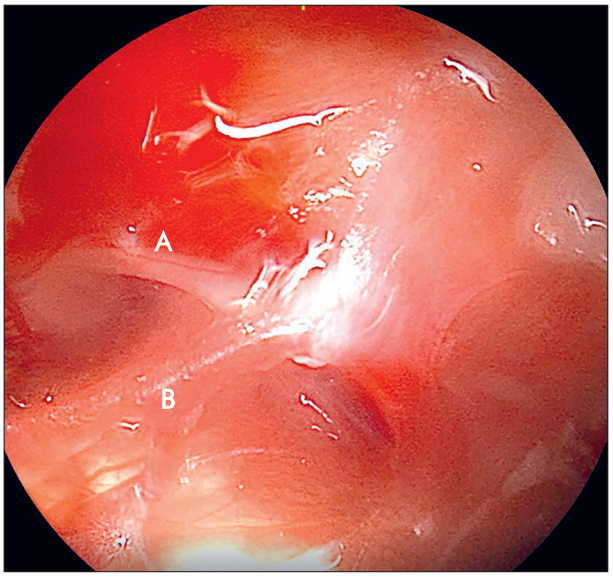


Figure 6. *Intraoperative endoscopic view of the relationship between the 4th nerve and the cisternal SCA:* **A**. *the 4th nerve,* **B**. *SCA*

ments (crural and ambient cisterns), including the origin of the nerve in the brain stem. The combined presigmoid-subtemporal transtentorial approaches provided visualization of the cisternal segment of the nerve and the free edge of the tentorium. In this study, the mean length and width of the trochlear nerve in the cisternal segment were 30.3 and 0.74 mm, respectively. The length of the trochlear nerve from its origin to its dural entrance was 37.2 mm, the tentorial dural entrance angle of the trochlear nerve and the exit angle of the trochlear nerve from the brain stem were 127.0 degrees and 54 degrees, respectively. The posterior cerebellar artery (PCA) to trochlear nerve distance in the mid ambient cistern and the superior cerebellar artery (SCA) to trochlear nerve distance in the mid ambient cistern were 5.8 mm and 3.7 mm, respectively **(Figures 1–4)**.

Discussion

The trochlear nerve has the longest course in the subarachnoid space, but it is also the thinnest cranial nerve[1, 7]. Its long intracranial course and thin structure make the nerve vulnerable to injury during surgery. The purpose of this cadaveric study was to have a safe access to the middle and posterior fossa regions with the help of craniometric and anatomical measurements.

The trochlear nerve usually arises as a single root from the inferolateral part of the inferior colliculus in the dorsal midbrain[2]. The trochlear nucleus is one of the smallest motor nuclei in the brain stem[8]. This nucleus is located near the midline at the level of the inferior colliculus and trochlear efferent fibers pass through the central gray matter posterolaterally, courses medially to reach the superior medullary velum, where they decussate[7, 9, 10].

The first part of the trochlear nerve is located laterally in the cerebellomesencephalic fissure. Then, the nerve crosses to the lateral side of the superior cerebellar peduncle. It courses along the quadrigeminal and ambient cisterns toward the tentorium on the upper side of the pons and joins the inferolateral side of the tentorium. In our study, the mean junction angle between the trochlear nerve and the tentorium was 127°.

Cisternal segment of the nerve can easily be seen when it courses in the subarachnoid space, but when it reaches the tentorial edge and turn downward, it becomes very difficult for surgeons to differentiate from the tentorium. After the posterior border of cerebral peduncle, the trochlear nerve joins the tentorium[7]. The conjoining angle is narrow and the nerve courses very close to the tentorium before the junction. Because of this, the tentorial incision must be planned very carefully and done before the posterior border of the cerebral peduncle. In this study, we intended to minimize the damage of the trochlear nerve by describing its conjoining angle to the tentorium. *Iaconetta* et al. divided the

Table 1. *Measurements of the determined parameters*

Anatomical landmark	Range	Mean	Median
SCA to trochlear nerve distance in the mid ambient cistern	2.7–6.1 mm	3.7 mm	3.25 mm
PCA to trochlear nerve distance in the mid ambient cistern	3.4–8.2 mm	5.8 mm	6.2 mm
Exit angle of the trochlear nerve from the brain stem	50.2–58.5 degree	54 degree	54 degree
Tentorial dural entrance angle of the trochlear nerve	99–154 degree	127.0 degree	128 degree
Origin of trochlear nerve to its dural entrance	32.2–42.6 mm	37.2 mm	36 mm
Lenght of trochlear nerve in the ambient cistern	19.4–41.8 mm	30.3 mm	30 mm
Thickness of trochlear nerve in the ambient cistern	0.44–1.03 mm	0.74 mm	0.75 mm

cisternal segment to quadrigeminal and ambient parts[11]. In the quadrigeminal cistern, the nerve courses along the lateral superior cerebellar peduncle in the subarachnoid space. It reaches the ambient cistern by piercing the cerebellar precentral membrane. In the ambient cistern, the trochlear nerve is adjacent to some important neurovascular structures like the SCA, PCA, and the basal vein of Rosenthal **(Figures 5, 6)**. It courses anteriorly and reaches its groove which is located on the inferior surface of the tentorium[12].

In our study, we found the mean distances between the SCA and the trochlear nerve (1st result) and the PCA and the trochlear nerve (2nd result) at the level of the ambient cistern (just before the posterior border of the cerebral peduncle) as 3.7 mm and 5.8 mm, respectively. The mean length of the trochlear nerve in the ambient cistern was 30.3 mm. The mean thickness of the trochlear nerve was 0.74 mm. The distal border of the cisternal segment was described as the point in tentorial groove before it became intradural[7, 9].

In previous studies, there was no mention of measurement of the arising angles of the nerves from the midbrain. All the angles were measured by using calipers, and it was calibrated in Surgimap software program. It was seen that all the nerves course asymmetrically. All of them were located inferior to the tentorial incisura and entered to the tentorium by rising in the cisterns. Courses of the nerves in the cisterns and craniometric relationships with adjacent neurovascular structures were determined. Since it is difficult to distinguish between the ambient and the crural cisterns anatomically, both were evaluated together under the name of ambient cistern in this study.

We believe that the information obtained from these measurements will be very helpful for the surgeons, especially in lateral infratentorial supracerebellar ipsilateral and contralateral approaches. In addition, the trochlear nerve–tentorium relationship will contribute to classical infratentorial supracerebellar and middle fossa approaches. The radiological imaging studies advancing and some high resolution sequences give adequate information about anatomical course of the trochlear nerve[13, 14]. But these sequences can be time consuming and not applicable to all cases[13, 14]. Although radiological assessments are very important in pre-operative evaluation, the cadaveric anatomical studies are very important in surgical aspect.

This study has some limitations. Endoscopic assistance helps us to reach and follow the nerves easily, but we cannot obtain 3D images. Microscopic studies can serve 3D images, but it is difficult to preserve anatomical structures under microscopic dissection. Although the use of fresh cadavers provided ease in terms of retraction, yet more satisfying images can be obtained by siliconized frozen cadavers.

Conclusion

In this study, we aimed to analyze the craniometric relationships between the trochlear nerve and the surrounding anatomical structures. Thus, we hope to improve the anatomical knowledge in the literature about the trochlear nerve and provide data to surgeons that help them navigate the trochlear nerve.

Accurate knowledge of the cisternal anatomy of the trochlear nerve and its relationship with the tentorium is important to prevent injury to the nerve during surgical procedures. With similar studies and continuous advances in the radiological techniques, we hope to discover more about the trochlear nerve.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

REFERENCES

1. *Villain M, Segnarbieux F, Bonnel F, Aubry I, Arnaud B*. The trochlear nerve: anatomy by microdissection. Surg Radiol Anat 1993;15(3):169-73. https://doi.org/10.1007/BF01627696
2. *Ammirati M, Musumeci A, Bernardo A, Bricolo A*. The microsurgical anatomy of the cisternal segment of the trochlear nerve, as seen through different neurosurgical operative windows. Acta Neurochir (Wien) 2002;144(12): 1323-7. https://doi.org/10.1007/s00701-002-1017-3
3. *Tubbs RS, Oakes WJ*. Relationships of the cisternal segment of the trochlear nerve. J Neurosurg 1998;89(6):1015-9. https://doi.org/10.3171/jns.1998.89.6.1015
4. *Bisaria KK*. Cavernous portion of the trochlear nerve with special reference to its site of entrance. J Anat 1988;159:29-35.
5. *Gupta T, Gupta SK, Sahni D*. Anatomy of the tentorial segment of the trochlear nerve in reference to its preservation during surgery for skull base lesions. Surg Radiol Anat 2014;36(10):967-71. https://doi.org/10.1007/s00276-014-1278-6
6. *Zhang Y, Liu H, Liu E-Z, Lin Y-Z, Zhao S-G, Jing G-H*. Microsurgical anatomy of the ocular motor nerves. Surg Radiol Anat 2010;32(7):623-8. https://doi.org/10.1007/s00276-009-0585-9
7. *Joo W, Rhoton AL*. Microsurgical anatomy of the trochlear nerve. Clin Anat 2015;28(7):857-64. https://doi.org/10.1002/ca.22602
8. *Yamaguchi K, Honma K*. Development of the human trochlear nucleus: a morphometric study. Ann Anat 2011;193 (2):106-11. https://doi.org/10.1016/j.aanat.2010.10.006
9. *Rhoton AL*. The posterior fossa cisterns. Neurosurgery 2000;47(3 Suppl):S287-297. https://doi.org/10.1097/00006123-200009001-00029
10. *Gray H, Williams PL, Gray H*. The mesencepahlon or midbrain. In: Gray's anatomy. 37th ed. 1989.
11. *Iaconetta G, de Notaris M, Benet A, et al.* The trochlear nerve: microanatomic and endoscopic study. Neurosurg Rev 2013;36(2):227-37; discussion 237-8. https://doi.org/10.1007/s10143-012-0426-x
12. *Herlan S, Hirt B, Tatagiba M, Ebner FH*. Focus on the lateral incisural space: Where is the trochlear nerve? J Neurol Surg B Skull Base 2013;74(5):271-3. https://doi.org/10.1055/s-0033-1347899
13. *Choi BS, Kim JH, Jung C, Hwang J-M*. High-resolution 3D MR imaging of the trochlear nerve. AJNR Am J Neuroradiol 2010;31(6):1076-9. https://doi.org/10.3174/ajnr.A1992
14. *Yousry I, Moriggl B, Dieterich M, Naidich TP, Schmid UD, Yousry TA*. MR anatomy of the proximal cisternal segment of the trochlear nerve: neurovascular relationships and landmarks. Radiology 2002;223(1):31-8. https://doi.org/10.1148/radiol.2231010612

NEONATAL BRACHIAL PLEXUS PALSY – EARLY DIAGNOSIS AND TREATMENT

Marianne BERÉNYI, Márta SZEREDAI, Ágnes CSEH

Department of Developmental Neurology, St. Margaret Hospital, Budapest

English | https://doi.org/10.18071/isz.75.0247 | www.elitmed.hu

Background and purpose – The incidence of brachial plexus palsy (BPP) has decreased recently, but the individual's quality of life is endangered. To provide better chances to BPP neonates and infants, the Department of Developmental Neurology worked out, introduced, and applied a complex early therapy, including nerve point stimulation.
Methods – After diagnosing the severity of BPP, early intensive and complex therapy should be started. Approximately after a week or ten days following birth, the slightest form (neurapraxia) normalizes without any intervention, and signs of recovery can be detected around this period. The therapy includes the unipolar nerve point electro-stimulation and the regular application of those elementary sensorimotor patterns, which activate both extremities simultaneously.
Results – With the guideline worked out and applied in the Department of Developmental Neurology, full recovery can be achieved in 50% of the patients, and even in the most severe cases (nerve root lesion), functional upper limb usage can be detected with typically developing body-scheme.
Conclusion – Immediately starting complex treatment based on early diagnosis alters the outcome of BPP, providing recovery in the majority of cases and enhancing the everyday arm function of those who only partially benefit from the early treatment.

Keywords: *brachial plexus palsy, early diagnosis, early complex treatment, functional electrotherapy through nerve points*

A SZÜLÉSI FELKARBÉNULÁS KORAI DIAGNÓZISA ÉS KEZELÉSE
Berényi M, MD, PhD, Szeredai M; Cseh Á
Ideggyogy Sz 2022;75(7–8):247–252.

Háttér és cél – A szülési plexus brachialis laesio gyakorisága az utóbbi években csökkenést mutat, a csökkenő szülésszámnak megfelelően. A szülési felkarbénulás – nem megfelelően kezelt – formában lényegesen rontja az egyén beilleszkedését, mindennapi életét és így életminőségét is. A szülési felkarbénult újszülöttek és csecsemők gyógyulásának elősegítése érdekében a Fejlődésneurológiai Osztály idegpont-stimulációt is magába foglaló, komplex kezelési módszert dolgozott ki.
Módszerek – A szülési felkarbénulás súlyosságának megállapítása után korai intenzív kezelést kell indítani. A legenyhébb forma (neurapraxia) a szülést követő 7–10 nap elteltével beavatkozás nélkül normalizálódik. Azokban az esetekben, amikor terápiára van szükség, többek között elektromos unipoláris idegpont-stimulációt alkalmazunk. A módszer magába foglalja az érintett idegek idegpont felőli rendszeres elektromos ingerlését, és azoknak a veleszületett, szenzomotoros elemi mozgásmintáknak a strukturált gyakorlását, melyek a két felső végtag szimmetrikus mozgását segítik elő.
Eredmények – A Fejlődésneurológiai Osztály által kidolgozott és rendszeresen alkalmazott komplex kezelési módszer az esetek közel felében teljes gyógyulást eredményez, és lényegesen javítja azok életkörülményeit is, akiknél csak részleges eredmények érhetőek el.
Következtetés – A korai diagnózison alapuló, azonnal megkezdett komplex terápia javítja a szülési plexus brachialis laesio kimenetelét, az esetek zömében teljes gyógyulást eredményezve, és a részleges gyógyulással járó esetekben is javítja a mindennapos karműködést.

Kulcsszavak: *szülési felkarbénulás, korai diagnózis, korai komplex kezelés, idegpont felőli funkcionális elektroterápia*

Correspondent: Prof. dr. BERÉNYI Marianne, Department of Developmental Neurology, St. Margaret Hospital; 1032 Budapest, Bécsi út 132. A épület, III. em.
T: +36-1-430-4800 #1198, fax: +36-1-430-4820, e-mail: berenyi@ella.hu
https://orcid.org/0000-0001-5307-3383

Érkezett: 2021. május 25. Elfogadva: 2021. augusztus 5.

The incidence of neonatal brachial plexus palsy (BPP) is 1,5/1000 (varies between 0,5-3/1000, according to published data)[1–3]. Full recovery is not uncommon with a rate between 7% to 97%, but severe, life-long mobility impairment can also be observed in 15% to 25% of the cases[4–6]. What can be done to prevent the limitation of shoulder mobility, the appearance of contractures, the deficit of manipulation skills or impairment of the body scheme? Can we avoid the development of length differences between the upper limbs, joint deformities, problems of bone mineralization, or abnormal body image[5–9]? More than 40 years of experience in the Department of Developmental Neurology (St. Margaret Hospital, Budapest) shows that early, complex therapy with the active contribution of parents can lead to good functional results[10–13].

Patients and methods

This retrospective research examines a population of patients admitted to and examined at the Department of Developmental Neurology between November of 2007 and November of 2017. The patient population received regular treatment and/or follow-up until 1.5 to 2 years of age. The current results were compared to previous research conducted by the same Department, published in 1993. The population of the current research consists of 111 infants with BPP symptoms out of the 3969 admitted during this period to the ward. This research focuses basically on the effectiveness of early electric stimulation. There is a significant relationship between the duration of the electric treatment and how the affected arm recovered. Infants that received more electric treatment were more likely to have better motor functions in their affected arm, X^2 (6, N = 103) = 30,232, $p < 0.01$.

This study's gender distribution is similar to other published data, i.e., no gender preference is shown. 55 female and 56 male infants with BPP symptoms were examined. In 76 cases, the right side was affected, while it was the left side for 35 infants. This distribution is also similar in the literature[14].

Narakas classification of obstetric BPP was used to assess the severity of upper-arm palsy **(Table 1)**. Distribution is the following: Type I - upper Erb-Duchenne's: 37 cases; Type II. extended Erb-Duchenne's - 32 cases; Type III - total palsy: 36 cases; Type IV. - total palsy with Horner's syndrome: 4 cases. Klumpke-Dejerine palsy (which does not appear in the Narakas classification) was observed in 2 cases[15, 16]. A chi-square test of independence showed that infants with a more severe noxa had worse motor functions at the time of their last check-up in their affected arm, X^2 (6, N = 103) = 61,623, $p < 0.01$. A chi-square test between Naracas groups and the motor functions of the affected arm at the time of the last check-up showed similar results, X^2 (8, N = 103) = 51,917, $p < 0.01$.

BPP usually affects term neonates with high birth weight[3, 5, 6, 17–19]. In the examined population, only eight infants were born before the 38th week of gestation, 89 infants were born between the 38th and 40th week, and 14 during the 41st and 42nd week. Sixteen infants had a birth weight under 3500 g, 31 between 3500 - 3999 g, 46 had 4000 - 4500 g, and 18 had over 4501 g. There is no significant association between birth weight and either the severity of the noxa [X^2 (9, N = 103) = 11,253, p=0,259)] or the Naracas group [X2 (12, N = 103) = 15,608, p =0,21)].

The average birth weight was 4042 g. The parity status in the examined cases was the following: 48 primipara, 59 multipara, and in 4 cases there were no data available. Mode of delivery: 109 cases vaginal delivery (PVN) 106 were in vertex, and 3 in breech presentation. Vacuum extraction was used in 19 cases, while obstetrical forceps were used only in 1 case. Two infants were born via caesarian section. In addition to the BPP, ipsilateral fracture of the clavicle was identified in 17 cases, and the

Table 1. *Distribution according to Naracas classification*

	Group	Nerve Roots	Deficit	N=111
1	Erb-Duchenne palsy	C5, C6	Disfunction of the deltoid and brachial biceps muscle	37
2	Extended Erb-Duchenne palsy	C5, C6, C7	Paralysis of shoulder, biceps, and wrist/extension of the fingers, carrying the worse prognosis	32
3	Total palsy without Horner's syndrome	C5, C6, C7, C8, T1	Total plexopathy with flail extremity involving all plexus roots	36
4	Total palsy with Horner's syndrome	C5, C6, C7, C8, T1	Flail extremity with Horner's syndrome indicating sympathetic chain involvement and avulsion injury	4

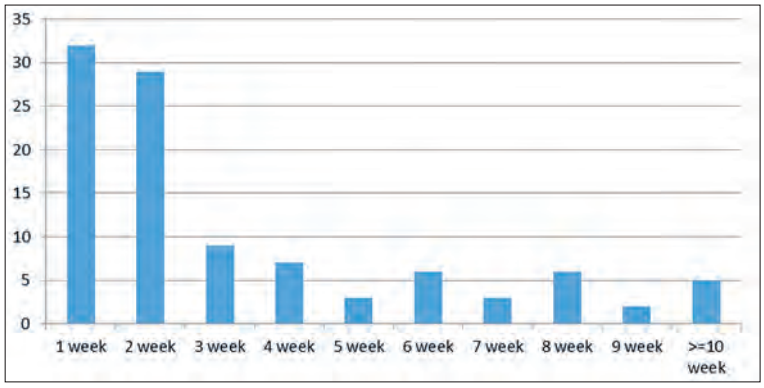


Figure 1. *Patients' age at initiation of treatment*

sternocleidomastoid muscles (SCOM) were affected in 4 infants. Shoulder dystocia appeared in 20 case histories. Stained amniotic fluid with meconium, indicating a prolonged delivery, was detected in 23 cases. Apgar score at one minute was lower than 7 (<7) in 49 infants. In 61 cases, complex resuscitation was needed. Among them, 10 had an Apgar score at 5 minutes lower than 6 (<6). Hypothermia was applied to 5 infants due to severe asphyxia.

Aside from identifying the presence of the peripheral lesion, it is also crucial to confirm or rule out other central nervous system (CNS) disorders. In this examination, two infants were diagnosed with CNS disorders. In these cases, complex, early, and intensive neurotherapy combined with the treatment of peripheral lesion resulted in complete recovery from both the central and peripheral symptoms. Out of the 111 examined infants, 102 received therapy. **Figure 1** shows the patients' age at the start of therapy. A chi-square test of independence showed a significant association between how early the infant received a diagnosis and how much the affected arm recovered, X^2 (2, N = 103) = 6,672, p=0,036. Those infants who received diagnosis and treatment during the first two weeks of life, had better motor functions in their affected arm at their last check-up.

The examination protocol includes evaluating the severity of the injury, the range of joint movements, and the muscle strength of the affected upper limb. Additional electro-diagnostic examinations were also conducted to evaluate the rheobase of the injured nerve. The parameters for electrotherapy can be determined after impulse diagnostics. The physiologic rheobase is 4 mA (i.e., the lowest stimulus that elicits movements), in those cases where the electro-diagnostics showed value at or under 4 mA electrotherapy was not part of the complex treatment.

The special electrotherapy used in this study is the unipolar stimulation of nerve points with pulse trains, with exponentially increasing rise time, where the individual rectangular impulse width is 2 msec., with a frequency of 90-100 Hz. Intensity varies between 5 – 20 mAs, rise time, train length, and interval can be changed according to needs (usually the rise time is 1 or 1.5 sec, the train width is approximately 3 sec, and the interval is 3 sec.). Stimulation points are found where the peripheral nerves are closest to the surface, in the axillar fossa (n. musculocutaneous, n. radialis, n. medianus, n. ulnaris) in the cubital fossa (n. radialis, n. medianus, n ulnaris), and at the lower third of the forearm ventrally (n. medianus, n. ulnaris) and dorsally (n. radialis) **(Figure 2.A, B)**.

EARLY COMPLEX THERAPY

The complex treatment of the patients consists of daily functional electrotherapy[11–13, 16, 20–25], the regular exercise elements of neurotherapy[10–13], the classic physical therapy of joints, and occasionally the application of a night-time, correctional splint, or the use of the tape-technic.

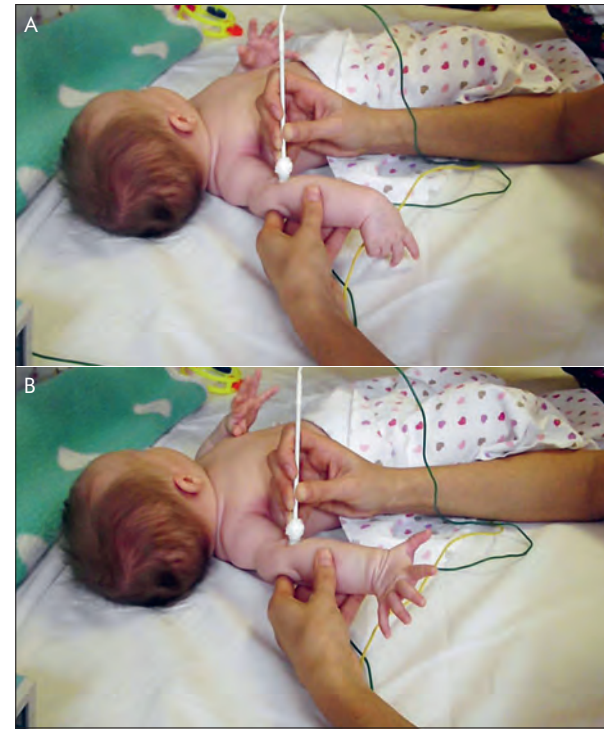


Figure 2.A, B *Nerve point stimulation in cubital fossa produces dorsiflexion of wrist together with finger extension*

Table 2. *Distribution according to Seddon classification*

Severity	Classification	N=111
1	Neurapraxia	34
2	Axonotmesis	66
3	Neurotmesis	11

Electrotherapy was applied in 82 out of 111 infants. It was performed twice a day during their stay in the ward and 3-5 times a week after emission on an outpatient basis. During their initial stay, this meant 27 occasions on average. The severity of the injury determines the number of necessary treatments; to achieve good results, the time needed is approximately six months with more or less 63 electric treatments. The shortest therapy lasted two months, the longest 24 months. The Seddon classification (Grade I., II., and III.) of nerve injuries shows the necessity of electrotherapy, predicting the duration. In neurapraxia, there is usually no need for electrotherapy, while axonotmesis requires prolonged therapy. Neurotmesis is the most severe condition and requires the most extended treatment.

Results

Out of the 111 patients, 34 were mildly affected (Grade I., neurapraxia), and only 6 of them required short treatment. All 66 infants with Grade II., i.e., moderate severity (axonotmesis) received electrotherapy during their hospital stay, and for 54 of them, the treatment continued after leaving the hospital. Eleven cases were severely affected (Grade III., neurotmesis), and surgery was necessary **(Table 2)**. Surgery was performed after three months of regular electrotherapy, and after the operation, the complex therapy continued for 10 out of 11 patients until the age of 1 to 2.

Out of the 34 cases, there were 29 infants with neurapraxia, and certain items of neurotherapy were applied six times a day by the parents who had been previously taught how to perform the techniques, which the professionals regularly checked. Follow-up took place every month to re-examine and evaluate the infant's current neurological state and supplement the therapy with new elements if necessary. The follow-up ended when the ability of independent, safe walking developed for each child who had received neurotherapy and/or electrotherapy or had undergone surgery.

Results of 70 infants until the ability of safe walking developed were analyzed. Nearly half (48.5%) of those who received treatment wholly recovered, 46% showed significant improvement, and in 5.5% of them, moderate improvement was observed **(Figure 3)**.

For the 60 infants who did not have surgery, no deviation was found in representing the body scheme, manipulation skills, and the movement range used in everyday life due to early, intense and complex therapy. The entire movement range of the joints and muscle strength was observed in 34 of them. In 26 infants, there was a 5-10 degree difference in the movement range of the shoulder joint in complete flexion or extension. Occasionally, flexion contracture can be observed, which prevents the elbow from straightening or extending fully, but the difference is so tiny that it does not hinder the individual's everyday functioning. The ten infants who underwent surgery, followed by the continuation of complex therapy and electrotherapy, showed clear signs of improvement **(Figure 4.A, B)**. Active usage of the affected limb was observed for 6 of them, with little muscle strength and movement range differences. An additional four infants were able to use the affected limb as a supporting arm. In every case where early therapy with no complete recovery was achieved, a recommendation was given to additional physical therapy to improve and retain the affected functions. During the outpatient treatment period of 111 BPP patients, the regular follow-up process was discontinued after 1-2 weeks or 2-3 months in 40 of these cases due to lack of parental compliance (in one patient, this happened

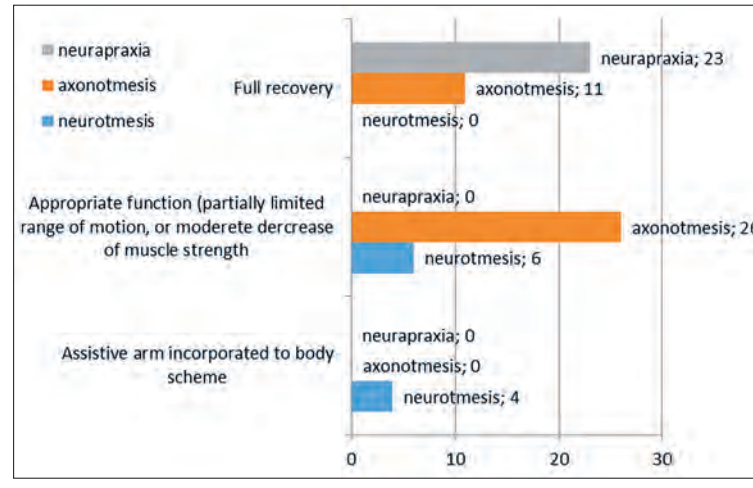


Figure 3. *Results according to severity*

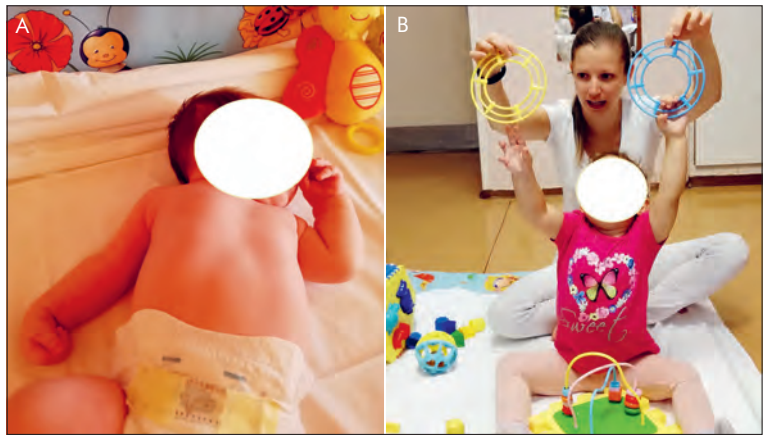


Figure 4.A, B *Patient went twice through surgery (Oberlin palstica) because of C5-6 avulsion and C7 strain, together with destructing rupture of scalenic muscles, received intensive complex therapy (electrotherapy was performed 179 (!) occasions), her upper extremitiy movements at initial phase and at completion of treatment.*

after discharging from the ward with a recommendation for surgery.)

Patients (with BPP and no CNS lesion) receiving and completed intensive neurotherapy to eliminate or decrease consequences of the peripheral palsy achieved sensorimotor milestones much earlier than their healthy peers. The use of training with regular therapy is therefore essential to consolidate and progress motor development. Turning and rolling over regularly from the prone or supine position in both sides appeared around five months, rhythmical crawling developed around eight months, and independent, stable walking around 12 months.

Comparing our results to our previous publication of cases from 1978 to 1993 (n=506), it is apparent that the incidence rate decreased to 1/3 since then. The decreasing incidence is probably the result of better obstetric care and the routine application of obstetric ultrasonography, but the decrease of the number of births is also an important factor. A striking difference compared to the early '90s is the availability of surgical care. Patients who had undergone surgery and received intense, complex therapy can use the affected limb adequately with minimal restriction and muscle strength reduction or use the limb as a supporting arm[7, 11, 26–30].

Summary

The incidence rate of brachial plexus palsy has decreased during recent years in Hungary, but the affected infants who do not receive early complex therapy still have a low chance of recovery. Delay or inadequate treatment can permanently influence the quality of life, worsen human-specific upper limb functions and deteriorate the development of body scheme.

This retrospective research examined patients admitted and examined at the Department of Developmental Neurology between November of 2007 and November of 2017. In 50% of the cases when complex intensive therapy initiated at 7 to 10 days after birth, it could produce complete recovery, and in 45% adequate functioning. The remaining 5% who suffered the most severe injury could integrate the affected upper limb into their body scheme, enabling the limb to function as an "assistive arm". The early, complex therapy consists of the regular, daily practice of elementary sensorimotor patterns. In addition to the regular application of congenital, elementary sensorimotor patterns, regular electrotherapy of the affected nerves is a crucial part of the complex treatment. It has to be emphasized that functional electric stimulation of the affected muscle or the application of TENS (transcutaneous electrical stimulation to reduce muscle pain) is not a sufficient treatment. Classic physiotherapy can be used as supplemental therapy (passive movement, stretching, tape, correctional splints). When surgery is needed due to the severity of the lesion, the best arm functions can only be achieved by complex therapy before and after nerve reconstruction surgery.

ACKNOWLEDGEMENT

Physiotherapists who are or were working at the Dept. of Developmental Neurology between 2007–2017 (in alphabetic order). Bajusz Szilvia, Bodnár Andrea, Csepeli Bernadett, Fülöp Petra, Gurbi Judit, Gyopár Dóra, Istvánffy Lea, Kara Enikő, Lőke Katalin, Papcsik Györgyi, Szalai Mária, Thomann Dóra, Tóth Réka, Tóth Zsuzsa, Med. Habil Dr. Sándor Pintér, PhD at Szeged University, performed the surgery.

Special thanks to Gergő Kober for the statistical analysis.

TUKEB (Medical Research Council): 23425-2/2019/EKU.

REFERENCES

1. *Fejes M, Koncz J, Szabó E, Székhelyi Zs, Váradi K*. Plexus Brachialis laesiok epidemiológiai adatai 2004-2008 között. Gyermekgyógyászat 2011;62:65-70.
2. *DeFrancesco CJ, Shah DK, Rogers BH, Shah AS*. The epidemiology of brachial plexus birth palsy in the United States: Declining incidence and evolving risk factors. J Pediatr Orthop 2019;39:e134-e140. https://doi.org/10.1097/BPO.0000000000001089
3. *Abzug JM, Mehlman CT, Ying J*. Assessment of current epidemiology and risk factors surrounding brachial plexus birth palsy. J Hand Surg Am 2018;25:PII:S0363-5023(17):31908-1. https://doi.org/10.1542/peds.141.1_MeetingAbstract.661
4. *Bains R, Kattan A, Curtis CG, Stephens D, Borschel G, Clarke HM*. Active Range of Motion Over Time in Patients With Obstetrical Brachial Plexus Palsy: A 10-Year Analysis. J Hand Surg Am 2018;43:386.e1-386.e7. https://doi.org/10.1016/j.jhsa.2017.10.024
5. *Heise CO, Martins R, Siqueira M*. Neonatal brachial plexus palsy: permanent challenge Arq Neuropsiquatr 2015;73: 803-8. https://doi.org/10.1590/0004-282X20150105
6. *Evans-Jones G, Kay SP, Weindling AM, Cranny G, Ward A, Bradshaw A, et al.* Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and the Republic of Ireland. Arch Dis Child Fetal Neonatal Ed 2003;88:f185-9. https://doi.org/10.1136/fn.88.3.F185
7. *Pintér S.* Plexus brachialis sérülés utáni vállövi mozgászavarok és ellátásuk. Fizioterápia 2014;23:3-6.
8. *Bertelli JA, Ghizoni MF, Soldado F.* Patterns of brachial plexus stretch palsy in a prospective series of 565 surgically treated patients. J Hand Surg Am 2017;42:443-46.e2. https://doi.org/10.1016/j.jhsa.2017.03.021
9. *Srtömbeck C, Remahl S, Krumlinde-Sundholm L, Sejersen T.* Long-term of children with obstetric brachial plexus palsy: functional aspects. Developmental Child Neurology 2007;49:198-203. https://doi.org/10.1111/j.1469-8749.2007.00198.x
10. *Vargyay É, Juhász J.* Neurohabilitációs training szerepe szülés plexus cervicobrachiális sérülés eseteiben. Pediáter 1994;3:46-48.
11. *Salman Ibrahim A, Fehér A, Katona F.* Hogyan befolyásolja az új, korai komplex kezelés a plexus brachialis sérülés rehabilitációját? Rehabilitáció 1993;3:118-122
12. *Berényi M, Katona F.* Fejlődésneurológia. Medicina Kiadó; Budapest: 2012. pp. 416-23.
13. *Berényi M.* A fejlődésneurológia módszere, a neuroterápia - II.rész. Gyermekgyógyászati Továbbképző Szemle 2016;21:94-97.
14. *Abazi N, Murtezani A, Ibraimi Z, et al.* Epidemiology of brachial plexus palsy in newborns. Pediatrics Today 2014; 10:129-34. https://doi.org/10.5457/p2005-114.98
15. *Al-Quattan MM.* Obstetric brachial plexus injuries. J Hand Surgery 2003;3:41-54. https://doi.org/10.1053/jssh.2003.50008
16. *El-Sayed AA*. Intermediate Type of Obstetric Brachial Plexus Palsy. J Child Neurol 2016;31:1628-30. https://doi.org/10.1177/0883073816669462
17. *Gilbert WM, Nesbitt TS, Danielsen B.* Associated factors in 1611 cases of brachial plexus injury. Obstet Gynecol 1999; 93:536-40. https://doi.org/10.1097/00006250-199904000-00013
18. *Wolf H, Hoeksma A.F, Oei S.L, Bleker OP.* Obstetric brachial plexus injury: risk factors related to recovery. Eur J Obstet Gynecol Reprod Biol. 2000;88:133-8. https://doi.org/10.1016/S0301-2115(99)00132-3
19. *Mollberg M, Hagberg H, Bager B, Lilja H, Ladfors L.* High birthweight and shoulder dystocia: the strongest risk factors for obstetrical brachial plexus palsy in a Swedish population-based study. Acta Obstet Gynecol Scand 2005;84: 654-9. https://doi.org/10.1111/j.0001-6349.2005.00632.x
20. *Sentilhes L, Sénat MV, Boulogne AI, Deneux-Tharaux C, Fuchs F, Legendre G, et al.* Shoulder dystocia: guidelines for clinical practice from the French College of Gynecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol 2016;203:156-61. https://doi.org/10.1016/j.ejogrb.2016.05.047
21. *Zaami S, Busardò FP, Signore F, Felici N, Briganti V, et al.* Obstetric brachial plexus palsy: a population-based retrospective case-control study and medicolegal considerations. J Matern Fetal Neonatal Med 2018;31:1412-7. https://doi.org/10.1080/14767058.2017.1317737
22. *Okafor UA, Akinbo SR, Sokunbi OG, Okanlawon AO, Noronha CC.* Comparison of electrical stimulation and conventional physiotherapy in functional rehabilitation in Erb's palsy. Nig Q J Hosp Med 2008;18:202-5. https://doi.org/10.4314/nqjhm.v18i4.45029
23. *Rák-Bodnár A, Berényi M.* Új ingerpont alkalmazása a szülési felkar bénulás elektroterápiás kezelésében. Fizioterápia 2014;4:12-5.
24. *Elnaggar RK.* Shoulder function and bone mineralization in children with obstetric brachial plexus injury after neuromuscular electrical stimulation during weight-bearing exercises. Am J Phys Med Rehabil 2016;95:239-47. https://doi.org/10.1097/PHM.0000000000000449
25. *Rakos M, Freudenschuss B, Girsch W, Hofer C, Kaus J, Meiners T, et al.* Electromyogram-controlled functional electrical stimulation for treatment of the paralyzed upper extremity. Artif Organs 1999;23:466-9. https://doi.org/10.1046/j.1525-1594.1999.06363.x
26. Physical Therapist's Guide to Infant Brachial Plexus Injury (Erb's Palsy, Klumpke's Palsy) APTA irányelv.
27. Understanding plexus brachial palsy Department of physiotherapy, occupational therapy, and plastic surgery Royal Children's Hospital Melbourne 2004.
28. *Grossman JAI, Alfonso I, et al.* Surgical Management of Brachial Plexus Injuries 2000, 7:1-64 https://doi.org/10.1016/S1071-9091(00)80008-X
29. *Davidge KM, Clarke HM, Borschel GH.* Nerve Transfers in Birth elated Brachial Plexus Injuries: Where Do We Stand? Hand Clin 2016;32:175-90. https://doi.org/10.1016/j.hcl.2015.12.006
30. Az Emberi Erőforrás Minisztériuma egészségügyi szakmai irányelve 002136 Egészségügyi Közlöny 2021, 71: 2122-2177

A CROSS-SECTIONAL STUDY ON THE QUALITY OF LIFE IN MIGRAINE AND MEDICATION OVERUSE HEADACHE IN A HUNGARIAN SAMPLE: UNDERSTANDING THE EFFECT OF HEADACHE CHARACTERISTICS

Máté MAGYAR[1, 2, 3], Gyöngyi KÖKÖNYEI[1, 4, 5], Dániel BAKSA[1, 5], Attila GALAMBOS[1, 4, 6], Andrea Edit ÉDES[1], Edina SZABÓ[1, 4, 7], Natália KOCSEL[1, 4], Kinga GECSE[1, 5], Dóra DOBOS[1, 5], Tamás GYÜRE[3], Gabriella JUHÁSZ[1, 5, 8, *], Csaba ERTSEY[2, *]

[1]SE-NAP 2 Genetic Brain Imaging Migraine Research Group, Semmelweis University, Budapest, Hungary
[2]Department of Neurology, Faculty of Medicine, Semmelweis University, Budapest, Hungary
[3]János Szentágothai Doctoral School of Neurosciences
[4]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary
[5]Department of Pharmacodynamics, Faculty of Pharmaceutical Sciences, Semmelweis University, Budapest, Hungary
[6]Doctoral School of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary
[7]Center for Pain and the Brain (PAIN Research Group), Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[8]MTA-SE, Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary
*Gabriella Juhász and Csaba Ertsey equally contributed to this article.

English | https://doi.org/10.18071/isz.75.0253 | www.elitmed.hu

A MIGRÉN ÉS A FÁJDALOMCSILLAPÍTÓ-TÚLFOGYASZTÁSHOZ TÁRSULÓ FEJFÁJÁS, VALAMINT A FEJFÁJÁS-KARAKTERISZTIKA ÉLETMINŐSÉGRE GYAKOROLT HATÁSA MAGYARORSZÁGI BETEGMINTÁN VÉGZETT KERESZTMETSZETI VIZSGÁLAT ALAPJÁN

Magyar M, MD; Kökönyei Gy, PhD; Baksa D; Galambos A; Édes AE; Szabó E, MD; Kocsel N; Gecse K; Dobos D; Gyüre T; Juhász G, PhD, DSc; Ertsey Cs, PhD

Ideggyogy Sz 2022;75(7–8):253–263.

Background and purpose – Previous studies using generic and disease specific instruments showed that both migraine and medication overuse headache are associated with lower health-related quality of life (HRQoL). The aim of our study was to assess HRQoL differences in migraineurs and in patients with MOH and to examine how headache characteristics such as years with headache, aura symptoms, triptan use, headache pain severity and headache frequency are related to HRQoL.
Methods – In this cross-sectional study 334 participants were examined (248 were recruited from a tertiary

Háttér és célkitűzés – Általános és betegségspecifikus életminőség-kérdőívet használó vizsgálatok eredményei alapján mind migrénben, mind fájdalomcsillapító-túlfogyasztáshoz társuló fejfájásban (FTTF) szenvedő betegek esetében alacsonyabb életminőség-értékeket mértek a kontrollrésztvevőkhöz hasonlítva. Vizsgálatunk célja egyrészt a migrénben és FTTF-ben szenvedő betegek életminőségének, valamint a fejfájás-karakterisztika (fejfájós évek száma, auratünetek, triptánhasználat, fejfájássúlyosság és fejfájás-gyakoriság) életminőségre gyakorolt hatásának vizsgálata volt.

Correspondent: Dr. Máté MAGYAR, Semmelweis University, Faculty of Medicine, Medical Imaging Centre, Department of Neuroradiology; 1086 Budapest, Balassa u. 6.
Phone: +36-20/666-3274, e-mail: magyar.mate@med.semmelweis-univ.hu
https://orcid.org/0000-0003-2589-9617

Érkezett: 2022. május 6. Elfogadva: 2022. június 26.

headache centre and 86 via advertisements). The Comprehensive Headache-related Quality of life Questionnaire (CHQQ) was used to measure the participants' HRQoL. Data showed normal distribution, therefore beside Chi-squared test parametric tests (e.g. independent samples t-test) were used with a two-tailed $p<0.05$ threshold. Linear regression models were used to determine the independent effects of sex, age, recruitment method, headache type (migraine vs. MOH) and headache characteristics (presence of aura symptoms, years with headache, headache pain severity, headache frequency and triptan use) separately for each domain and for the total score of CHQQ. Significance threshold was adopted to $p \leq 0.0125$ (0.05/4) to correct for multiple testing and avoid Type I error.
Results – Independent samples t-tests showed that patients with MOH had significantly lower scores on all CHQQ domains than migraineurs, except on the social subscale. Results of a series of regression analyses showed that triptan use was inversely related to all the domains of HRQoL after correction for multiple testing ($p<0.0125$). In addition, headache pain severity was associated with lower physical ($p=0.001$) and total scores ($p=0.002$) on CHQQ subscales.
Conclusion – Based on the results, different headache characteristics (but not the headache type, namely migraine or MOH) were associated with lower levels of HRQoL in patients with headache. Determining which factors play significant role in the deterioration of HRQoL is important to adequately manage different patient populations and to guide public health policies regarding health service utilization and health-care costs.

Keywords: *headache characteristics, health-related quality of life, medication overuse headache, migraine, triptan use*

Módszerek – Keresztmetszeti vizsgálatunkban 334 beteg vett részt (248 beteg fejfájás-ambulanciánkról, valamint 86 beteg hirdetés útján). A résztvevők életminőségének értékeléséhez az Átfogó Fejfájással Kapcsolatos Életminőség kérdőívet (CHQQ) használtuk. Adataink normáleloszlást mutattak, így χ^2-próba mellett parametrikus teszteket alkalmaztunk (például független mintás t-próba), a szignifikanciaszintet $p < 0,05$-ban határoztuk meg. A nem, életkor, beválogatási kritériumok, fejfájástípus, valamint fejfájás-karakterisztika (auratünetek megléte, fejfájós évek száma, fejfájás súlyossága, fejfájás gyakorisága, triptánhasználat) életminőségre gyakorolt hatásának vizsgálatához lineáris regressziós modelleket használtunk mind a három CHQQ-alskála és az összpontszám tekintetében is. Az utóbbi esetében az I. típusú hiba elkerülésének érdekében a szignifikanciaszintet $p \leq 0,0125$ (0,05/4) értékben határoztuk meg.
Eredmények – A fejfájástípust önmagában vizsgálva az FTTF-ben szenvedő betegek a szociális alskála kivételével szignifikánsan alacsonyabb CHQQ-értékeket értek el, mint a migrénes betegek. A többi változó bevonásával elvégzett regressziós elemzések alapján a triptánhasználat mutatott fordított összefüggést az összes CHQQ-alskála-értékkel ($p < 0,0125$). A vizsgált fejfájás-karakterisztikák közül a fejfájás súlyossága mutatott szignifikáns kapcsolatot az alacsonyabb fizikaialskála-értékekkel ($p = 0,001$), valamint az alacsonyabb CHQQ-összpontszámmal ($p = 0,002$).
Következtetés – Eredményeink azt mutatják, hogy a fejfájás-karakterisztika (és nem a fejfájás típusa önmagában) összefüggést mutat a fejfájós betegek alacsonyabb életminőségével. Az életminőség-változást előidéző faktorok meghatározása fontos a különböző betegpopulációk adekvát kezelésének, valamint az egészségügyi szolgáltatások igénybevételével és az egészségügyi költségekkel kapcsolatos népegészségügyi intézkedéseknek a megtervezése érdekében.

Kulcsszavak: *egészséggel összefüggő életminőség, fájdalomcsillapító-túlfogyasztáshoz társuló fejfájás, fejfájás-karakterisztika, migrén, triptánhasználat*

Objective and subjective indicators are available to study the impact of headache disorders. Assessing the quality of life (QoL), as a subjective indicator, is an established tool for measuring the burden of headache from a patient's perspective. For instance, generic QoL instruments, such as Medical Outcome Survey 36-item Short-Form Health Survey (SF-36)[1], and disease-specific ones, such as the Migraine-specific Quality of Life Questionnaire (MSQ2.1)[2] were successfully used in headache trials. It has been demonstrated that migraineurs report lower health-related quality of life (HRQoL), measured by SF-36[3, 4] and Short Form (SF)-12[5], compared to the general non-migraineur population. Similarly, patients with medication overuse headache (MOH) have shown decreased scores in all health-related domains of SF-36 compared to healthy individuals, with the highest differences for bodily pain and physical activity[6]. In addition, significantly impaired QoL was found in patients with MOH in the fields of role–physical functioning (problems with work or other daily activities as a result of physical health), bodily pain (interference of normal activities because of pain), general health (personal evaluation of health including current health, health out-

look, and resistance of illness), and social functioning (impact of physical health or emotional problems on social activities) compared to patients with episodic migraine, but there was no significant difference between chronic migraine and MOH groups in QoL measured by SF-36[7]. In a previous study analgesic overuse caused significantly lower values on the physical functioning and bodily pain subscales of SF-36 in a mixed group of chronic migraine, chronic tension-type headache, and new daily persistent headache patients[8]. It is possible that headache sufferers with the highest functional impact are those who tend to automedicate[8] which could explain the impairment of QoL in patients with analgesic overuse. Alternatively, analgesic overuse may worsen primary headaches and thereby explaining the decrease in QoL[8].

However, only a small number of studies have investigated the association between HRQoL and headache characteristics. These studies reported that increased migraine severity (indexed by the combination of migraine frequency and pain intensity)[3], lower patient age[9], longer disease duration[9], higher headache frequency[9, 10] and female gender[11] were related to decreased HRQoL in migraineurs. Thus, it would be important to further investigate which aspect of headache characteristics, such as the above mentioned headache frequency and severity, extended by the presence of aura symptoms, years with headache, or painkiller, especially triptan use, have significant effect on HRQoL in migraine and MOH. Regarding migraine aura symptoms, we did not find any studies investigating the association of migraine aura and HRQoL – which is surprising as patients usually indicate that the aura symptoms cause significant distress in daily functioning[12]. In a real-world analysis, patients with insufficient response to triptans reported significantly greater HRQoL burden, with lower MSQ scores (after controlling for age, sex, migraine frequency, comorbidities, duration of illness, preventive medication use and presence of aura) than triptan responders (pain freedom within 2 h in 4/5 attacks)[13], but more studies are needed to understand the association between triptan use and QoL in migraineurs or in patients with MOH.

Regarding the instruments measuring QoL in patients with headache, most of them were specifically developed for migraineurs, thus leaving patients with other headache types without a suitable tool. This limitation was addressed by the development of the Comprehensive Headache-related Quality of life Questionnaire (CHQQ) which is intended for use in all headache types[14]. The CHQQ is a validated tool in Hungarian[14] and Serbian[15] patients and is being validated in ongoing studies among English patients with episodic and chronic migraine and tension-type headache. In addition, in a pilot study, significant improvements were detected in QoL after successful treatment of MOH, which indicates that CHQQ may be an adequate tool for assessing QoL in headache treatment trials[16]. It should be also noted that the headache-specific CHQQ better reflected the decrease of QoL than the generic SF-36 instrument in patients with cluster headache during the active phase[17].

Therefore, in the present study our aim was to use CHQQ in patients with migraine and in patients with MOH to examine the relationship between inter-individual differences in headache characteristics and HRQoL. We hypothesized that poorer HRQoL would be related to the headache type (migraine or MOH), the presence of aura symptoms, years with headache, headache pain severity, headache frequency, and triptan usage.

Material and methods

SUBJECTS

The present study was part of a research program conducted in the Headache Center of the Semmelweis University. The participants were recruited between 2015 and 2019 from the headache clinic and by advertisements (university advertisements, and newspapers). In the headache clinic population (later referred to as *clinical group*) no exclusion criteria were applied. In the population recruited through advertisement (later referred to as *research group*) exclusion criteria were the following: current or past history of serious medical, major psychiatric or neurologic disorders, use of daily medication (except contraceptives and acute headache medication in MOH patients), and the use of preventive headache medications. In both subgroups, episodic migraine and MOH patients were diagnosed by neurologists. Migraine and MOH patients were eligible if they fulfilled the diagnostic criteria of ICHD-3[18] of migraine and MOH, with or without aura symptoms in both groups. Altogether 334 subjects were recruited and completed all study assessments (in the clinical group, migraine: 198, MOH: 50; in the research group, migraine: 71, research MOH: 15). Among patients with MOH 34 patients had migraine, 9 patients had tension-type headache and 22 patients had mixed (migraine and tension-type) headache before the development of MOH. The demographic characteristics of the investigated populations are

displayed in **Table 1**. The study was approved by the local ethics committees (ethical permission numbers: 23421/2015/EKU, 014946/2016/OTIG, OGYÉI/49553/2017, 204/2011) and the ethics committee of Semmelweis University, and was carried out in accordance with the Declaration of Helsinki.

QUESTIONNAIRES

Demographic data (e.g., sex, age), and the following headache-related variables were collected during the clinical assessment: years with headache, migraine frequency (average number of migraine days per month), presence of aura symptoms (yes/no), painkiller usage (patients reported drug names, which were clustered to three groups based on the ingredients, namely NSAID [Non-Steroidal Anti-Inflammatory Drug], combined analgesics, and triptan, and if the patient has not used painkiller drug, we coded as "no") and migraine severity (assessed by a visual analogue scale [VAS]). We used the simplest VAS, a straight horizontal line of 100 mm. The ends were defined as the extreme limits of the headache, orientated from the left (pain free) to the right (worst pain).

CHQQ was used to measure the headache-related QoL of the subjects. The CHQQ is a 23-item headache-specific QoL questionnaire developed and validated by the Headache Research Group, Department of Neurology, Semmelweis University[12, 14]. The questionnaire measures patients' QoL in detail covering the last four weeks. A 5-point Likert scale was used to answer the questions (for example: *How much did you bother with the headache in your free time (reading, listening to music, hobby, etc.)?* or *How much did the headache interfere with your work activity?*) ranging from the absolute absence of restriction (*not bother at all*) to maximal restriction (*made it impossible*), then the values are transformed to a 0-100-point scale, on which the absence of restriction is equal to 100 points and the full restriction to 0 point. Three dimensions (Physical, Mental, and Social) and the Total score were calculated without weighting the item scores. All CHQQ domain scores were scaled from 0%=worst to 100%=best health/function/ability in accordance with the original scoring of the CHQQ[14]. In our study, the questionnaire demonstrated excellent internal consistency on the total score (Cronbach's alpha: 0.913) and good internal consistency on physical (Cronbach's alpha: 0.807), mental (Cronbach's alpha: 0.828), and social scales (Cronbach's alpha: 0.802).

STATISTICAL ANALYSIS

All analyses were performed using the statistical software package IBM SPSS 21.0 for Windows (IBM). Based on Skewness and Kurtosis, the data showed normal distribution, therefore we used parametric tests. Independent samples t-test was applied to calculate the differences of age, years with headache, headache frequency, headache pain severity, and each domain of CHQQ between migraine and MOH patients. Chi-squared test was used to determine differences in sex, the presence of aura and triptan medication across groups. All statistical testing above adopted a two-tailed $p<0.05$ threshold. To determine the independent effects of sex, age, recruitment method, headache type (migraine vs. MOH) and headache characteristics (presence of aura symptoms, years with headache, headache pain severity/VAS, headache frequency and triptan use) we tested them in linear regression models (all factors were included to the model in one step with enter method) separately for each domain and for the total score of CHQQ. Taking into account the 4 multiple regression models we set the significance threshold to $p\leq0.0125$ (0.05/4) to correct for multiple testing and avoid Type I error.

Results

DESCRIPTIVE STATISTICS

The demographic characteristics of the investigated populations and the statistical comparison of the migraine and MOH subgroups are displayed in **Table 1**.

Patients with MOH were significantly older than patients with migraine and reported significantly higher headache frequency in the last month. The pain severity of the headaches measured by VAS was approximately the same in migraine and MOH groups and no significant difference was found in years with headache between migraine and MOH patients. The proportion of patients with or without aura, with or without triptan use, and belonging to clinical or research group in the migraine and MOH subgroups showed no significant differences. 97.8% of the migraineurs used at least one type of painkiller, while all the patients with MOH used painkiller (as expected). In the whole sample, 71.3% used NSAID, 23.7% combined analgesics and 18% triptan, and 13.5% used at least two types of painkillers. Thus, because of the widespread application of non-triptan painkillers we only included triptan use to the further analysis to inves-

Table 1. *Demographic and clinical characteristics of migraine and medication overuse headache groups*

	Whole sample (N=334)	Migraine (N=269)	MOH (N=65)	Test statistic (t/χ^2)	Effect size (Cohen's d)
Female (n, %)	288 (86.2%)	235 (87.4%)	53 (81.5%)	χ^2: 1.494	–
Age (mean, SD)	35.57 (11.89)	34.03 (10.85)	41.98 (13.81)	t: 4.334**	0.69
Headache years (mean, SD)	13.77 (11.20)	13.23 (10.16)	16.00 (14.62)	t: 1.452	0.25
Headache frequency (mean, SD)	9.90 (9.66)	6.56 (6.85)	23.71 (7.01)	t: 17.773**	2.49
Headache pain severity (VAS, mean, SD)	53.87 (28.29)	54.25 (28.19)	52.29 (28.90)	t: 0.492	0.07
Aura (n, %)	yes: 44 (13.2%)	yes: 37 (13.8%)	yes: 7 (10.8%)	χ^2: 0.408	–
Painkillers	yes: 328 (98.2%)	yes: 263 (97.8%)	yes: 65 (100%)	χ^2: 1.476	–
Triptan medication (n, %)	yes: 60 (18%)	yes: 46 (17.1%)	yes: 14 (21.5%)	χ^2: 0.700	–
Recruitment method	clinical: 248 (74.3%) research: 86 (25.7%)	clinical: 198 (73.6%) research: 71 (26.4%)	clinical: 50 (76.9%) research: 15 (23.1%)	χ^2: 0.301	–
CHQQ Physical (mean, SD)	41.19 (17.88)	42.05 (18.44)	37.59 (14.93)	t: 2.085*	0.25
CHQQ Mental (mean, SD)	47.65 (16.72)	48.72 (16.83)	43.23 (15.59)	t: 2.505*	0.33
CHQQ Social (mean, SD)	48.14 (21.60)	49.11 (22.03)	44.15 (19.36)	t: 1.801	0.23
CHQQ Total (mean, SD)	45.51 (16.09)	46.48 (16.39)	41.47 (14.20)	t: 2.475*	0.31

MOH: medication overuse headache, SD: standard deviation, CHQQ: Comprehensive Headache-related Quality of life Questionnaire, VAS: visual analogue scale
*p<0.05, **p<0.001

tigate predictors of QoL. Patients with MOH reported lower physical, mental, social, and total CHQQ scores compared to migraine, the differences were significant on all dimensions except the social subscale using pairwise comparisons without covariates **(Table 1)**.

RELATIONSHIP BETWEEN QUALITY OF LIFE AND HEADACHE-RELATED VARIABLES

The following explanatory variables were used to explain physical, mental, social and total CHQQ scores in the total population: sex, age, recruitment method (belonging to the clinical or research subgroup), headache type (migraine/MOH), years with headache, aura symptoms, triptan use, headache pain severity and headache frequency. Results are presented in **Table 2**. The regression models explained 22.0% of the total variance of CHQQ social, 20.3% of the total variance of CHQQ physical, and 19.6% of the variance of the CHQQ total score, while only 11.1% variance was explained of the CHQQ mental subscale.

After correction for multiple testing, better physical QoL was associated with research subsample status, younger age, no triptan use, and less severe headache pain. Higher scores on the mental subscale were associated with no triptan use. Better social QoL was related to research subsample status and no triptan use. Regarding the total score, significant association was found with recruitment method, triptan use and headache pain severity.

Notably, headache type was not a significant explanatory variable on any of the CHQQ subscales after controlling for demographic and other headache characteristics. The most consistently associated variables with higher CHQQ scores were no triptan use and less severe headache pain.

POST HOC TEST: THE RELATIONSHIP BETWEEN TRIPTAN USE AND OTHER HEADACHE-RELATED VARIABLES

Taking into account that triptan use was consistently associated with all CHQQ subscales, for exploratory purposes we tested how triptan use was related to other headache-related variables. Our results demonstrated that triptan users reported significantly more years of headache, but headache frequency and headache pain severity were independent of triptan use **(Table 3)**. In addition, we compared the two groups on CHQQ subscales, and the results were in accordance with the results of regression analyses. Namely, those who use triptans reported worse QoL **(Table 3)**.

Table 2. *Standardized regression weights between headache-related quality of life and demographic and headache-related variables*

	Physical headache related QoL		Mental headache related QoL		Social headache related QoL		CHQQ total	
	stand. beta	p value	stand. beta	p value	stand. beta	p value	stand. beta	p value.
Sex (male/female)	*–0.114*	*0.023*	–0.091	0.086	–0.054	0.27	*–0.101*	*0.045*
Age	–0.182	0.005	–0.100	0.15	–0.085	0.19	–0.140	0.032
Clinical/research subsample	0.286	<0.001	0.082	0.17	0.322	0.001	0.241	0.001
Headache type (migraine/MOH)	–0.051	0.48	0.006	0.94	–0.016	0.83	–0.022	0.77
Headache years	0.056	0.34	0.088	0.16	–0.060	0.30	0.044	0.46
Aura (yes/no)	0.054	0.30	0.074	0.18	*0.125*	*0.016*	0.091	0.085
Triptan use (yes/no)	0.163	0.002	0.171	0.002	0.160	0.002	0.187	0.001
Headache pain severity (VAS)	–0.166	0.001	*–0.128*	*0.017*	*–0.122*	*0.015*	–0.158	0.002
Headache frequency	–0.004	0.95	*–0.171*	*0.041*	–0.059	0.46	–0.096	0.23
R^2/Adjusted R^2	0.203/0.180		0.111/0.086		0.220/0.198		0.196/0.174	

QoL: quality of life, MOH: medication overuse headache, CHQQ: Comprehensive Headache-related Quality of life Questionnaire, VAS: visual analogue scale, stand. beta: standardized beta coefficient, normal: significant results after correction for multiple testing, italic: nominally significant results

Discussion

In this study, we examined the quality of life in migraine and MOH patients. Based on group comparison, MOH patients reported worse HRQoL on all CHQQ subscales and on total scores compared to migraine patients, although the differences were small in magnitude. Notably, our further analyses revealed that not the headache-type but other headache characteristics were important in explaining interindividual differences in quality of life. Our results demonstrated that triptan use and headache pain severity assessed with VAS were most consistently associated with HRQoL measured by CHQQ after controlling for sex, age, recruitment method and other headache-related variables, such as headache type, aura symptoms, years with headache and headache frequency. Interestingly, headache type, namely migraine or MOH, was not significantly associated with any CHQQ subscales in our study after controlling for other headache characteristics.

MOST CONSISTENTLY ASSOCIATED FACTORS WITH ALL HRQOL DOMAINS

Triptan use was associated with lower scores on all CHQQ subscales, while headache pain severity was associated with lower scores on physical and total CHQQ subscales.

Triptans, i.e. serotonin (5-hydroxytryptamine [5-HT]) agonists with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors, are commonly prescribed agents for the acute treatment of migraine[19]. Our knowledge about the link between triptan use and HRQoL is quite scarce. In a recent study, HRQoL and work productivity were significantly impacted in triptan non-responders compared to triptan responders[13], which observation might be explained by the ongoing severe headaches. However, according to our findings, triptan use was associated with poor HRQoL even though headache frequency and headache pain severity (VAS) were not significantly different between triptan users and non-users. Thus, one possible explanation for the association between triptan use and impaired HRQoL in our study could be that patients with higher burden of headache and lower HRQoL prefer to use triptans. Indeed, triptan users reported significantly more years with headache than non-users in our study, supporting that triptan use might be a surrogate marker of patients with longer disease duration, as it was suggested also by previous studies[1, 20]. In addition, 21.5% of MOH patients used triptans while only 17.1% of migraine patients; although this difference was not significant but the overrepresentation of MOH patients might partially contribute to the lower HRQoL in triptan users. Another potential explanation for our results could be that well-known side effects of triptans (sleepiness/tiredness, difficulty in thinking, dizziness, nausea, racing heartbeat, muscle weakness, warm sensation, chest pressure) are also important factors in migraine management and significantly affect patient compliance and satisfaction[21]. Therefore, it would be important to investigate the HRQoL in users of calcitonin gene-related peptide (CGRP) receptor antagonist second generation gepants, a

Table 3. *Differences in headache frequency, headache years, headache pain severity, and quality of life scores between triptan users (N=60) and non-users (N=274)*

		Mean (SD)	Test statistics (t)	Effect size (Cohen's d)
Headache frequency	Triptan users	9.33 (7.54)	0.602	0.07
	Triptan non-users	10.03 (10.08)		
Headache years	Triptan users	18.03 (13.18)	2.862*	0.41
	Non-triptan users	12.83 (10.52)		
Headache pain severity (VAS)	Triptan users	50.35 (33.52)	0.927	0.15
	Non-triptan users	54.64 (27.02)		
CHQQ Physical	Triptan users	35.10 (15.63)	3.230*	0.42
	Non-triptan users	42.52 (18.09)		
CHQQ Mental	Triptan users	42.17 (15.07)	3.044*	0.40
	Non-triptan users	48.85 (16.85)		
CHQQ Social	Triptan users	40.92 (20.18)	3.023*	0.41
	Non-triptan users	49.73 (21.61)		
CHQQ Total	Triptan users	39.44 (13.45)	3.704**	0.46
	Non-triptan users	46.84 (16.34)		

SD: standard deviation, CHQQ: Comprehensive Headache-related Quality of life Questionnaire
*p<0.01, **p<0.001

novel group of acute migraine drugs, where side effects and rebound headaches are much less prevalent[22, 23].

Headache pain severity, measured by pain intensity on a VAS, was associated with physical domain and total HRQoL scores after controlling for multiple testing, and at nominal level with mental and social domains as well, even after controlling for other headache-related variables. To the best of our knowledge, only one study investigated the effect of migraine severity on HRQoL reporting a negative relationship between HRQoL and migraine severity (indexed by the combination of migraine frequency and pain intensity)[3] and our result is in line with this observation. In addition, pain severity in other pain-related conditions, such as multiple myeloma[24], fibromyalgia[25], or chronic low back pain[26] also has a major impact on HRQoL.

HRQOL AND OTHER HEADACHE-RELATED FACTORS

Contrary to previous studies[9, 10], headache frequency was not consistently associated with HRQoL domains. However, headache frequency showed negative relationship with mental health domain of CHQQ, although only at nominal level, which is in line with a previous study that found an association between higher migraine frequency (either with or without aura) and depression and anxiety symptoms (measured by Beck Depression Inventory and Hospital Anxiety and Depression Subscales)[27]. Indeed, this relationship between migraine and depression is also supported by genetic findings[28]. It is also worth mentioning that our regression model with demographic and headache-related variables explained the lowest total variance in the mental health domain of CHQQ supporting that different domains of HRQoL are not equally affected by headache-related variables.

In our sample, aura symptoms were nominally associated with worse social HRQoL. Regarding migraine aura symptoms, we did not find any studies investigating the association with HRQoL. Important to note that other disorders with transient neurological symptoms, for example Ménière's disease[29], benign paroxysmal positional vertigo[30] were also associated with significantly worse HRQoL. These findings may support our observation that besides migraine severity and triptan use, additional transient aura symptoms might contribute to further impairment in HRQoL by limiting social activities.

HEADACHE TYPE AND HRQOL

Importantly, although all CHQQ domains (except for the social subscale) differed significantly between migraine and MOH patients, the headache type did not remain significantly associated with any CHQQ subscales or the total score after controlling for other variables

In a cross-sectional study from the Medication Overuse Treatment Strategy trial EuroQol EQ-5D-5L questionnaire was used to measure QoL in patients with MOH according to the ICHD-3 beta

criteria. Similarly to our results quality of life scores were lower in patients with higher headache frequency for all EQ-5D-5L measures except for self-care scale[31]. In line with the previous study an increase in the number of headache free days in migraineurs with equal or more than 4 headache days in a month was associated with improved HRQoL measured by the EuroQol-5D questionnaire[32]. However, we could not replicate these findings in our study after controlling for other headache-related factors. Headache chronicity had both indirect and direct effects on QoL, measured by MSQ2.1 questionnaire in episodic and chronic migraine patients[11]. Interestingly in this study one of the directly contributing factors in determining lower QoL was female gender, but the pathophysiology is still unclear[11]. In our study we found similar trends for the CHQQ total score and the physical subscale even after correction of other headache-related factors suggesting that HRQoL in females is more affected by migraine than in males. In another study, both episodic and chronic migraineurs had significantly lower mental composite scores (MCS) and physical composite scores (PCS) on SF-36 (MCS and PCS are norm-based scores, with higher scores reflecting better HRQoL) compared to non-migraine controls, but the HRQoL of episodic and chronic migraineurs was not compared[33]. *Matilde Leonardi* et al. observed a lower SF-36 MCS and PCS in patients with increased migraine severity (according to frequency and pain intensity), but only MCS showed significant change[3]. These studies above, using SF-36 to measure patients HRQoL used only MCS and PCS, but not each subscale separately. In an older study significantly lower values on the physical functioning and bodily pain subscales of SF-36 were detected in a mixed group of chronic migraine, chronic tension-type headache, new daily persistent headache with analgesic overuse[8]. Therefore, based on previous studies and our results, it is important to take headache-related factors into account in future studies focusing on the effect of migraine and analgesic overuse on HRQoL.

In addition, the use of preventive headache medication, which is taken on a daily basis in order to reduce the frequency, severity and duration of headaches, may also interfere with HRQoL. Based on previous studies, different types of preventive medications can lead to QoL improvement both in episodic and in chronic migraine patients[34–37] and also in patients with MOH[38, 39]. As we will discuss in the limitation section, migraine preventive medication was an exclusion criterion in the research subsample, but not in the clinical subsample, however we have not recorded the exact type and dose of the preventive medications. Therefore, in further studies it would be valuable to evaluate the interaction between different types of preventive medications, headache-related variables and variance of HRQoL in a bigger sample size.

Limitations

While comorbidity was an exclusion criterion in the research subsample, in our clinical subsample psychiatric and somatic comorbidities were not systematically explored which might have influenced our results. Another limitation is the difference in preventive medication use: in the research subsample neither migraine nor MOH patients received headache preventive medication, but in the clinical group, preventive headache medication was not an exclusion criterion. In addition, we did not record the exact dose and frequency of the preventive medications in the clinical sample. The evaluation of the difference of HRQoL among patients with and without preventive medication would also be valuable. Finally, MOH develops in patients with a pre-existing primary headache, in most of the cases in patients with migraine[40], but in a lesser extent in patients with history of tension-type headache[40] or cluster headache alone[41]. This was the case in our study: 52% of the MOH patients had migraine, 34% had both migraine and tension-type headache, and 14% had pure tension-type headache before MOH developed. Therefore, it is possible that pre-existing primary headache disorders may influence HRQoL in MOH patients that should be further investigated in future studies.

Conclusion

Despite the significant difference in HRQoL between migraine and MOH patients, the variance of HRQoL was not explained by the headache type itself, but rather by other headache-related variables, among which the most consistent factors were triptan use and headache pain severity. Our results support that investigating the relationship of different headache-related variables with HRQoL is important to determine the key factors in the deterioration in HRQoL, to adequately manage different patient populations and to guide public health policies regarding health service utilization and health-care costs.

CONFLICT OF INTEREST

AEE is an employee of Gedeon Richter Plc. Medical Division, but the company did not provide any funding, or have any further role in the preparation of the article. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions: MM: substantial contributions to the conception; interpretation of data; have drafted the work or substantively revised it; GyK: substantial contributions to the conception; the acquisition, analysis; interpretation of data; have drafted the work and substantively revised it; DB: acquisition of data; substantively revised the work; AG: acquisition of data; substantively revised the work; AEÉ: acquisition of data; substantively revised the work ; ES: acquisition of data; substantively revised the work; KG: acquisition of data; substantively revised the work, DD: acquisition of data; substantively revised the work, NK: acquisition of data; substantively revised the work; TGy: acquisition of data; substantively revised the work ; GJ: substantial contributions to the conception; design of the work; the acquisition, analysis; interpretation of data; have drafted the work and substantively revised it; CsE: substantial contributions to the conception; the acquisition, analysis; have drafted the work and substantively revised it.

All authors have approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

FUNDING

This study was supported by the Hungarian Brain Research Program (Grants: 2017-1.2.1-NKP-2017-00002); by the Hungarian Academy of Sciences, Hungarian National Development Agency, Semmelweis University and the Hungarian Brain Research Program (Grant: KTIA_NAP_13-2-2015-0001; MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group); by the Thematic Excellence Programme (Tématerületi Kiválósági Program, 2020-4.1.1.-TKP2020) of the Ministry for Innovation and Technology in Hungary, within the framework of the Neurology and Translational Biotechnology thematic programmes of the Semmelweis University; by TKP2021-EGA-25 supported by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, under the TKP2021-EGA funding scheme; by the National Research, Development and Innovation Office, Hungary (2019-2.1.7-ERA-NET-2020-00005), under the frame of ERA PerMed; and by the ÚNKP-20-3-II-SE-51 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund.

ETHICS STATEMENT

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional (Semmelweis University Ethics Committee) and national research committee (Medical Research Council, Hungary) and with the Helsinki Declaration. Informed consent was obtained from all individual participants involved in the study.

REFERENCES

1. D'*Amico D, Grazzi L, Usai S, Leonardi M, Raggi A*. Disability and quality of life in headache: where we are now and where we are heading. Neurol Sci 2013;34:1-5. https://doi.org/10.1007/s10072-013-1378-9
2. *Cole JC, Lin P, Rupnow MF*. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. Qual Life Res 2007;16(7):1231-7. https://doi.org/10.1007/s11136-007-9217-1
3. *Leonardi M, Raggi A, Bussone G, D'Amico D.* Health-related quality of life, disability and severity of disease in patients with migraine attending to a Specialty Headache Center. Headache 2010;50(10):1576-86. https://doi.org/10.1111/j.1526-4610.2010.01770.x
4. *Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF*. Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. Cephalalgia 2003;23(6):441-50. https://doi.org/10.1046/j.1468-2982.2003.00546.x
5. *Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF*. Migraine, quality of life, and depression. Neurology 2000;55(5):629-35. https://doi.org/10.1212/WNL.55.5.629
6. *Colas R, Munoz P, Temprano R, Gomez C, Pascual J*. Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology 2004;62(8): 1338-42. https://doi.org/10.1212/01.wnl.0000120545.45443.93

7. *Altinta E, Karakurum GB, Ta kintuna N, Saritürk Ç*. Correlation between life events and quality of life in patients with medication-overuse headache. Noro Psikiyatri Ars 2015;52(3):233-9. https://doi.org/10.5152/npa.2015.8799
8. *Guitera V, Munoz P, Castillo J, Pascual J*. Quality of life in chronic daily headache: a study in a general population. Neurology 2002;58(7):1062-5. https://doi.org/10.1212/wnl.58.7.1062
9. *AlHarbi FG, AlAteeq MA*. Quality of life of migraine patients followed in neurology clinics in Riyadh, Saudi Arabia. J Family Community Med 2020;27(1):37-45. https://doi.org/10.4103/jfcm.JFCM_185_19
10. *Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ*. The impact of migraine on quality of life in the general population: the GEM study. Neurology 2000;55(5):624-9. https://doi.org/10.1212/wnl.55.5.624
11. *Kim S, Park S*. The role of headache chronicity among predictors contributing to quality of life in patients with migraine: a hospital-based study. J Headache Pain 2014; 15(1):68. https://doi.org/10.1186/1129-2377-15-68
12. *Manhalter N, Palasti A, Bozsik G, Afra J, Ertsey C*. Examining the psychometric properties of a new quality of life questionnaire in migraineurs. Ideggyogy Sz 2010;63(9-10): 305-13.
13. *Lombard L, Farrar M, Ye W, Kim Y, Cotton S, Buchanan AS, et al*. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication. J Headache Pain 2020;21(41):1-16. https://doi.org/10.1186/s10194-020-01110-9
14. *Manhalter N, Bozsik G, Palasti A, Csepany E, Ertsey C*. The validation of a new comprehensive headache-specific quality of life questionnaire. Cephalalgia 2012;32(9):668-82. https://doi.org/10.1177/0333102412447702
15. *Jankovic SM, Andjelkovic M, Zaric RZ, Vasic M, Csépány É, Gyüre T, et al*. The psychometric properties of the Comprehensive Headache-related Quality of life Questionnaire (CHQQ) translated to Serbian. Springerplus 2016;5(1):1416. https://doi.org/10.1186/s40064-016-3109-1
16. *Gyure T, Csepany E, Hajnal B, Kellermann I, Balogh E, Nagy Z, et al*. The comprehensive headache-related quality of life questionnaire shows significant improvement after withdrawal treatment in medication overuse headache: a pilot study. Ideggyogy Sz 2014;67(5-6):169-76.
17. *Diossy M, Balogh E, Magyar M, Gyure T, Csepany E, Bozsik G, et al*. The quality of life of the cluster headache patients during the active phase of the headache. Ideggyogy Sz 2020;73(1-2):15-26. https://doi.org/10.18071/isz.73.0015
18. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1): 1-211. https://doi.org/10.1177/0333102417738202
19. *Smitherman TA, Burch R, Sheikh H, Loder E*. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache 2013;53(3):427-36. https://doi.org/10.1111/head.12074
20. *Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB*. Transformed migraine and medication overuse in a tertiary headache centre—clinical characteristics and treatment outcomes. Cephalalgia 2004;24(6):483-90. https://doi.org/10.1111/j.1468-2982.2004.00691.x
21. *Gallagher RM, Kunkel R*. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. Headache 2003;43(1):36-43. https://doi.org/10.1046/j.1526-4610.2003.03006.x
22. *Yang CP, Liang CS, Chang CM, Yang CC, Shih PH, Yau YC, et al*. Comparison of New Pharmacologic Agents With Triptans for Treatment of Migraine: A Systematic Review and Meta-analysis. JAMA Netw Open 2021;4(10):e2128544. https://doi.org/10.1001/jamanetworkopen.2021.28544
23. *Negro A, Martelletti P*. Gepants for the treatment of migraine. Expert opinion on investigational drugs. Expert Opin Investig Drugs 2019;28(6):555-67. https://doi.org/10.1080/13543784.2019.1618830
24. *Ludwig H, Bailey A, Marongiu A, Khela K, Milligan G, Carlson K, et al*. Patient-reported pain severity and health-related quality of life in patients with multiple myeloma in real world clinical practice. Cancer Rep 2021:e1429. https://doi.org/10.1002/cnr2.1429
25. *Bennett R, Schein J, Kosinski M, Hewitt D, Jordan D, Rosenthal N*. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum 2005;53(4):519-27. https://doi.org/10.1002/art.21319
26. *Mutubuki EB, Maas Y, Huygen ET, Ostelo FJPM, van Tulder RWJG, MW van Dongen JM*. The longitudinal relationships between pain severity and disability versus health-related quality of life and costs among chronic low back pain patients. Qual Life Res 2020;29(1):275-87. https://doi.org/10.1007/s11136-019-02302-w
27. *Chu HT, Liang CS, Lee JT, Yeh TC, Lee MS, Sung YF, et al*. Associations between depression/anxiety and headache frequency in migraineurs: A Cross-Sectional Study. Headache 2018;58(3):407-15. https://doi.org/10.1111/head.13215
28. *Ligthart L, Hottenga JJ, Lewis CM, Farmer AE, Craig IW, Breen G, et al*. Genetic risk score analysis indicates migraine with and without comorbid depression are genetically different disorders. Hum Genet 2014;133(2):173-86. https://doi.org/10.1007/s00439-013-1370-8
29. *Anderson JP, Harris JP*. Impact of Ménière's disease on quality of life. Otol Neurotol 2001;22(6):888-894. https://doi.org/10.1097/00129492-200111000-00030
30. *Gámiz MJ, Lopez-Escamez JA*. Health-related quality of life in patients over sixty years old with benign paroxysmal positional vertigo. Gerontology 2004;50(2):82-6. https://doi.org/10.1159/000075558
31. *Schwedt T, Hentz J, Sahai-Srivastava S, Spare N, Martin V, Treppendahl C, et al*. Headache characteristics and burden from chronic migraine with medication overuse headache: Cross-sectional observations from the Medication Overuse Treatment Strategy trial. Headache 2021;61(2):351-62. https://doi.org/10.1111/head.14056
32. *Doane M, Gupta S, Vo P, Laflamme A, Fang J*. Associations Between Headache-Free Days and Patient-Reported Outcomes Among Migraine Patients: A Cross-Sectional Analysis of Survey Data in Europe. Pain Ther 2019;8(2): 203-16. https://doi.org/10.1007/s40122-019-0133-1
33. *Vo P, Fang J, Bilitou A, Laflamme A, Gupta S*. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain 2018;19 (1):82. https://doi.org/10.1186/s10194-018-0907-6
34. *Bordini CA, da Silva M, Garbelini RP, Teixeira SO, Speciali JG*. Effect of preventive treatment on health-related quality of life in episodic migraine. J Headache Pain 2005;6(5):387-91. https://doi.org/10.1007/s10194-005-0233-7

35. *Dodick DW, Silberstein S, Saper J, Freitag FG, Cady RK, Rapoport AM, et al*. The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache 2007;47(10):1398-408. https://doi.org/10.1111/j.1526-4610.2007.00950.x
36. *D'Amico D, Solari A, Usai S, Santoro P, Bernardoni P, Frediani F, et al*. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. Cephalalgia 2006;26(6):691-6. https://doi.org/10.1111/j.1468-2982.2005.01094.x
37. *Spierings ELH, Ning X, Ramirez Campos V, Cohen JM, Barash S, Buse DC*. Improvements in quality of life and work productivity with up to 6 months of fremanezumab treatment in patients with episodic and chronic migraine and documented inadequate response to 2 to 4 classes of migraine-preventive medications in the phase 3b FOCUS study. Headache 2021;61(9):1376-86. https://doi.org/10.1111/head.14196
38. *Cainazzo MM, Baraldi C, Ferrari A, Lo Castro F, Pani L, Guerzoni S*. Erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache: an observational, retrospective, 12-month real-life study. Neurol Sci 2021;42(10):4193-202. https://doi.org/10.1007/s10072-021-05105-5
39. *Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P*. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. Springerplus 2015; 4:826. https://doi.org/10.1186/s40064-015-1636-9
40. *Castillo J, Muñoz P, Guitera V, Pascual J*. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. Headache 1999;39(3):190-6. https://doi.org/10.1046/j.1526-4610.1999.3903190.x
41. *Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ.* Medication-overuse headache in patients with cluster headache. Neurology 2006;67(1). https://doi.org/10.1212/01.wnl.0000223332.35936.6e

TELECARE IN PARKINSON'S DISEASE: A NATIONWIDE SURVEY AMONG HUNGARIAN NEUROLOGISTS

Dávid PINTÉR[1, 2], Evelyn JÁRDAHÁZI[1], József JANSZKY[1, 2], Norbert KOVÁCS[1, 2]

[1]Department of Neurology, Medical School, University of Pécs, Pécs
[2]ELKH-PTE Clinical Neuroscience MR Research Group, Pécs

English | https://doi.org/10.18071/isz.75.0265 | www.elitmed.hu

Background and purpose – COVID-19 has made providing in-person care difficult. In most countries, including Hungary, telemedicine has partly served as a resolution for this issue. Our purpose was to explore the effects of COVID-19 on neurological care, the knowledge of neurology specialists on telemedicine, and the present state of telecare in Hungary, with a special focus on Parkinson's disease (PD).
Methods – Between July and October 2021, a nationwide online survey was conducted among actively practicing Hungarian neurology specialists who were managing patients with PD.
Results – A total of 104 neurologists were surveyed. All levels of care were evaluated in both publicly funded and private healthcare. Both time weekly spent on outpatient specialty consultation and the number of patients with PD seen weekly significantly decreased in public healthcare, while remained almost unchanged in private care ($p<0.001$); higher portion of patients were able to receive in-person care in private care (78.8% vs. 90.8%, $p<0.001$). In telecare, prescribing medicines has already been performed by the most (n=103, 99%). Electronic messages were the most widely known telemedicine tools (n=98, 94.2%), while phone call has already been used by most neurologists (n=95, 91.3%). Video-based consultation has been more widely used in private than public care (30.1% vs. 15.5%, p=0.001). Teleprocedures were considered most suitable for monitoring progression and symptoms of Parkinson's disease and evaluating the need for adjustments to antiparkinsonian pharmacotherapy.
Conclusion – COVID-19 has had a major impact on the care of patients with PD in Hungary. Telemedicine has mitigated these detrimental effects; however, further

TÁVELLÁTÁS PARKINSON-KÓRBAN: ORSZÁGOS FELMÉRÉS A MAGYAR NEUROLÓGUSOK KÖRÉBEN
Pintér D, MD, PhD; Járdaházi E, MA; Janszky J, MD, DSc; Kovács N, MD, DSc
Ideggyogy Sz 2022;75(7–8):265–273.

Bevezetés és cél – A Covid-19-világjárvány jelentősen nehezíti a személyes betegellátást. A legtöbb országban, köztük Magyarországon is, a telemedicina részben megoldást jelent ezen problémára. A Covid-19 neurológiai betegellátásra gyakorolt hatásainak, a neurológus szakorvosok telemedicinával kapcsolatos ismereteinek és a távellátás hazai helyzetének feltárását tűztük ki célul, elsősorban a Parkinson-kóros betegek ellátására fókuszálva.
Módszertan – 2021 júliusa és októbere között országos online felmérést végeztünk olyan aktívan praktizáló magyar neurológus szakorvosok körében, akik részt vesznek a Parkinson-kóros betegek ellátásában.
Eredmények – Összesen 104 neurológus töltötte ki kérdőívünket. Az ellátás minden szintjét elemezhettük mind a közfinanszírozott, mind a magánellátásban. A járóbeteg-szakrendelésre fordított heti idő és a hetente látott Parkinson-kóros betegek száma egyaránt jelentősen csökkent a közfinanszírozott ellátásban, míg a magánellátásban szinte változatlan maradt ($p < 0,001$). A magánellátásban a betegek nagyobb arányban vehettek igénybe személyes ellátást (78,8% vs. 90,8%, $p < 0,001$). A legtöbb neurológus által már végzett távkonzultációs tevékenység a gyógyszerfelírás volt (n = 103, 99%). Az elektronikus üzenet volt a legtöbbek által ismert telemedicinális eszköz (n = 98, 94,2%), és a telefonhívást alkalmazta már a legtöbb neurológus (n = 95, 91,3%). A videóalapú konzultációt a magánellátásban szélesebb körben használták (30,1% vs. 15,5%, p = 0,001). A megkérdezettek a telemedicinális ellátás eszközeit a Parkinson-kór progressziójának és tüneteinek követésére, illetve az antiparkinson gyógyszerelésben módosítás szükségességének megítélésére tartották a legalkalmasabbnak.

Correspondent: Dr. Dávid PINTÉR, Department of Neurology, University of Pécs; 7623 Pécs, Rét u. 2.
Telephone: +36 72 535 900, fax: +36 72 535 911, e-mail: david_pinter@outlook.com
https://orcid.org/0000-0002-0734-6878

Érkezett: 2022. március 13. Elfogadva: 2022. június 10.

developments could make it an even more reliable component of care.

Keywords: *neurology, Parkinson's disease, telemedicine, COVID-19, pandemic*

Konklúzió – A Covid-19 jelentős hatással volt a Parkinson-kóros betegek ellátására hazánkban. A telemedicina enyhítette ezen káros hatásokat, ugyanakkor további fejlesztések a betegellátás még megbízhatóbb elemévé tehetnék a telemedicinát.

Kulcsszavak: *neurológia, Parkinson-kór, telemedicina, Covid-19, pandémia*

The COVID-19 pandemic has worldwide made it difficult, and in some areas completely impossible, to provide in-person patient care in several disorders including Parkinson's disease (PD)[1, 2]. Further digitalization of the healthcare and the introduction or the expansion of telemedicine has been most frequently considered a resolution for this problem[3–7]. Telecare in neurology has started to be more widely used even in countries where digitalization of the healthcare had already begun prior to the pandemic[8, 9]. The reported increase in the use of different telemedicine tools for managing neurologic disorders during the pandemic differed among countries and varied between 200% and 3,000%[10–13].

Since November 2017, Hungarian medical care has been documented in a centralized, government-controlled cloud space, and prescriptions and referrals have also been made through this electronic system. After the outbreak of the pandemic, in March 2020, using this regulated and secure National Electronic Healthcare System strictly compliant with the European and Hungarian data protection regulations and complemented by cloud-based documentation, establishing diagnoses, making therapeutic recommendations, counselling, consultations, patient management and referrals, therapeutic and rehabilitation activities, and prescription of medicines and medical aids with infocommunication tools have been made available for both publicly and privately funded healthcare[14]. The treating physicians can electronically review all medical records, medicine orders and referrals for tests of their patients in a secure way. The system also allows physicians to both prescribe medications or request medical examinations and check whether patients refill the prescribed medicines or attend the indicated examinations.

Although telemedicine has several advantages, its applicability may be limited, among others by the lack of an appropriate technological background and procedures to replace traditional examinations[15]. In the field of movement disorders, there are freely accessible tools (e.g. the Parkinson's Disease Composite Scale/PDCS[16]) and procedures (e.g. video-based consultation) that are considered effective enough by the International Parkinson's Disease and Movement Disorders Society and enable telecare[17].

Via a nationwide survey, the present study aimed to explore the effects of the COVID-19 pandemic on neurological care, the knowledge of neurology specialists on telemedicine, and the present state of telecare in Hungary, with a special focus on PD.

Materials and methods

The study protocol was approved by the National Ethical Board (IV/4508- 3 /2021/EKU).

THE QUESTIONNAIRE

The questionnaire was designed in a secure online system and released online only. Its final version consisted of 68 questions and was divided into ten parts.

Part I checked if the physicians to be surveyed fulfill all inclusion criteria.

Part II included the characterization of the participants including age, duration of practicing as a neurology specialist, type of workplace (publicly funded, privately funded, or both), and whether the respondent is retired and specialized in PD.

Part III and IV respectively recorded characteristics of publicly and privately funded workplaces such as location (e.g. capital city, county seat, or other city or town), type (e.g. university clinic, hospital, or ambulatory neurology canter), and time weekly spent on outpatient specialty consultation and number of PD patients seen weekly before the outbreak of COVID-19 pandemic in Hungary (March 2020) and during the pandemic (during the first quarter of 2021).

Part V measured knowledge on telemedicine (e.g. procedures allowed to be performed and tools allowed to be used) and assessed telemedicine practice

(e.g. procedures already performed and tools already used).

Part VI and VII respectively assessed the availability of telemedicine in publicly and privately funded workplaces.

Part VIII specifically focused on telecare in PD (e.g. knowledge on telemedicine for PD and effectiveness of different telemedicine tools in the management of PD patients).

Part IX included questions on the future of telemedicine (e.g. intention of physicians to improve telemedicine services at their workplaces and use telemedicine after the pandemic).

Part X briefly assessed the opinion of respondents on the questionnaire.

Table 1. *Characteristics of the respondents (n=104)*

Characteristic		Number and percentage of respondents
Age (years)	<40	14 (13.5)
	41-50	29 (27.9)
	51-60	35 (33.7)
	61-70	26 (25.0)
	>71	0 (0.0)
Duration of practicing as a neurology specialist (years)	<5	8 (7.7)
	5-10	6 (5.8)
	11-20	25 (24.0)
	21-30	39 (37.5)
	>30	26 (25.0)
Retired but still actively practicing neurologists		7 (6.7)
Workplace	Publicly funded	62 (59.6)
	Privately funded	2 (1.9)
	Both	40 (38.5)
Specialized in Parkinson's disease		42 (40.4)

PARTICIPANTS

An invitation to fill out the questionnaire was sent to all physicians who met the following criteria: (1) being a neurology specialist in Hungary, (2) actively practicing, and (3) managing patients with PD. We aimed to recruit as many respondents as possible. The survey was first distributed in July 2021. Participants had the opportunity to complete the questionnaire until the end of September 2021. Subsequently, a reminder was circulated to recruit further respondents until the end of October 2021 when the survey was closed.

STATISTICAL ANALYSIS

Answers were first exported to an Excel file. Subsequently, text information was transformed to numeric data that were descriptively analyzed and used for further statistical analyses. To test normality, the Kolmogorov-Smirnov test was used. For comparing categorical data, Chi-squared tests, while for comparing continuous data, Mann-Whitney U tests were used. The level of statistical significance was set at 0.05. All statistical analyses were performed using jamovi version 2.2.5.

Results

CHARACTERISTICS OF THE RESPONDENTS

The questionnaire was sent to 125 physicians. Finally, a total of 104 respondents participated in the survey resulting a 83.2% response rate. Almost two-third of the neurologists included were aged between 41 and 60 years and were practicing for 11-30 years (61.6% and 61.5%, respectively). Most of the respondents (n = 102, 98.1%) were working in publicly funded healthcare, however, 38.5% of the surveyed neurologists (n = 40) also had a privately financed workplace. Forty-two neurologists (40.4%) considered themselves PD specialists. Detailed characteristics of the participants can be found in **Table 1**.

CHARACTERISTICS OF WORKPLACES

A total of 102 neurologists (98.1%) were working in the publicly funded healthcare. Of them, 15 respondents (14.7%) were working at a university clinic, while 53 (52.0%) and 34 (33.3%) participants in other hospitals and ambulatory neurology centers, respectively. Forty neurologists (38.5%) were practicing in both publicly and privately funded healthcare, while two respondents (1.9%) were working exclusively in the private care. Both publicly (n = 62, 60.8%) and privately funded workplaces of the respondents (n = 29, 69%) mainly lied in the capital city or a county seat. The portions of neurologists who were managing exclusively or mainly PD patients in public and private healthcare were 18.6% (n = 19) and 7.1% (n = 3), respectively. Most of the respondents (n = 76, 74.5%) were working in full-time (8 hours per day) at publicly funded workplaces, while part-time working of less than 4 hours was the most common in private healthcare (n = 33, 78.6%).

Considering the change in time weekly spent on outpatient specialty consultation during COVID-19

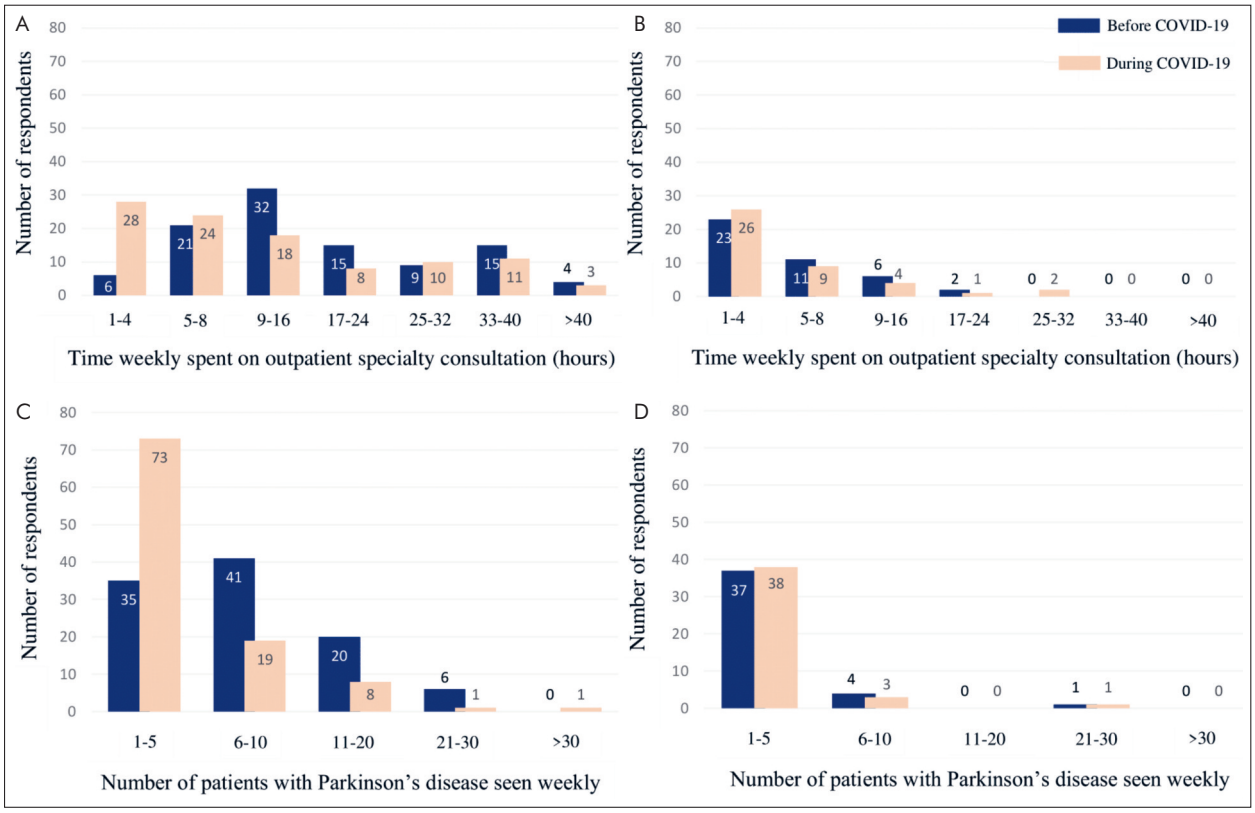


Figure 1. *Time surveyed neurologists weekly spent on outpatient specialty consultation at their publicly* **(A)** *and privately funded workplaces* **(B)** *and number of patients with Parkinson's disease they weekly saw in publicly* **(C)** *and privately funded healthcare* **(D)** *before and during COVID-19 pandemic*

pandemic, the portions of participants who reported a decrease, no change, and an increase were 51.0%, 45.1%, and 3.9% in publicly funded healthcare, while 11.9%, 78.6%, and 9.5% at privately funded workplaces, respectively ($p < 0.001$). Similarly, the portions of respondents who indicated a decrease, no change, and an increase in the number of PD patients seen weekly during the pandemic were 50.0%, 49.0%, and 1.0% at publicly funded workplaces, while 7.1%, 88.1%, and 4.8% in privately funded healthcare, respectively ($p < 0.001$, **Figure 1**). There was no significant difference in the change in time weekly spent on outpatient specialty consultation and the number of PD patients seen weekly between PD specialists and non-specialists.

KNOWLEDGE ON AND PRACTICE WITH TELEMEDICINE

Almost all respondents (n = 99, 95.2%) knew that teleconsultation and several other telemedicine procedures had been legally available in Hungary since March 2020. The most widely known telemedicine activities were prescription of medicines (n = 103, 99%), counselling and consultation (n = 100, 96.2%), and guiding patients (n = 87, 83.7%). These were also the procedures that had already been performed by the most **(Figure 2)**.

Electronic messages (e.g. short text message) were the most widely known telemedicine tools (n = 98, 94.2%) followed by phone call (n = 97, 93.3%) and e-mail (n = 96, 92.3%). Of these, phone call had already been used by most (n = 95, 91.3%) of the surveyed neurologists **(Figure 2)**. Higher portion of neurologists who were working in only publicly funded healthcare had already used phone calls for telemedical purposes compared to those who were employed at both publicly funded and private units (94.5% vs. 80.1%, $p = 0.017$), while video-based consultation had already been used more widely in private care (30.1% vs. 15.5%, $p = 0.001$). We detected no significant difference in knowledge and practice with telemedicine between PD specialists and non-specialists.

AVAILABILITY OF TELEMEDICINE

Comparing availability of telemedicine between publicly and privately funded healthcare, the lack of telemedicine tools at privately funded workplaces was significantly more frequently reported (2 vs. 5

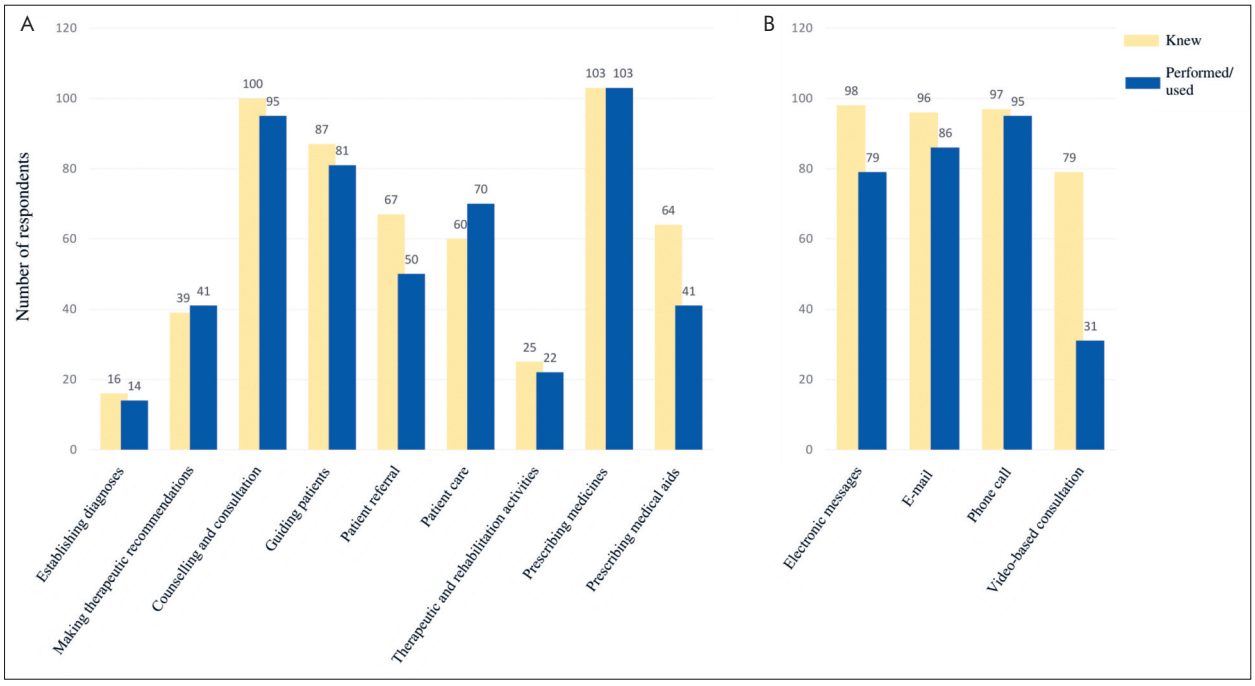


Figure 2. *Numbers of respondents who knew and performed or used the different telemedicine procedures* **(A)** *and tools* **(B)**

respondents, p = 0.012). Institutional protocols and patient information leaflets and informed consent forms for telemedicine are available in 41.2% and 24.5% of publicly funded workplaces, while in 26.2% and 14.3% of private care units **(Table 2)**.

Considering both general neurological and PD patients, higher portion of patients receive in-person care at privately funded workplaces (77.1% vs. 88.2%, p < 0.001 and 78.8% vs. 90.8%, p < 0.001, respectively), while phone calls are more frequently used in publicly funded healthcare (15.1% vs. 5.4%, p < 0.001 and 15.5% vs. 4.9%, p < 0.001, respectively).

TELEMEDICINE IN PD

Most of the respondents (n = 64, 61.5%) considered video-based consultation the most effective telemedicine tool in PD. However, almost all neurologists (n = 99, 95.2%) agreed with the statement of the International Parkinson's Disease and Movement Disorders Society that video-based consultation is the most effective way of telecare for PD patients[17]. The PDCS was known by 39.4% (n = 41) of the respondents.

Proportions of neurologists who considered tele-

Table 2. *Availability of telemedicine in publicly and privately funded healthcare*

	Publicly funded healthcare[a] (n=102)	Privately funded healthcare[a] (n=42)	p value[b]
Availability of telemedicine services	96 (94.1)	37 (88.1)	0.216
Availability of a telemedicine protocol	42 (41.2)	11 (26.2)	0.090
Availability of patient information leaflet and informed consent form for telemedicine	25 (24.5)	6 (14.3)	0.175
Availability of electronic messages	51 (50.0)	26 (61.9)	0.193
e-mail	76 (74.5)	32 (76.2)	0.832
phone call	90 (88.2)	32 (76.2)	0.068
video-based consultation	20 (19.6)	12 (28.6)	0.240
other	0 (0.0)	1 (2.4)	0.118
No telemedicine tools are available	2 (2.0)	5 (11.9)	0.012

[a]Data are n (%).
[b]For comparisons, Chi-squared tests were used.

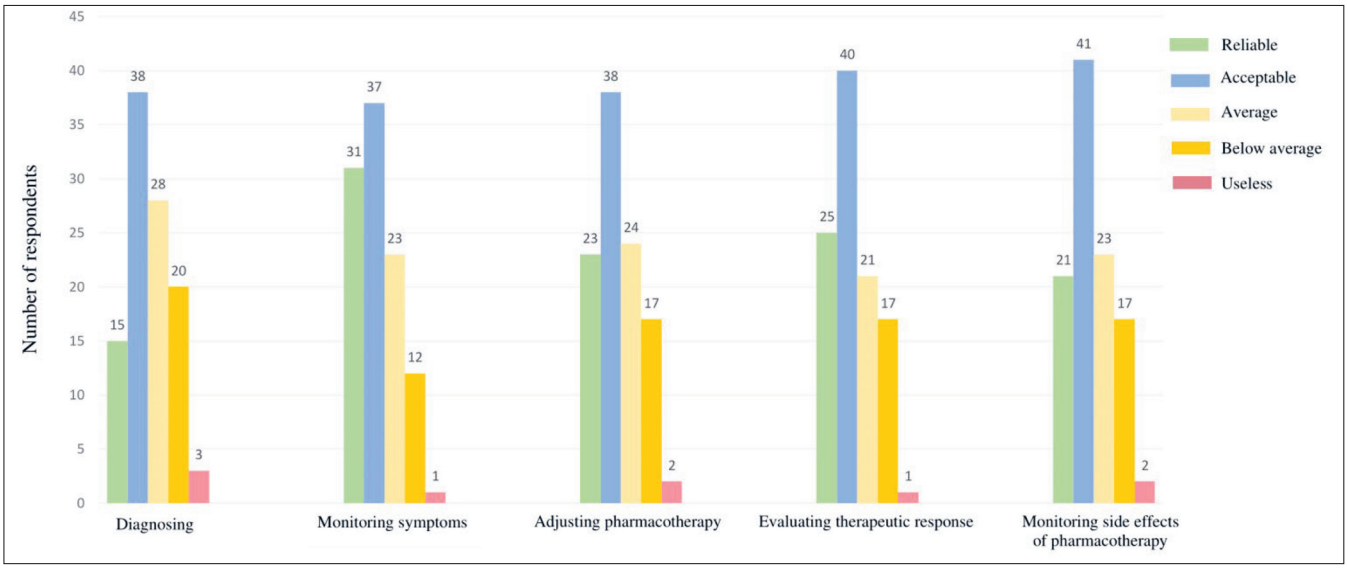


Figure 3. *Effectiveness of telemedicine in different areas of managing Parkinson's disease according to the opinion of the surveyed neurologists*

medicine reliable or acceptable in diagnosing PD, monitoring the symptoms of the disease, adjusting antiparkinsonian medications, evaluating therapeutic response, and identifying side effects of pharmacotherapy were 50.9% (n = 53), 65.4% (n = 68), 58.6% (n = 61), 62.5% (n = 65), and 59.6% (n = 62), respectively **(Figure 3)**.

Most respondents (n = 48, 46.2%) reported that 1-25% of PD patients reject telecare.

FUTURE OF TELEMEDICINE

Sixty-two neurologists (59.6%) were planning to improve telecare at their workplaces, while 65 respondents (62.5%) intended to improve video-based telemedicine services. Almost all participants (n = 90, 86.5%) supported the maintenance of telecare also after the pandemic.

Most neurologists (n = 50, 48.1%) reported that telemedicine and in-person care would be needed in equal proportions for managing PD patients after the pandemic, while 47 and 7 participants (45.2% and 6.7%) indicated that telecare would be needed less frequently and more often than in-person examinations, respectively.

According to the opinions of most neurologists, teleprocedures would be the most suitable for monitoring progression and symptoms of PD (n = 45, 43.3%) and evaluating the need for adjustments to antiparkinsonian pharmacotherapy (n = 34, 32.7%). After the pandemic, telemedicine in PD would be most widely used for adjusting pharmacotherapy (n = 69, 66.3%), evaluating therapeutic response (n = 63, 60.6%) and monitoring the symptoms and the progression of the disease (n = 62, 59.6%).

There was no significant difference in future plans with telemedicine between PD specialists and non-specialists.

Discussion

In parallel with the development of information technology and telecommunication tools, telemedicine has also undergone significant progress in recent years and become a key element of some healthcare areas[3, 4]. The applicability, clinical and economic importance of telemedicine and the possibilities for its further development have been the fields of intensive research. Using the search term "telemedicine", the PubMed database generates 47,721 hits between 1962 and 2021, half of which are from the last 4 years. In particular, the outbreak of the COVID-19 pandemic has led to a surge in research on telemedicine, with almost 15,000 publications on this topic in 2020 and 2021. Despite this extensive research activity on telemedicine, to the best of our knowledge, no studies have thus far revealed how COVID-19 pandemic changed the care of Hungarian PD patients.

Compared to the care before COVID-19, our survey showed that the time neurologists weekly spent on outpatient specialty consultation in publicly funded units decreased from the average 5-16

hours to 1-8 hours, thus halved on average during the pandemic. The number of PD patients had been seen weekly also parallelly decreased from the mostly reported 6-10 patients per week before COVID-19 to 1-5 PD subjects per week. This tendency is in line with a recent analysis of the Hungarian Central Statistical Office data on care provided under public insurance showing that the number of outpatient medical examinations fell by 28% on average (10-41%) during the waves of the COVID-19 pandemic. Considering neurological care only, this analysis detected a 17% decrease[18]. Based on these and our data, the publicly funded management of patients with PD seems to be among the areas most affected by COVID-19.

In contrast, the present survey did not detect considerable decrease in the time surveyed neurologists weekly spent on outpatient specialty consultation at their private workplaces. The number of PD patients seen weekly in privately funded healthcare also remained almost unchanged. According to these findings, the role of patient care provided under private funding seems to become important in maintaining the continuous management of PD patients during the pandemic. However, regular visits at private offices can be a high financial burden for patients or for some of them, so completely impossible. Therefore, increased use of private care alone, which is even not shown by our data, cannot be a resolution to the difficulties caused by the pandemic.

Almost unchanged number of patients have been managed in privately funded healthcare compared to public care can be partly explained by the fact that several restrictions were introduced at publicly funded units that primarily had to focus on the care of patients infected with COVID-19 during the waves of the pandemic. In addition, according to our data, a higher portion of PD patients were able to receive in-person care at private offices. Although PD patients have been shown to be mostly satisfied with virtual care[19], it has also been found that they still prefer in-person visits to telehealth appointments or at least the combination of in-person and telecare[20]. Furthermore, in private offices, twice as many PD patients were managed via video-based consultation, a highly effective tool feasible for assessing all main motor symptoms of PD with the exemption of rigidity and postural instability[17, 21], than in public healthcare where telephone was the almost exclusive telemedical tool. This is in line with the results of another nationwide survey from Norway[22], although a recent review has found that video-based consultation has several advantages over telephone including fewer medication errors, greater diagnostic accuracy, and improved decision-making accuracy[23]. Some other studies have also shown that patients prefer not just in-person care but also video over phone calls[24, 25]. Considering all of the above, improving video-based teleprocedures could help the maintenance of a more secure delivery of care for PD patients in special situations such as the COVID-19 pandemic. This might have been recognized by 62.5% of the respondents who plan to improve video-based services at their workplaces. The more frequent use of video-based consultation in private healthcare can be partly explained by financial reasons because video-based consultation requires a more extensive technical background than phone calls, therefore, its installations and maintenance are more expensive. In addition, telemedicine protocols, if they are available, may differ in public and private health care. Last but not least, video-based care is more time-consuming than phone calls because it may take longer to establish connection, technical problems may occur, patient education on use may be necessary, and activities that cannot be done over phone call (e.g. monitoring of symptoms of patients with PD) can also be performed. As private healthcare is generally more predictable and the number of patients managed per unit of time is lower, the opportunity for providing video-based care is higher.

Considering that telemedicine was made legally available only after the outbreak of the pandemic in most areas of Hungarian neurology care also including movement disorders, and in-person visits were therefore the almost exclusive ways of patient management prior to COVID-19, we found that telemedicine use increased by about 1,000%-2,000% both in general neurology and PD care. Compared to international data[10–13], Hungary is among the countries where use of teleneurology showed the greatest increase.

A surprising result of our study was that although teleprocedures have been increasingly used in the management of neurology patients, the availability of both institutional protocols for telemedicine and patient information leaflets and informed consent forms was found poor. However, regularly updated protocols could improve the quality of telecare, while informing and educating patients could help to increase the acceptance and use of telemedicine services among PD patients. In addition, the PDCS, a freely available, valid tool, was known only by 39.4% of the respondents. However, incorporation of such scales into everyday telemedicine

practice could help the effective and reliable follow-up of disease progression and symptomatic changes due to treatment[16, 26].

The most widely performed telemedical procedure was the prescription of medications. According to this, telemedicine has played an important role in maintaining the uninterrupted supply of medicines for patients. Monitoring progression and symptoms of PD and evaluating the need for adjustments to antiparkinsonian pharmacotherapy are issues of PD care that were generally managed via in-person visits before the pandemic. The surveyed neurologists also found telemedicine reliable enough to perform these activities and would use teleprocedures for these purposes even after the pandemic. However, several other important areas of PD care such as diagnosing the disease and following side effects of treatment have also been affected by COVID-192[27]. Only a few of our respondents considered remote procedures acceptable enough for these activities, and another analysis also found teleconsultations to be better suited for follow-ups than for new referrals[22]. Therefore, among others, diagnosing seems to be a field on which telemedicine needs to be improved.

Our study has several strengths. First, because our questionnaire was released on a nation-wide level, a relatively high number of neurologists representing a wide range of age and time of practicing from different parts of the country and types of workplaces could be surveyed. Because the number of practicing neurologists is estimated about 750 in Hungary[28], our study population represented 13.9% of active neurological healthcare providers. In addition, our survey could evaluate all levels of care in both publicly and privately funded healthcare[29]. Furthermore, to provide as complete picture of telecare in PD as possible, our questionnaire was designed to study several aspects of telemedicine. Finally, our survey was released after three waves of COVID-19, therefore, included neurologists had plenty of experience with managing PD under conditions of pandemic and telecare.

To conclude, the COVID-19 pandemic has had a major impact on the care of patients with PD in Hungary. Telemedicine has mitigated the detrimental effects of the pandemic on the management of PD in many areas, however, further developments and regular training of neurologists and their patients would be essential to make telemedicine an even more reliable component of care for PD patients during and beyond the possible further waves of the pandemic.

FINANCIAL DISCLOSURE

DP was supported by the ÚNKP-21-4 New National Excellence Program of the Ministry for Innovation and Technology from the Source of the National Research, Development and Innovation Fund for conducting this study and preparing the manuscript. EJ reported no financial disclosure. JJ received <1000 EUR consultation fees from Hungarian subsidiaries of UCB, Richter, and Gerot. Regarding this study, the author did not receive any corporate funding. NK received <1000 EUR consultation fees from Hungarian subsidiaries of Medtronic, Boehringer Ingelheim, Novartis, GlaxoSmithKline, UCB, Krka, and AbbVie. Regarding this study, the author received a research grant from OrionPharma for conducting the study and preparing the manuscript.

CONFLICT OF INTEREST

Norbert Kovács received a research grant from OrionPharma for conducting the study and preparing the manuscript.

Funding: This study was supported by the ÚNKP-21-4 New National Excellence Program of the Ministry for Innovation and Technology from the Source of the National Research, Development and Innovation Fund, a research grant from OrionPharma, the Hungarian Brain Research Program (2017-1.2.1-NKP-2017-00002), NKFIH EFOP-3.6.2-16-2017-00008, NKFIH SNN125143, and NKFIH EFOP-3.6.1.-16-2016-00004 government-based funds. Our research was partly financed by the Thematic Excellence Program 2021 Health Sub-program of the Ministry for Innovation and Technology in Hungary, within the framework of the EGA-16 project of the University of Pécs.

AUTHOR ROLES

1. Research project: A. Conception B. Organization C. Execution

2. Statistical Analysis: A. Design B. Execution C. Review and Critique

3. Manuscript: A. Writing of the first draft B. Review and Critique

DP: *1, 2, 3;* EJ: *1B, 2C, 3B;* JJ: *1A, 2C, 3B;* NK: *1, 2, 3*

REFERENCES

1. *Brown EG, Chahine LM, Goldman SM, et al*. The Effect of the COVID-19 Pandemic on people with Parkinson's disease. J Parkinsons Dis 2020;10(4):1365-77. https://doi.org/10.3233/JPD-202249
2. *Fearon C, Fasano A*. Parkinson's disease and the COVID-19 pandemic. J Parkinsons Dis 2021;11(2):431-44. https://doi.org/10.3233/JPD-202320
3. *Wilson LS, Maeder AJ*. Recent directions in telemedicine: Review of trends in research and practice. Healthc Inform Res 2015;21(4):213-22. https://doi.org/10.4258/hir.2015.21.4.213
4. *Schneider RB and Biglan KM*. The promise of telemedicine for chronic neurological disorders: the example of Parkinson's disease. Lancet Neurol 2017;16(7):541-51. https://doi.org/10.1016/S1474-4422(17)30167-9
5. *Bhaskar S, Bradley S, Chattu VK, et al.* Telemedicine Across the Globe-Position Paper From the COVID-19 Pandemic Health System Resilience PROGRAM (REPROGRAM) International Consortium (Part 1). Front Public Health 2020; 8-:556720. https://doi.org/10.3389/fpubh.2020.556720
6. *Gyorffy Z, Bekasi S, Szathmari-Meszaros N, et al.* Possibilities of telemedicine regarding the COVID-19 pandemic in light of the international and Hungarian experiences and recommendations. Orv Hetil 2020;161(24):983-92. https://doi.org/10.1556/650.2020.31873
7. *García-Azorín D, Seeher KM, Newton CR, et al*. Disruptions of neurological services, its causes and mitigation strategies during COVID-19: a global review. J Neurol 2021;268(11):3947-60. https://doi.org/10.1007/s00415-021-10588-5
8. *Smith AC, Thomas E, Snoswell CL, et al.* Telehealth for global emergencies: implications for coronavirus disease 2019 (COVID-19). J Telemed Telecare 2020,26(5):309-13. https://doi.org/10.1177/1357633X20916567
9. *Hong YR, Lawrence J, Williams D Jr, et al*. Population-level in-terest and telehealth capacity of US hospitals in response to COVID-19: cross-sectional analysis of Google search and national hospital survey data. JMIR Public Health Surveill 2020;6: e18961. https://doi.org/10.2196/18961
10. *Shivkumar V, Subramanian T, Agarwal, et al.* Uptake of telehealth in Parkinson's disease clinical care and research during the COVID-19 pandemic. Parkinsonism Relat Disord 2021;86:97-100. https://doi.org/10.1016/j.parkreldis.2021.03.032
11. *da Silva Aquino ER, Domingues RB, Mantese CE, et al.* Telemedicine use among neurologists before and during COVID-19 pandemic. Arq Neuropsiquiatr 2021;79(7):658-64. https://doi.org/10.1590/0004-282x-anp-2020-0488
12. *Demaerschalk BM, Blegen RN, Ommen SR*. Scalability of Telemedicine Services in a Large Integrated Multispeciality Health Care System During COVID-19. Telemed J E Health 2021;27(1):96-8. https://doi.org/10.1089/tmj.2020.0290
13. *Duncan C, Macleod AD*. Video consultations in ordinary and extraordinary times. Pract Neurol 2020;20(5):396-403. https://doi.org/10.1136/practneurol-2020-002579
14. Decree 33/2020 (IX.16.) of the Ministry of Human Resources of Hungary. Available from https://www.hbcs.hu/uploads/jogszabaly/3220/fajlok/33_2020_IX_16_EMMI_rendelet.pdf. Downloaded on May 7, 2021.
15. *Almathami HKY, Win KT, Vlahu-Gjorgievska E.* Barriers and facilitators that influence telemedicine-based, real-time, online consultation at patients' homes: systematic literature review. J Med Internet Res 2020;22(2):e16407. https://doi.org/10.2196/16407
16. *Martinez-Martin P, Radicati FG, Rodriguez Blazquez C, et al*. Extensive validation study of the Parkinson's disease composite scale. Eur J Neurol 2019;26(10):1281-8.
17. *Achey M, Aldred JL, Aljehani N, et al.* The past, present, and future of telemedicine for Parkinson's disease. Mov Disord 2014;29(7):871-83. https://doi.org/10.1002/mds.25903
18. Qubit, Egyetlen ábrán, hogyan szorította háttérbe a járóbeteg-ellátást 2020-ban a járvány. Available from https://qubit.hu/2022/02/21/egyetlen-abran-hogyan-szoritotta-hatterbe-a-jarobeteg-ellatast-2020-ban-a-jarvany. Downloaded on 26 February, 2022.
19. *Korn RE, Shukla AW, Katz M, et al.* Virtual visits for Parkinson disease: A multicenter noncontrolled cohort. Neurol Clin Pract 2017;7(4):283-95. https://doi.org/10.1212/CPJ.0000000000000371
20. *Qiang JK, Marras C.* Telemedicine in Parkinson's disease: A patient perspective at a tertiary care centre. Parkinsonism Relat Disord 2015;21(5):525-8. https://doi.org/10.1016/j.parkreldis.2015.02.018
21. *Larson DN, Schneider RB, Simuni T*. A new era: the growth of video-based visits for remote management of persons with Parkinson's disease. J Parkinsons Dis 2021;11(s1): S27-S34. https://doi.org/10.3233/JPD-202381
22. *Kristoffersen ES, Sandset EC, Winsvold BS, et al*. Experiences of telemedicine in neurological out-patient clinics during the COVID-19 pandemic. Ann Clin Transl Neurol 2021,8(2):440-7. https://doi.org/10.1002/acn3.51293
23. *Rush KL, Howlett L, Munro A, et al.* Videoconference compared to telephone in healthcare delivery: A systematic review. Int J Med Inform 2018;118:44-53. https://doi.org/10.1016/j.ijmedinf.2018.07.007
24. *Paras M, Leyva O, Berthold T, et al*. Videoconferencing medical interpretation: the results of clinical trials. Oakland, California: Health Access Foundation; 2002.
25. *Saint-Louis L, Friedman E, Chiasson E, et al.* Testing new technologies in medical interpreting. Somerville, Massachusetts: Cambridge Health Alliance; 2003.
26. *Pinter D, Martinez-Martin P, Janszky J, et al*. The Parkinson's disease composite scale is adequately responsive to acute levodopa challenge. Parkinsons Dis 2019;2019:1412984. https://doi.org/10.1155/2019/1412984
27. *Lau YH, Lau KM, Ibrahim NM*. Management of Parkinson's disease in the COVID-19 pandemic and future perspectives in the era of vaccination. J Mov Disord 2021;14(3):177-83. https://doi.org/10.14802/jmd.21034
28. *Bereczki D, Csiba L, Komoly S, et al.* Endangered future: education and replacement of specialists in neurology – a survey in Hungary, 2010. Ideggyogy Sz 2010;63(7-8):259-65.
29. *Bereczki D, Csiba L, Komoly S, et al*. The carrier model of neurology in Hungary: a proposal for the solution until 2020. Ideggyogy Sz 2011;64(11-12):377-84.

A CASE STUDY OF ACUTE OROPHARYNGEAL PALSY CONCOMITANT WITH DIABETIC KETOACIDOSIS

Judit LANTOS[1, *], Zsanett BARTA[2, *], Albert NAGY[1], Rita VINCZE[1], Kálmán FÜLE[1], Katalin BIHARI[1]

[1]Bács-Kiskun County Hospital, Neurology and Stroke Department, Kecskemét
[2]University of Szeged, Department of Surgery, Szeged
*Judit Lantos and Zsanett Barta equally worked on this article, so both are first authors.

English | https://doi.org/10.18071/isz.75.0275 | www.elitmed.hu

Acute oropharyngeal palsy is a rare variant of Guillain-Barré syndrome. In our study we present the case of a 63-year-old man with general symptoms who was diagnosed with diabetic ketoacidosis and prescribed insulin therapy. Two weeks later, the patient complained of paraesthesia of the perioral region and the tip of the tongue, dysphagia, and dysarthria. These symptoms were initially thought to be complications of the patient's type-1 diabetes. Due to rapidly developing paraparesis, the patient became bedridden. Clinical symptoms, cerebrospinal fluid analysis and a nerve conduction study resulted in a diagnosis of acute oropharyngeal palsy, a variant of Guillain-Barré syndrome. After five consecutive days of intravenous immunoglobulin treatment, neurological symptoms improved and the need for insulin ceased. One year later, the patient's only remaining neurological symptom was loss of tendon reflexes in the lower extremities. Furthermore, the patient's blood glucose level was normal without the use of medications or a special diet.
Here, we report that oropharyngeal palsy can co-occur with diabetic ketoacidosis, and that immuntherapy is effective in treating both oropharyngeal palsy and type-1 diabetes. To our knowledge, this is the first description of a patient presenting with acut oropharyngeal palsy concomitant with diabetic ketoacidosis.

Keywords: *oropharyngeal palsy, diabetes, ketoacidosis, immuntherapy*

AKUT OROPHARYNGEALIS PARESISSEL JÁRÓ DIABETESES KETOACIDOSIS – ESETTANULMÁNY

Lantos J, MD; Barta Zs, MD; Nagy A, MD; Vincze R, MD; Füle K, MD; Bihari K, PhD

Ideggyogy Sz 2022;75(7–8):275–278.

Az akut oropharyngealis paresis a Guillain–Barré-szindróma ritka variánsa. Munkánkban egy 63 éves férfi beteg esetét mutatjuk be, akinél az általános tünetek hátterében a kivizsgálás diabeteses ketoacidosist igazolt, emiatt inzulinterápiát indítottak. Két héttel később a beteg perioralis és nyelvcsúcsi zsibbadásról, dysphagiáról panaszkodott, beszéde dysarthriás lett. Kezdetben ezeket a panaszokat a beteg frissen diagnosztizált 1-es típusú cukorbetegségének tulajdonították. A gyorsan kialakuló paraparesis miatt a beteg mozgásképtelenné vált.
A klinikai kép, a liquor és az elektrofiziológiai vizsgálat alapján akut oropharyngealis paresis igazolódott. Öt egymást követő napon át alkalmazott intravénás immunglobulin-terápia hatására a neurológiai tünetek javultak, az inzulinigény megszűnt. Egy évvel később egyedüli neurológiai eltérés az alsó végtagi areflexia volt. A beteg vércukorszintje normáltartományban volt diéta és gyógyszeres kezelés nélkül is.
Az akut oropharyngealis paresis együtt járhat diabeteses ketoacidosissal, s mindkettő kezelésében hatékony lehet az immunglobulin-terápia. Tudomásunk szerint ez az első esetleírás az irodalomban, ahol az oropharyngealis paresis diabeteses ketoacidossal szövődött.

Kulcsszavak: *oropharyngealis paresis, diabetes, ketoacidosis, immunterápia*

Correspondent: Dr. LANTOS Judit, Bács-Kiskun County Hospital, Neurology and Stroke Department; 6000 Kecskemét, Szitakötő u. 13. Telefon: 06-70-249-9194, e-mail: lantos.judith@gmail.com
https://www.orcid.org/0000-0001-5814-8030

Érkezett: 2021. május 31. Elfogadva: 2021. augusztus 1.

There are approximately 0.6-4 cases of Guillain-Barré syndrome (GBS) per 100,000 people in Europe and North America[1]. GBS is a dysimmune neuropathy and the most widely accepted theory of its pathogenesis is molecular mimicry. According to this theory, antibodies against lipooligosaccharides on microorganisms that have entered the human body (e.g. *Campylobacter jejuni*) are immunologically cross-reactive with gangliosides on the cell membrane of human cells[1–3]. This immunological cross-reaction leads to the development of acute motor axonal neuropathy (AMAN) in Asia and acute inflammatory demyelinating polyneuropathy (AIDP) in Europe and North America, where AMAN is less common[1, 4]. The most common clinical symptoms of GBS are an ascending pattern of paraesthesia, weakness, and areflexia. The diagnosis of GBS is supported by albuminocytologic dissociation in the cerebrospinal fluid and electrophysiological studies. The disease is self-limited; after 4 weeks, progression stops and a slow improvement begins. GBS is treated with plasma exchange or intravenous administration of immunoglobulin (IVIG).

The first variant of GBS to be described was Miller-Fisher syndrome (MFS), which is characterized by the triad of ophthalmoplegia, ataxia, and areflexia without any weakness. MFS accounts for 5-10% of GBS cases in Europe and the USA and about 25% of GBS cases in Eastern Asia. The second most common form of GBS is pharyngeal-cervical-brachial motor variant (PCB), which is characterized by ptosis and facial, pharyngeal, and neck muscle weakness. PCB accounts for approximately 2-3% of GBS cases[1].

Extensive research on anti-ganglioside antibodies has led to the identification of many more diseases that are related to GBS. One such example is acute oropharyngeal palsy (AOP), which is associated with the GQ1b and GT1a antibodies, with GT1a being the dominant antibody[5]. AOP is characterized by oropharyngeal palsy with a loss of tendon reflexes, hypotonic paresis, dysphagia, dysarthria, and perioral paraesthesia[5]. The classification of AOP has been debated in the literature; some authors believe that it is a sub-variant of MFS, while others believe it to be a more limited form of PCB weakness[6]. Prior to our study, the incidence of acute oropharyngeal palsy (AOP) was unknown.

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus that is caused by absolute insulin deficiency. This is typical in type-1 diabetes and is due to the production of antibodies against B-cells of the islets of Langerhans in the pancreas. The symptoms are hyperglycaemia, metabolic acidosis, and an increase in ketone bodies[7]. In this study, we show that AOP can co-occur with DKA. To our knowledge, this is the first time a case of AOP concomitant with DKA has been published.

Case report

A 63-year-old man was admitted to an internal medicine department with general symptoms, including a 6 kg weight loss, general weakness, and a loss of appetite. His medical history included only hypertension. The patient was participating in daily bodybuilding and other active training. He had no complaints of diarrhoea or upper respiratory symptoms. A culture for enteral bacteria was negative. The first internal medical examination revealed leucocytosis (17.88 g/L), hyperglycaemia (8-9 mmol/L), glycosuria (50-150 mg/dL) and metabolic acidosis. The patient was then put on insulin treatment. Due to his general symptoms, a tumour screening was also performed, but the chest X-ray was negative and the abdominal computerized tomography (CT) scan revealed only splenomegaly without any malignancies. In addition, a colonoscopy with a polypectomy from the ileum was performed, and histology identified aspecific inflammation with lymphoid hyperplasy.

Two weeks later, the patient complained of paraesthesia of the perioral region and the tip of the tongue, dysphagia, and dysarthria. These new symptoms were initially thought to be a complication of the patient's type-1 diabetes, but the symptoms had progressed faster than usual. Paraesthesia and a burning pain on both soles and calves began to develop, as did progressive leg weakness. Brain and lumbar spine magnetic resonance imaging (MRI) after the first neurological examination did not show evidence of a neurological disorder. At this time, the patient was admitted into our neurological department.

At the patient's admission, we found paraesthesia of the perioral region and the tip of the tongue, dysphagia, dysarthria, and left side deviation of the tongue and hypotonic paraparesis, general areflexia, and acroparaesthesia. MFS and PCB were excluded due to the absence of ophthalmoplegia, ptosis, arm and neck weakness, and armataxia. Based on the literature, it was supposed that our patient had acut oropharyngeal paresis, the rare variant of GBS **(Table 1)**.

Analysis of the cerebrospinal fluid (CSF) after a lumbar puncture revealed albuminocytologic dissociation (2.32 g/l protein; 6 lymphocytes; 0 granulo-

Table 1. *Clinical features of Guillain-Barré syndrome variants*

Clinical features	MFS	PCB	AOP	Our patient
Ophthalmoplegia	+	–	–	–
Ataxia	+	–	–	–
Areflexia	+	–	+	+
Upper limb weakness	–	+	–	–
Lower limb weakness	–	–	+	+
Ptosis	–	+	–	–
Neck flexor muscle weakness	–	+	–	–
Dysarthria	–	+	+	+
Dysphagia	–	+	+	+
Perioral paraesthesia	–	–	+	+
Limb paraesthesia	–	–	+	+

MFS: Miller-Fisher syndrome, PCB: pharyngeal-cervical-brachial motor variant, AOP: acut oropharyngeal palsy

cytes). Electroneurography (ENG) showed serious temporal dispersion without conduction block in the lower extremities and all motor nerves showed prolonged distal latency (125%-190%) and slow conduction velocity (90%-80%). F wave could be found only on the right ulnar nerve. Electromyography showed high voltage-positive sharp waves in every needle position. Given the combined results of these examinations and the symptoms of the patient, he was diagnosed with AOP, the rare variant of GBS. Results of the CSF analysis showed very high global protein and albumin levels, as well as high levels of IgG. No abnormalities in anti-ganglioside antibodies were found in the serum, however the typical GTla ganglioside analysis is unable to be performed in our country.

After the first course of intravenous immunoglobulin (IVIG) treatment (0.4 g/kg/day for 5 consecutive days), the neurological symptoms of the patient gradually improved. After the second course of IVIG treatment, the patient no longer needed insulin. After 6 weeks of rehabilitation, the patient's motor function improved and he was able to walk without any aid. One year later, the only remaining deficit was a loss of tendon reflexes in the lower extremities. Furthermore, his blood glucose level was normal without the use of medications or a special diet.

Discussion

Prior to our study, the incidence of AOP had not been defined in the literature. *O'Leary* et al. described 3 patients with AOP in the only known case series on AOP[5]. Given the rare occurrence of AOP, its classification is debated in the literature. Some authors have classified it as a sub-variant of MFS, while others classify it as a more limited form of PCB weakness[4].

In our case, a correct and rapid diagnosis was difficult due to several factors. First, the patient's AOP began with general symptoms, such as general weakness and a loss of appetite and weight, which led to a screening for malignancy. In addition, these symptoms could also have been due to intestinal infection leading to aspecific terminal ileitis. In the cases described by O'Leary et al., the patients' first symptoms were neurological[5]. Second, the first neurological symptoms of GBS are typically numbness and weakness in the limbs but in our patient, the initial symptoms were paraesthesia of the perioral area and the tip of the tongue, dysphagia, and dysarthria. In all three patients described by O' Leary et al., the patients' first symptoms were also central[5]. The third factor was that our patient was newly diagnosed with type-1 diabetes, and the peripheral neurological symptoms were thought to be due to complications from diabetes. Type-1 diabetes was not present in the cases published by O'Leary et al[5]. The co-occurrence of GBS and DKA is very rare, and only a small number of case reports can be found in the literature[8, 9]. *Rouanet-Larriviere* et al. hypothesized that GBS and DKA have common autoimmune pathogeneses that are caused by the same microorganism, such as a virus[10, 11].

We believe that the trigger agent entered the body via the gastrointestinal tract in our patient, as the colonoscopy revealed aspecific terminal ileitis with lymphoid hyperplasia.

The high level of IgG and global protein that was detected in our patient's CSF supported the hypothesis that immunological processes were responsible for the disease, despite the fact that tests for specific ganglioside antibodies were negative. In the AOP

cases published by O'Leary et al., there were high levels of GQ1b and GTla ganglioside antibodies[5]. In a report of the co-occurrence of GBS and DKA by *Kanemasa* et al., tests for ganglioside antibodies, including GQ1b and GT1b, were also negative[9]. In the publication of *de Bruyn,* among 8 patients with anti-GQ1b antibodies there was no AOP[12].

In our patient's case, IVIG therapy not only improved the neurological symptoms, but completely ameliorated DKA. This adds further support to the hypothesis that the diseases share a common autoimmune background. IVIG therapy had a similar effect in other published cases of GBS and DKA[8, 9], but, to our knowledge, our report is the first to show that IVIG therapy is successful in treating AOP and DKA.

Conclusion

In our patient AOP began with paraesthesia of the perioral region and the tip of the tongue, dysphagia, and dysarthria, and the GBS-like symptoms were developing later. Our report shows that AOP can co-occur with DKA. Given the common pathological background of these two diseases, IVIG therapy is effective in treating both AOP and type-1 diabetes.

REFERENCES

1. *Dimachkie M, Barohn R.* Guillain-Barré syndrome and variants. Neurol Clin 2013;31(2):491-510. https://doi.org/10.1016/j.ncl.2013.01.005
2. *Alter M*. The epidemiology of Guillain-Barré syndrome. Ann Neurol 1990;27:S7-S12. https://doi.org/10.1002/ana.410270704
3. *Zhang G, Li Q, Zhang R, et al*. Subtypes and prognosis of Guillain-Barré syndrome in southwest China. PloS One 2015;10(7): e0133520 https://doi.org/10.1371/journal.pone.0133520
4. *Yuki N*. Guillain-Barré syndrome and anti-ganglioside antibodies: a clinician-scientist's journey. Proc Jpn Acad Ser B Phys Biol Sci 2012;88(7):299-326. https://doi.org/10.2183/pjab.88.299
5. *O'Leary C, Veitch J, Durward W, et al.* Acute oropharyngealpalsy is associated with antibodies to GQ1b and GT1a gangliosides. J Neurol Neurosurg Psychiatry 1996;61:649-51. https://doi.org/10.1136/jnnp.61.6.649
6. *Hughes R, Cornblath D.* Guillain-Barré syndrome. Lancet 2005;366(9497):1653-66. https://doi.org/10.1016/S0140-6736(05)67665-9
7. *Trachtenbarg D*. Diabetic ketoacidosis. Am Fam Physician 2005;71:1705-14.
8. *Fujiwara S, Oshika H, Motoki K, et al.* Diabetic ketoacidosis associated with Guillain-Barré syndrome with autonomic dysfunction, Intern Med 2000;39(6):495-8. https://doi.org/10.2169/internalmedicine.39.495
9. *Kanemasa Y, Hamamoto Y, Iwasaki Y, et al.* A case of diabetic ketoacidosis associated with Guillain-Barré syndrome. Intern Med 2011;50:2201-05. https://doi.org/10.2169/internalmedicine.50.5553
10. *Rouanet-Larriviere M, Vital C, Arne P, et al*. Guillain-Barré syndrome occurring in two women after ketoacidosic comatose state disclosing an insulin-dependent diabetes mellitus. J Peripher Nerv Syst 2000;5:7-31.
11. *Niklasson B, Hérnfeldt B, Lundman B.* Could myocarditis, insulin dependent diabetes mellitus, and Guillain-Barré syndrome be caused by one or more infectious agents carried by rodents? Emerg Infect Dis 1998;4:187-93. https://doi.org/10.3201/eid0402.980206
12. *de Bruyn A, Poesen K, Bossuyt X, et al.* Clinical spectrum of the anti-GQ1b antibody syndrome: a case series of eight patients. Acta Neurol Belg 2019;119;29-36. https://doi.org/10.1007/s13760-019-01093-8

THE PEAK LATENCY PROLONGATION OF THE BLINK REFLEX IN A PATIENT WITH TRIGEMINAL NEURALGIA OF MECKEL'S CAVE MASS

Bon D. KU[1], Hyun Young SHIN[2]

[1]Department of Neurology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea
[2]Department of Health and Hygiene, Songpa Public Health Center, Seoul, South Korea

English | https://doi.org/10.18071/isz.75.0279 | www.elitmed.hu

Background and aims – The blink reflex test of the trigeminal nerve can provide valuable information about lesions site. However it may not find small compressive lesions.
Case report – We observed peak latency prolongation of the blink reflex test in a patient with trigeminal neuralgia caused by a small Meckel's cave mass, in whom the onset latency was normal.
Conclusion – We suggest peak latency of the blink reflex might be a valuable aid for discerning small mass in patients with trigeminal neuralgia. This is the first case report of compressive trigeminal neuralgia showing peak latency prolongation of the blink reflex test.

Keywords: *trigeminal neuralgia, blink reflex, peak latency, Meckel's cave mass*

A PISLOGÁSI REFLEXCSÚCS LATENCIÁJÁNAK MEGNYÚLÁSA EGY MECKEL-BARLANG-TERIME KÖVETKEZTÉBEN KIALAKULÓ TRIGEMINUSNEURALGIA ESETBEN
Ku BD, MD; Shin HY, MD
Ideggyogy Sz 2022;75(7–8):279–283.

Háttér és cél – A trigeminus ideget vizsgáló pislogási-reflex-teszt hasznos információt nyújthat a laesiók helyéről. Előfordulhat azonban, hogy kis kompressziós elváltozások kimutatása nem lehetséges.
Esetismertetés – Megfigyeltük a pislogási reflexcsúcs latenciájának megnyúlását olyan trigeminusneuralgiában szenvedő betegnél, akinél egy kis Meckel-barlang-terime volt e tünetekért felelős, és a kezdeti (onset) latencia (onset) normális volt.
Következtetés – Vizsgálatunk alapján a pislogási reflexcsúcs latenciájának kimutatása értékes segítség lehet azoknál a trigeminusneuralgiában szenvedő betegeknél, akiknél valamilyen kis terime okozza a kompressziót. Ez az első esetbemutatás, ami kompressziós trigeminusneuralgiában a pislogási reflexcsúcs latenciájának megnyúlását igazolta.

Kulcsszavak: *trigeminusneuralgia, pislogási reflex, reflexcsúcs-latencia, Meckel-barlang terime*

Correspondent: Bon D. KU, MD, Department of Neurology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea 25, Simgok-ro 100beon-gil, Seo-gu, Incheon 22711, South Korea.
Phone: +82-32-290-3792, fax:+82-32-290-3879, mobile:+82-10-3038-5231, e-mail:bondku34@cku.ac.kr
https://doi.org/0000-0003-4324-6513

Érkezett: 2020. december 26. Elfogadva: 2021. május 16.

The blink reflex test can provide valuable information about the peripheral and central trigeminopathy. However, this test may not reveal quite small compressive lesions[1]. The term blink reflex latency means the response of the fastest conduction fiber of the trigeminal nerve[2]. Clinicians used the conventional onset latency measurement of the blink reflex, however, the exact onset latency measurement is sometimes difficult especially when the nerve potential fluctuates at baseline,

which occurs in many pathological conditions[3]. Recently, we observed a peak latency prolongation of the blink reflex test in a patient with trigeminal neuralgia caused by a small Meckel's cave mass, whereas the onset latency of blink reflex was unremarkable. As far as we know, this is the first case report of compressive trigeminal neuralgia resulting peak latency prolongation of the blink reflex test.

Case report

A 45-year-old man visited our clinic due to experiencing aggravated left cheek pain for over 6 months. He complained of having experienced spontaneous, left-side lancinating pain in the maxillary and mandibular areas. The patient had an unremarkable medical history. Upon examination there was no sign of sensory deficit in the trigeminal nerve dermatomes. Laboratory examinations were also unremarkable. To evaluate his trigeminal nerve function, we administered the blink reflex test to the patient according to the previously reported guidelines[3]. The active surface electrode was placed on the both sides of the belly of the orbicularis oculi. An isolated ground electrode was attached on his mid-forehead. We placed the reference on the side of his nose. We applied electrical stimulation over the supraorbital notch, using 15 mA intensity and 0.1 msec duration. To prevent habituation, we applied each stimulus 5 time set intervals of 2 sec. The electromyographic (EMG) settings for testing of the blink reflex are as follow: Frequency, 8ep Speed, 5 msec/div; and Gain, 50-100 μV/div. The blink reflex was tested with Sierra Wave from Cadwell (USA). During the test the room temperature was kept at 22~26 . The blink reflex response latencies to supraorbital nerve stimulation on both sides were recorded.

The patient's blink reflex test results showed no definite abnormalities in the conventional onset latency measurement (left side onset latency of R_1, 10.00 msec; right side onset latency of R_1, 10.05 msec; normal value: 10.6±2.5 msec, **Figure 1** & **Table 1**). However, compared to the right side, the waveform of the left side blink reflex showed a fluctuating baseline potential and amplitude variation in the R_1. When we measured the R_1 peak latency, the left side R_1 peak latency showed greater delay than the right side (left side peak latency of R_1, 16.52 msec; right side peak latency of R_1, 13.54 msec; left-right side differences of R_1 peak latency, 2.98 msec; **Figure 1** & **Table 1**). This peak latency differentiation of the blink reflex suggested a possi-

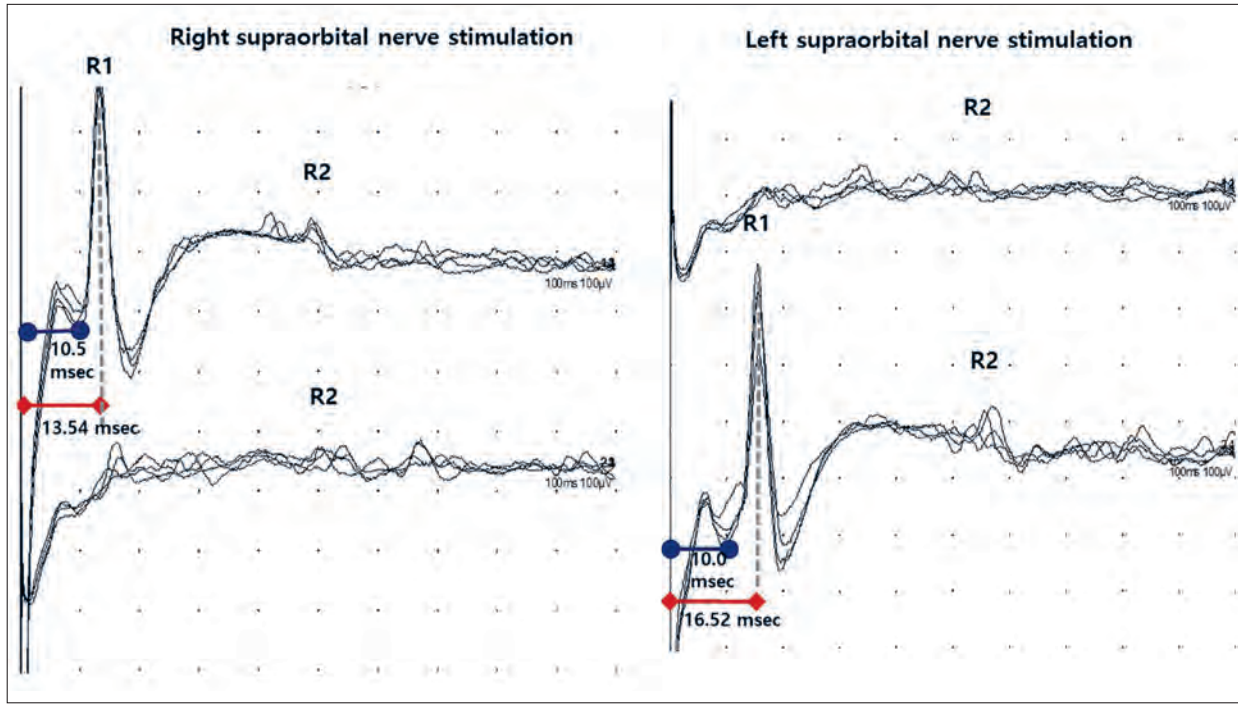


Figure1. *The patient's blink reflex test showed unremarkable onset latency but a side difference of the peak latency of R1 on the orbicularis oculi during left supraorbital nerve stimulation was observed. The blue and red lines represent onset and peak latencies of the blink reflex, respectively*

Table 1. *The results of the patient's blink reflex test*

Stimulation	Response	Onset R_1	Peak R_1	Peak R_1 – Onset R_1	R_2
Right supraorbital nerve	Ipsilateral	10.05 ms	13.54 ms	3.49 ms	37.70 ms
	Contralateral				36.20 ms
Left supraorbital nerve	Ipsilateral	10.00 ms	16.52 ms	6.52 ms	35.45 ms
	Contralateral				38.35 ms

Onset R_1: onset latency of R_1, Peak R_1: peak latency of R_1

ble afferent defect involving the left trigeminal nerve. Based on these findings, we performed thin slice magnetic resonance imaging (MRI) with gadolinium, from the Gasserian ganglion to the peripheral branch. The MRI revealed a 1.1 × 1.2 × 1.3 cm, well-defined, lobulated mass in the left Meckel's cave. The lesion was slightly hypointense on T1-weighted imaging with inhomogeneous high-signal intensities on fat suppression T2-weighted imaging, and it showed intense enhancement with focal cystic change (**Figure 2**).

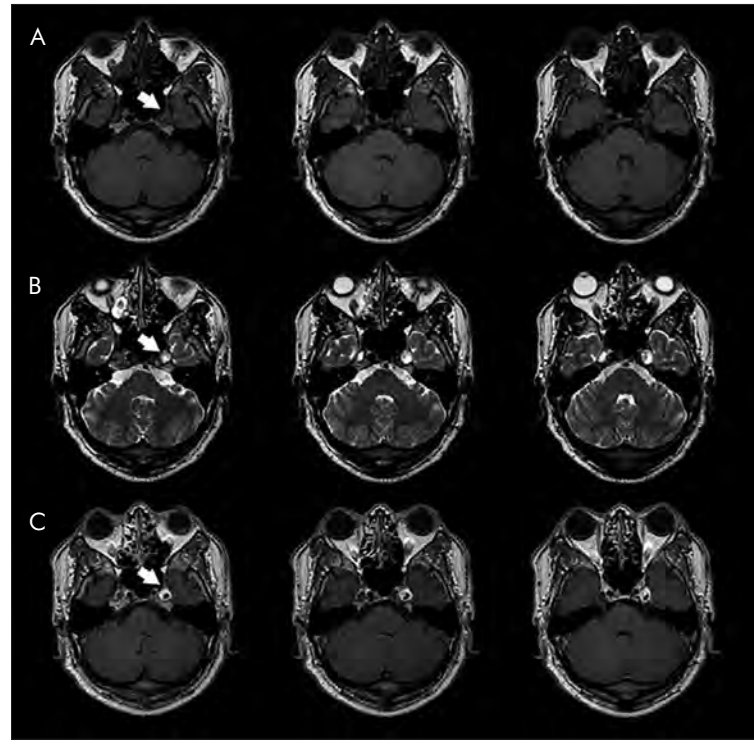


Figure 2. *The patient's thin-slice, gadolinium-enhanced MRI, which revealed a 1.1 × 1.2 × 1.3 cm, well-defined, lobulated mass (arrow) compressing the trigeminal nerve in the left Meckel's cave (arrow). The lesion was slightly hypointense on T1-weighted imaging* **(A)** *with inhomogeneous high-signal intense on fat suppression T2-weighted imaging* **(B)**, *and it showed intense enhancement with focal cystic change* **(C)**

Discussion

Meckel's cave is a dural recess in the posteromedial portion of the middle cranial fossa that acts as a conduit for the trigeminal nerve between the prepontine cistern and the cavernous sinus. Although small, Meckel's cave is a complex space containing important structures such as the Gasserian ganglion and the proximal rootlets of the trigeminal nerve. Meckel's cave can be involved in various spectrum of pathological conditions such as congenital, infectious, inflammatory, vascular or neoplastic lesions[4]. The masses of Meckel's cave account for less than 0.5% of all intracranial lesions including nerve sheath tumours, perineural tumours and leptomeningeal metastases which are usually associated with trigeminal nerve dysfunctions[1, 4]. Key imaging features of pathology of Meckel's cave are effacement of cerebrospinal fluid signal in Meckel's cave, enhancement greater than the perineural vascular plexus, nerve enlargement with perineural fat plane effacement and osseous foraminal erosion[4]. In our patient the MRI of the brain showed an extraaxial mass filling and enlarging Meckel's cave on the left side, hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging with enhancing cystic mass.

The EMG investigation of the trigeminal nerve reflexes, including the blink reflex, may provide valuable additional information about the site of a lesion that cannot be obtained with physical information[3, 5]. In the present case, the conventional onset latency measurement showed unremarkable findings on both sides. However, the peak latency measurement showed a greater delay on the left than on the right side, by 2.98 msec. In the blink reflex test, a side differentiation greater than 1.2 msec can constitute a remarkable finding[2, 3]. Onset

latency measures the intervals from stimulus onset to the initial deflection of the major negative deflection which represents the fastest fiber's conduction velocity. The peak latency measures from the onset of the stimulus to the peak of the major negative deflection which represents the average conduction of the group A-beta fibers[2, 3, 5].

The blink reflex is a polysynaptic reflex that is composed of an afferent arc through sensory nerve fibers in the trigeminal nerve and an efferent arc through motor nerve fibers in the facial nerve[2, 3]. Though the blink reflex arc has sensory (R_1) and motor (R_2) components, no previous report has discussed the meaning of onset and peak latency differences in the blink reflex.

It is unclear why this small lesion causes the peak latency prolongation while the onset latency and amplitude remain normal. There are several previous reports of trigeminal neuralgia caused by Meckel's cave mass[6–11], however as well as we know, only 2 cases showed abnormal blink reflex findings relevant to the lesion site[10, 11]. Unlike the present case, previous cases showed persistent focal neurological deficits in the affected area. The compressive masses of previous reports were large enough to interfere blink reflex potentials. The afferent pathway of the blink reflex test is usually the supraorbital nerve – a branch of the ophthalmic division. A small compressive lesion limited to the maxillary or mandibular division of Gasserian ganglion was too small to interfere with the blink reflex potential.

The latency of the blink reflex can be affected by non-pathologic factors such as the psychological condition of the subject, medication, wakefulness, and electrical stimulations[3]. In case of uncontrollable stimulus artifacts, peak latencies may be used instead. In the blink reflex tests, the conduction distances are rather small, and this inherent small distance between stimulus cathode and recording electrode may cause stimulus artifacts. These stimulus artifacts may hamper accurate defining of the onset latencies[12]. Because onset latency represents the fastest conducting fibers, we recommend to use initially onset latencies. However when significant variations in the onset latency of responses (latency jitter) are observed, we suggest the use of peak latencies additionally.

The most of the benign masses that give rise to symptomatic trigeminal neuralgia compress the trigeminal root in the posterior fossa, near its entry into the pons. The neurovascular contacts of trigeminal neuralgias take place in the same area. It is commonly believed that the trigeminal root entry zone represents a sort of locus minoris resistentiae due to changing from peripheral to central type of myelin sheet[6, 9]. However, the present case showed symptomatic trigeminal neuralgia originating from a mass at ganglion level.

This is a single case study and some limitations exist to generalize the peak-latency prolongation of this case. First, the postsurgical follow up blink reflex test was not performed. Second, we also recognize that our study represents a single case in a specific clinical situation, so more patients or health control studies are warranted to validate conclusions. Third, there can be many technical artifacts such as skin preparation, recording electrode asymmetry and inadequate stimulation. As peak latency can be influenced by electrode position and the time constant of EMG integration, the measurement of peak latency should be interpreted with caution. In the present case, the variations in onset latency could be latency jitter, because the individual peaks occurred at different points in time, possibly resulting in amplitude variation on the left side[3, 4]. As the EMG time constant or the degree of smoothing can affect the peak latency[6], we recommend the interpretation of peak latency of blink reflex to be limited to a comparison of the two sides or to an additional measure of onset latency.

Conclusion

We report a rare case of trigeminal neuralgia, with a small mass in the Meckel's cave, showing delayed peak latency in the blink reflex of the affected side. The present case suggests the peak latency measurement of the blink reflex might be a valuable aid for discerning the presence of a small compressive element in patients with trigeminal neuralgia who are referred for MR imaging.

ACKNOWLEDGEMENTS

No grants or other financial resources were utilized for this case.

None of the authors have any conflicts of interest to disclose.

The authors would like to thank Harrisco (www.harrisco.net) for the English language review.

REFERENCES

1. *Majoie CB, Aramideh M, Hulsmans FJ, Castelijns JA, van Beek EJ, Ongerboer de Visser BW.* Correlation between electromyographic reflex and MR imaging examinations of the trigeminal nerve. Am J Neuroradiol 1999; 20:1119-25.
2. *Oh SJ.* Clinical Electromyography nerve conduction studies. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.
3. *Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp OV, van Boxtel A.* Committee report: Guidelines for human startle eye blink electromyographic studies. Psycho-physiology 2005;42:1-15. https://doi.org/10.1111/j.1469-8986.2005.00271.x
4. *Malhotra A, Tu L, Kalra VB, Wu X, Mian A, Mangla R, et al*. Neuroimaging of Meckel's cave in normal and disease conditions. Insights Imaging 2018;9:499-510.
5. *Medvedeva LA, Syrovegin AV, Avakian GN, Gnezdilov AV, Zagorul'ko OI.* The methodology on the study of blink reflex and its normative parameters. Zh Nevrol Psikhiatr Im S S Korsakova 2011;111:62-7.
6. *Croutch KL, Wong WH, Coufal F, Georgy B, Hesselink JR.* En plaque meningioma of the basilar meninges and Meckel's cave: MR appearance. AJNR Am J Neuroradiol 1995;16:949-51.
7. *Yu E, de Tilly LN.* Amyloidoma of Meckel's cave: a rare cause of trigeminal neuralgia. Am J Roentgenol 2004;182: 1605-6. https://doi.org/10.2214/ajr.182.6.1821605
8. *Kapila A, Steinbaum S, Chakeres DW.* Meckel's cave epidermoid with trigeminal neuralgia: CT findings. J Comput Assist Tomogr 1984;8:1172-4. https://doi.org/10.1097/00004728-198412000-00027
9. *Mehta DS, Malik GB, Dar J.* Trigeminal neuralgia due to cholesteatoma of Meckel's cave. Case report. J Neurosurg 1971;34:572-4. https://doi.org/10.3171/jns.1971.34.4.0572
10. *Yamazaki Y, Ochi K, Nakata Y, Dohi E, Eguchi K, Yamaguchi S, et al.* Trigeminal neuropathy from perineural spread of an amyloidoma detected by blink reflex and thin-slice magnetic resonance imaging. Muscle Nerve 2010; 41:875-8. https://doi.org/10.1002/mus.21608
11. *Chmielewska B, Kamiński LM.* Progression of pre-existing trigeminalgia to Tolose-Hunt-like syndrome. The importance of neuroimaging for early differential diagnosis. Neurol Sci 2003;24:281-5. https://doi.org/10.1007/s10072-003-0157-4
12. *Rubin D, Dimberg EL, Kennelly KD.* The effect of paired stimuli on blink reflex latencies in normal subjects. Muscle Nerve 2011;44:235-40. https://doi.org/10.1002/mus.22034

KÉT COVID-19-BETEG KÜLÖNÖS HALLUCINÁCIÓKKAL ÉS FOKÁLIS EEG-ELTÉRÉSEKKEL

Clemens Béla

Debreceni Egyetem Klinikai Központ, Kenézy Gyula Campus, Neurológiai Osztály, Debrecen

PRINT | Hungarian | https://doi.org/10.18071/isz.75.0284 | www.elitmed.hu

A 2019 végén kezdődött Covid-19 betegség és pandémia szakmai irodalma kiterjedt, de a nagy betegcsoportokat ismertető közlések a súlyos esetekre szorítkoznak, és ugyanez áll a központi idegrendszeri (KIR-) manifesztációkra is. E munkában két nőbeteg esetét ismertetjük, akikben a szerológiailag igazolt SARS-CoV-2-fertőzés igen enyhe légúti tünetekkel és szintén nem súlyos KIR-panaszokkal jelentkezett. Az utóbbiak közül kiemelendők az igen élénk és különös tartalmú látási és hallási hallucinációk, amelyek részben elemiek, részben összetettek voltak. Az utóbbiak legjellemzőbb eleme egy emberi alak volt, aki jól érthetően beszélt hozzájuk. Mindössze három hasonló esetleírást találtunk az irodalomban, amelyeket a saját esetekkel összevetve, kiemeljük az öt esetre jellemző közös elemeket. Az összegzés felhívja a figyelmet arra, hogy enyhe vagy akár hiányzó légúti tünetek és szintén nem súlyos KIR-panaszok és -tünetek is lehetnek a Covid-19 velejárói. A két saját esetben a koponya-MRI normális volt, az EEG viszont a hallucinációknak megfelelő lokalizációban körülírt rendellenességeket mutatott, ami az EEG diagnosztikai, differenciáldiagnosztikai jelentőségére utal.

Kulcsszavak: *Covid-19, fokális EEG-eltérések, hallucinációk*

COVID-19 WITH STRANGE HALLUCINATIONS AND FOCAL EEG ABNORMALITIES: TWO CASE REPORTS

Clemens B, MD, PhD

Ideggyogy Sz 2022;75(7–8):284–288.

Scientific literature about the ongoing COVID-19 disease and pandemic is considerable, though articles concentrate on the severe cases and their central nervous system manifestations. This article demonstrates two cases: middle-aged female patients who had serologically proven SARS-CoV-2 infection with mild upper airway and central nervous system symptoms. The patients reported vivid, strange, simple, and complex visual and auditory hallucinations. A characteristic element of these complex hallucinations was a talking human-shaped figure. Only three similar cases have been published; this article discusses common features of all five patients. This summary highlights that in COVID-19 cases, minor central nervous system symptoms can accompany mild or even missing upper respiratory symptoms. The cranial MRIs of the presented patients were normal, but the EEG showed focal abnormalities in localizations related to hallucinations, which emphasizes the importance of EEG in differential diagnostic procedures.

Keywords: *COVID-19, focal EEG abnormalities, hallucinations*

Levelezési cím (correspondence): Dr. CLEMENS Béla, Debreceni Egyetem Klinikai Központ, Kenézy Gyula Campus, Neurológiai Osztály; 4031 Debrecen, Bartók Béla u. 2–26.
Telefon: +36 52 511792, fax: +36 52 511729, e-mail: clemensphd@gmail.com
https://orcid.org/0000-0002-2587-149X

Érkezett: 2021. december 13. Elfogadva: 2022. június 19.

A 2019 decemberében felbukkant, azelőtt nem ismert SARS-CoV-2 koronavírus által előidézett betegség és pandémia (rövidítve Covid-19) szakmai irodalma kiterjedt. A PubMed adatbázisban nyilvántartott közlések száma havi 2000–2500 között van[1]. A Covid-19 betegség KIR-manifesztációit áttekintő elemzések úgynevezett „systematic review" és „meta-analysis" típusúak[2–5]. Magyar nyelven is elérhetők a betegség KIR-manifesztációit számba vevő munkák[6–9]. Az angol nyelvű áttekintésekben beválogatási kritérium volt a kórházban, fekvőbeteg- vagy intenzív osztályon történő

kezelés, ami már önmagában is meghatározta a betegcsoportok összetételét[2–5]. A többségében idős betegek (a csoportokban a medián életkor 60 év felett volt) a légzőszervi érintettség mellett több szervrendszer, köztük a KIR károsodásának tüneteit mutatták. E vizsgálatokban a KIR érintettségét széles diagnosztikai kategóriák szerint tagolják, úgymint encephalopathia, meningitis, encephalitis, stroke, rohamok vagy epilepszia[2–5]. A pszichiátria területéről delírium, pszichózis, szorongásos betegségek, a hangulati élet zavarai és tudatzavar a leggyakrabban használt kategóriák[2–5]. Az időskor, a komorbiditás, a Covid-19 előtt meglevő vagy annak kapcsán kialakuló KIR-állapot, a betegség súlyossága igen komoly mintavételi hibát eredményeznek, ami ma még beláthatatlan mértékben nehezíti a KIR-érintettség teljes spektrumának megismerését. Ugyanez elmondható a betegek agyi állapotát tükröző képalkotó vizsgálatokról[10, 11] és az EEG-vizsgálatokról[11–14].

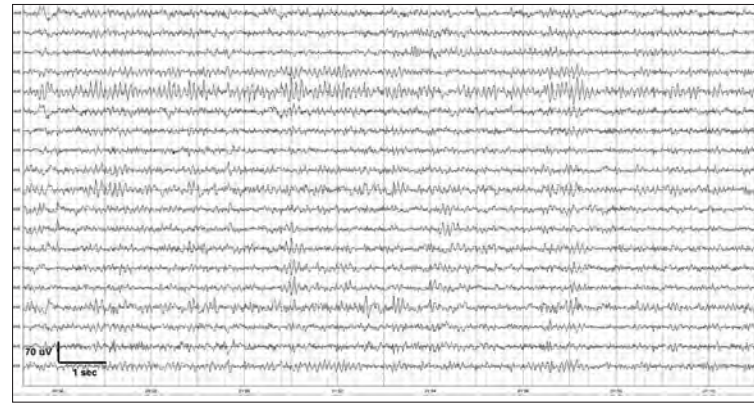
Esetismertetésünkben arra hívjuk fel a figyelmet, hogy tünetszegény Covid-19-hez is csatlakozhatnak szintén nem súlyos és különös KIR-tünetek.

Esetismertetések

1. ESET

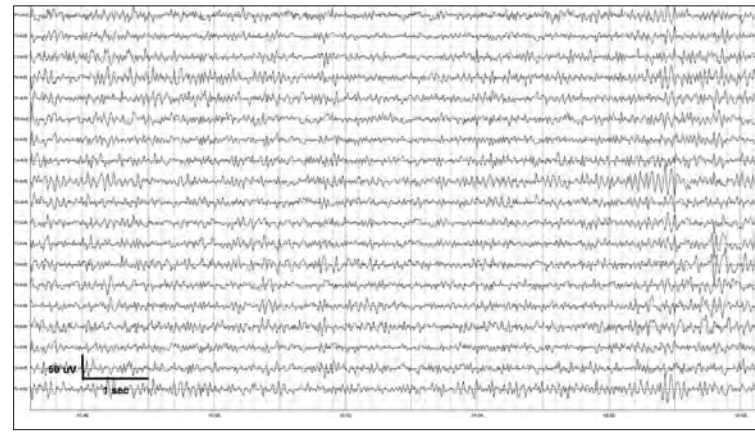
A beteg édesanyjának agyi sinusthrombosishoz köthető gócos epilepsziája van. A családban egyéb neurológiai és pszichiátriai betegség nem fordult elő. A beteg 1997-ben, zavartalan terhességből született, perinatalis és későbbi kórelőzménye eseménytelen. Testi-szellemi fejlődése rendben zajlott. Közepes képességű, szakiskolát végzett. 2015-ben jellegtelen panaszok (hiperventilációra, orrfújásra jelentkező fejfájás, borzongás) miatt vizsgálták; az EEG-vizsgálat generalizált tüske-hullám paroxysmusokat mutatott. Ezért került epilepsziaambulanciánkra, ahol – rákérdezésre – édesanyja elmondta, hogy az említett panaszok mellett 2013 óta napi néhány alkalommal „elbambulást” észlelnek, amit nem gondoltak kórosnak. Belgyógyászati, neurológiai és pszichés státusza normális volt. Rutin laboratóriumi értékei normális intervallumban voltak. Videó-EEG-felvételen 9-10 Hz szimmetrikus háttértevékenységet és két alkalommal két másodperc időtartamú, 150 mikrovolt feszültségű, generalizált, kétoldali szinkron-szimmetrikus tüske-hullám paroxysmust észleltünk. A paroxysmusok alatt a reaktivitás vizsgálata és a motoros tevékenység (ujjakkal folyamatos köröző mozgás) megszakadása alapján a rohamokat absence-nak, a betegséget juvenilis absence epilepsziának véleményeztük. A kezelést lamotrigin-monoterápiával kezdtük, ami csak részleges javulást eredményezett. Rohammentességet lamotrigin és levetiracetam biterápiával értünk el. A kezelés kezdeti nehézségei miatt további két alkalommal készült EEG-vizsgálat. E felvételeken a háttértevékenység szimmetrikus volt, a generalizált tüske-hullám paroxysmusok az utolsó felvételen már nem jelentkeztek.

Öt roham- és panaszmentes év után, 2020 őszén addig nem észlelt panaszok – bal oldali hemicrania, bal faciobrachialis zsibbadás, átmeneti szédülés, az ízérzés elvesztése – miatt jelentkezett. Néhány napon belül mindennapi, gyakori, de rövid ideig tartó vizuális vagy akusztikus hallucinációk jelentkeztek, élénk érzékszervi jeggyel. Emberi alakot vagy nem megnevezhető tárgyat látott jobb vagy bal oldalról feltűnni, de mire odafordult, az alak eltűnt. Máskor sikítást vagy robbanásra emlékeztető hangot hallott a háta mögött, ismét máskor egy nem ismerős személy jól érthetően a nevén szólította, holott senki nem volt a szobában. Tisztában volt a hallucinációk nem valóságos természetével, ezért nem érzett félelmet. Feledékeny lett, jegyzetekkel járt mindenhová, emellett állandóan fáradt, álmos volt. Láza, légúti panasza nem volt, de SARS-CoV-2-infekcióra utaló ageusia és a fenti panaszok miatt újravizsgáltuk. Az ageusiát leszámítva neurológiai eltérés nem volt, a szokásos, rutin laboratóriumi értékek normálisak voltak. A két, változatlanul szedett antiepileptikum szérumszintje a terápiás tarto-



1. ábra. *Az első beteg ébrenléti EEG-felvételéből vett minta. Közösátlagreferencia-montázs. A bal occipitalis (O1) elvezetésben folyamatos, fiziológiás α-ritmus látható. A jobb occipitalis (O2) elvezetésben az α-ritmus nem folyamatos, szabálytalan θ-csoportokkal váltakozik; az utóbbi kiterjed a szomszédos hátsó temporalis (T6) elvezetésre is*

mányban volt. A SARS-CoV-2 elleni IgG-ellenanyag jelenléte igazolta a fertőzést. Az ekkor készült EEG-felvételen bal occipitalisan fiziológiás α-ritmust, a jobb occipitalis és a hátsó temporalis elvezetésekben nagyobb részt szabálytalan, körülírt lassú aktivitást észleltünk *(1. ábra)*. Az eltérés kóros jellege különösen akkor volt feltűnő, amikor azt az előző három EEG-felvételen látható szimmetrikus occipitalis α-aktivitással hasonlítottuk össze. Az akkori EEG-felvételek és a Covid-19 jelentkezése között idegrendszeri tünete, panasza nem volt, ezért valószínű, hogy a körülírt lassú aktivitás megjelenése a SARS-CoV-2-fertőzéshez köthető. Az EEG-felvétel idején hallucinációk nem jelentkeztek. A koponya-MRI normális volt. 2021. januárban a hallucinációk és a fáradékonyság továbbra is fennállt, a többi panasz megszűnt. 2021 májusában két, Covid-19 elleni védőoltást kapott. Ekkorra az ageusia és a végtagzsibbadás már megszűnt, de a hallucinációk fennálltak, ezért pszichiátriai véleményt kértünk. A beteg azóta nem jelentkezett ambulanciánkon.



2. ábra. *A második beteg ébrenléti EEG-tevékenységéből vett minta. Közösátlagreferencia-montázs. A háttértevékenység α- és β-ritmusok és kevés lassú hullám keveredéséből áll. Bal középső-hátsó temporalisan (T3, T5) több θ-csoport látható, mint az ellenoldalon. Az aszimmetria mérsékelt, de a felvételen következetesen látható*

2. ESET

Az 1973-ban született nőbeteg hozzátartozói között neurológiai, pszichiátriai betegség nem fordult elő. Perinatalis és későbbi kórelőzménye, ötéves korában végzett appendectomiától eltekintve, eseménytelen. Testi-szellemi fejlődése rendben zajlott. Az általános iskola befejezése óta otthon dolgozik, ruhakészítő bedolgozó.

Férje 2021 márciusában szerológiailag igazolt SARS-CoV-2-fertőzés, légzési nehézség miatt kórházba került. Ugyanakkor ő maga is orrváladékozást, addig nem jellemző fáradékonyságot, aluszékonyságot észlelt, de láz, légzési nehézség nem jelentkezett, szaglása, ízérzése nem csökkent. Beszéde kissé meglassult, nehezen fejezte ki magát, amit azelőtt nem tapasztalt. Néhány nappal később egyik vagy másik oldalon felvillanó fényeket vagy emberi alakot látott. Máskor tisztán érzékelte, hogy valamelyik lánya mellette van és szólítja, de odafordulva már senkit nem látott; lányai akkor nem is tartózkodtak otthon. Máskor tisztán hallotta és értette, hogy férje beszél hozzá, holott a férj akkor már kórházban volt. A hallucinációkat egyértelműen a valósághoz nem tartozónak ítélte meg, ezért nem érzett szorongást, félelmet. A panaszokat feltehetően nem említve, felvette az első, később a második Covid-19 elleni védőoltást. Orvoshoz csak három hét elteltével fordult, a nem szűnő fáradékonyság, aluszékonyság miatt, amelyek gátolták munkájában, és beszédnehezítettsége is zavarta. Az EEG-vizsgálat ekkor normális háttértevékenységet mutatott, a bal temporalis elvezetésekben jelentkező körülírt, szabálytalan θ-csoportokkal *(2. ábra)*. Az EEG-felvétel idején a beteg nem hallucinált. Az EEG-vizsgálat eredménye miatt került járóbeteg-rendelésünkre. A kórelőzmény felvétele során említette férje Covid-19 betegségét. A neurológiai vizsgálat során szótalálási nehézséget észleltünk, a beszéd tempója kissé meglassult; egyéb eltérés nem volt. Rutin laboratóriumi értékei normálisak voltak. Koponya-MR-vizsgálat az agyállományban kóros eltérést nem mutatott. Szerológiai vizsgálat SARS-CoV-2 elleni IgG-antitest jelenlétét igazolta. Követés, kezelés céljából visszakértük, de mindeddig nem jelentkezett.

Megbeszélés

A Covid-19-betegek 8%-ában jelentkezik vizuális hallucináció, azonban nem egyedüli tünetként. Jellemzően egyéb KIR-tünetekkel jár együtt, mint fotofóbia, mentális zavar, látászavar, beszédzavar, rohamok, stroke és egyensúlyzavar[15]. „COVID and hallucination" kifejezéssel, Google és Google Scholar útján történő irodalomkereséssel egyetlen közlést találtunk, amelyben hallucináció a vezető KIR-tünet[16]. Az esetismertésben szereplő 46 éves nő SARS-CoV-2-infekció előtti anamnézise eseménytelen. Betegsége légúti és gyomor-bél hurutra utaló tünetekkel és lázzal kezdődött, emellett fele-

dékenységet észlelt. Mellkasröntgenlelete pneumoniára gyanús, ismételve normális volt, a hasi ultrahang kóros eltérést nem jelzett. A KIR-érintettségét elsősorban vizuális és akusztikus hallucinációk jelezték. Egy személyt vélt látni, aki állandóan a szoba sarkában állt, és folyamatosan, jól érthetően beszélt hozzá, hívta magához. Ha kiment a fürdőszobába, az alak nem követte, de amikor visszatért, ismét ugyanott látta. Koponya-MRI-lelete normális volt, egyéb KIR-vizsgálat nem történt. A hallucinációk pszichiátriai kezelés ellenére 15 hétig változatlanul fennálltak. Egy magyar tanulmány[9] két, középkorú nőbetegről számol be, akiknek Covid-19 okozta légúti tünetei enyhék voltak. Egyikük ingerlékenységről, alvászavarról, álomszerű állapotokról, gondolkodásának töredezettségéről és elemi vizuális hallucinációkról számolt be. A másik betegnek szürkületben intenzív vizuális hallucinációi jelentkeztek, kisállatok vonulását látta, ami szorongással töltötte el. A pszichés eltérések – a szerzők megfogalmazásával élve – a pszichózis és delírium szintjét nem érték el.

Az ismertetett esetekben több, feltűnően közös elem szerepel. Mindegyik beteg középkorú nő volt. Ez figyelmet érdemel, bár a kis esetszám miatt a nem szerinti megoszlásra nézve nem vonható le következtetés. A betegekben közös volt a delírium és pszichózis súlyosságát el nem érő, élénk érzékszervi jeggyel megélt hallucináció mint vezető tünet. Az elemi hallucinációk a primer, az összetettek az interpretatív látó- és hallókérgi (occipitalis és temporalis) mezők, más néven az unimodális asszociációs kéreg aktivációja során állnak elő[17]. A vivid, mozgó vizuális hallucinációk keletkezésében a jobb medialis temporalis gyrus és az occipitalis cortex bántalma a döntő[18], az auditoros hallucinációk elsősorban a bal gyrus temporalis superior működészavarához köthetők[19]. E területek kulcsszereplők, de nem egyedüli szereplők a hallucinációk mechanizmusában, amelyben közvetve a frontális kéregnek, a törzsdúci és az agytörzsi területeknek is szerepük van[18, 19]. A vizuális hallucinációk lokalizációs értékét tovább csökkenti, hogy a hallucinációval egy időben ritkán készült agyi képalkotó vizsgálat, és azok eredménye is nagy individuális variabilitást mutatott[18].

Az EEG-vizsgálat mindkét betegünk esetében hallucinációtól mentes időszakban történt. Egyik esetben sem volt olyan KIR-betegség a Covid-19 előtt, ami indokolta volna körülírt lassú aktivitás jelentkezését. Az 1. betegnél a generalizált epilepszia nem járt körülírt EEG-eltérésekkel. Ezért valószínű, hogy a SARS-CoV-2-infekció idején észlelt EEG-eltéréseket mindkét esetben a betegséggel járó KIR-érintettség okozta. Az occipitalis, temporalis EEG-eltérések mindkét beteg esetében átfedők voltak a hallucinációkban főszerepet játszó temporalis és occipitalis kérgi területekkel[18, 19], ami szintén oki összefüggés mellett szól.

Fontosnak tartjuk, hogy két esetünkben az EEG az MRI-nél érzékenyebbnek bizonyult a kóros agyi állapot kimutatásában. EEG-vizsgálatot enyhe KIR-tünetekkel jelentkező Covid-19 vagy arra gyanús betegekben egyelőre nem szokás végezni, de ezt csak járványtani meggondolás indokolja[20]. Az EEG-vizsgálat mint a (vitatható szóhasználattal élve) „organikus" okú működészavart kimutató és lokalizáló eljárás, hasznos lehet az EEG-eltérésekkel nem járó, hallucinációkkal járó állapotoktól történő elkülönítésben[21]. Ilyen esetekben az EEG a diagnosztikai és differenciáldiagnosztikai folyamat része, ezért nem sorolandó a minden esetben következmény nélkül halasztható vizsgálatok közé[20].

IRODALOM

1. *https://www.google.com/search?client=firefox-b-d&q=lit-covid+an+open+database+of+covid-19+literature*
2. *Chou SH, Beghi E, Helbok R, Moro E, Sampson J, Altamirano V, et al*. Global incidence of neurological manifestations among patients hospitalized with COVID-19-A report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open 2021;4: e2112131.
3. *Hewitt KC, Marra DE, Block C, Cysique LA, Drane DL, Haddad MM, et al*. Central nervous system manifestations of COVID-19: A critical review and proposed research agenda. J Int Neuropsychol Soc 2021:1-15. https://doi.org/10.1017/S1355617721000345
4. *Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, et al*. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med 2021;9:239-50. https://doi.org/10.1016/S2213-2600(20)30552-X
5. *Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ*. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 2021;8:416-27. https://doi.org/10.1016/S2215-0366(21)00084-5
6. *Bereczki D, Stang R, Böjti P, Kovács T*. A SARS-CoV-2 koronavírus által okozott COVID-19-járvány neurológiai vonatkozásai. Ideggyogy Sz 2020;73(5-6):171-5. https://doi.org/10.18071/ISZ.73.0171
7. *Szőts M, Péterfi A, Geröly J, Nagy F*. Covid-19 encephalitis esetünk és a betegség egyéb neurológiai szövődményei. Ideggyogy Sz 2020;73(11-12):427-30. https://doi.org/10.18071/isz.73.0427
8. *Varannai L, Magyar Z, Baranyai B, Ajzner É, Czurkó M.*

Covid-19 betegséget követő encephalitis. Ideggyogy Sz 2021;74(7-8):277-85. https://doi.org/10.18071/isz.74.0277
9. *Frecska E, Balla P*. A Covid-19-fertőzés neuropszichiátriai szövődményei. Lege Artis Medicinae 2021;31:267-73. https://doi.org/10.33616/lam.31.019
10. *Egbert AR, Cankurtaran S, Karpiak S*. Brain abnormalities in COVID-19 acute/subacute phase: A rapid systematic review. Brain Behav Immun 2020;89:543-54. https://doi.org/10.1016/j.bbi.2020.07.014
11. *Lambrecq V, Hanin A, Munoz-Musat E, Chougar L, Gassama S, Delorme C, et al*. Association of Clinical, Biological, and Brain Magnetic Resonance Imaging Findings With Electroencephalographic Findings for Patients With COVID-19. JAMA Netw Open 2021;4:e211489.
12. *Antony AR, Haneef Z.* Systematic review of EEG findings in 617 patients diagnosed with COVID-19. Seizure 2020; 83:234-41. https://doi.org/10.1016/j.seizure.2020.10.014
13. *Waters BL, Michalak AJ, Brigham D, Thakur KT, Boehme A, Claassen J, et al*. Incidence of Electrographic Seizures in Patients With COVID-19. Front Neurol 2021;12:614719. https://doi.org/10.3389/fneur.2021.614719
14. *Kubota T, Gajera PK, Kuroda N*. Meta-analysis of EEG findings in patients with COVID-19. Epilepsy Behav 2021; 115:107682. https://doi.org/10.1016/j.yebeh.2020.107682
15. *Mirfazeli FS, Sarabi-Jamab A, Jahanbakhshi A, Kordi A, Javadnia P, Shariat SV, et al.* Neuropsychiatric manifestations of COVID-19 can be clustered in three distinct symptom categories. Sci Rep 2020;10:20957. https://doi.org/10.1038/s41598-020-78050-6
16. *Clouden TA*. Persistent Hallucinations in a 46-year-old woman after COVID-19 infection: A Case Report. Cureus 2020;12:e11993. https://doi.org/10.7759/cureus.11993
17. *Mesulam M-M*. Patterns in behavioral neuroanatomy: Association areas, the limbic system, and hemispheric specialization. In: *Marsel M-M* (ed.). Principles of behavioral neurology. Philadelphia: FA Davis; 1985. p. 1-70.
18. *Meppelink AM*. Imaging visual hallucinations. In: The neuroscience of visual hallucinations, First Edition. Eds. *Collerton D, Mosimann UP, Perry E*. Published 2015 by John Wiley & Sons, Ltd. 2015. https://doi.org/10.1002/9781118892794.ch7
19. *Lutterveld R van, Sommer IEC, Ford JM*. The neurophysiology of auditory hallucinations - a historical and contemporary review. Frontiers in psychiatry May 2011. https://doi.org/10.3389/fpsyt.2011.00028
20. *San-Juan D, Jiménez CR, Camilli CX, de la Cruz Reyes LA, Galindo EGA, Burbano GER, et al*. Guidance for clinical neurophysiology examination throughout the COVID-19 pandemic. Latin American chapter of the IFCN task force - COVID-19. Clin Neurophysiol 2020;131:1589-98. https://doi.org/10.1016/j.clinph.2020.04.011
21. *Kanner AM, Bermeo-Ovalle A*. EEG in psychiatric disorders: does it have a role in their evaluation? In: *Schoemer DL, Lopes da Silva FH* (eds.) Niedermeyer's Electroencephalography. Basic Principles, Clinical Applications and Related Fields. Seventh Edition. New York: Oxford University Press; 2018. p. 686-95. https://doi.org/10.1093/med/9780190228484.003.0025