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H-1083 Budapest, Balassa u. 6.
Dr. Kovács Tibor/Tibor Kovács MD
Semmelweis Egyetem Neurológiai Klinika/Department of Neurology, Semmelweis University
Telefon: 36 1 2100337; fax: 36 1 2101368;
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BOBEST MÁTYÁS (1940–2019) EMLÉKÉRE

KUNCZ Ádám

Pécsi Tudományegyetem, Klinikai Központ, Idegsebészeti Klinika, Pécs

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Bobest Mátyás 2019 májusában, 79 éves korában, türelemmel viselt betegség következtében hunyt el. A szombathelyi Markusovszky Egyetemi Oktatókórház önálló Idegsebészeti Osztálya első főorvosának 1980-ban nevezték ki, és 23 évig vezette az osztályt. Szorgalmas, igényes munkával sikerült egy nyugat-magyarországi idegsebészeti centrumot kialakítania. A mindennapi sebészeti feladatok mellett fontosnak tartotta a folyamatos továbbképzést, és a gerinc degeneratív folyamatának kutatásával foglalkozott.

Kulcsszavak: *idegsebészet, regionális központ, folyamatos orvosi továbbképzés, csigolyaközti porckorong-degeneráció*

IN MEMORIAM MÁTYÁS BOBEST

Kuncz Á, MD
Ideggyogy Sz 2019;72(7–8):222–223.

Mátyás Bobest died in May, 2019, at the age of 79, following a disease tolerated with patience. He was the 1st nominated Chef of the independent Neurosurgical Department at the Markusovszky University Teaching Hospital, Szombathely in 1980, and under his leadership it worked for 23 years. He succeed to create a Neurosurgical Centre of West Hungary with his diligent and ambitious work. Beside his everyday surgical duties he paid attention to the continuing medical education and made research on the intervertebral disc degeneration.

Keywords: *neurosurgery, regional centre, continuing medical education, intervertebral disc degeneration*

Levelezési cím (correspondence): Dr. KUNCZ Ádám, Pécsi Tudományegyetem, Klinikai Központ, Idegsebészeti Klinika; 7623 Pécs, Rét u. 2. Telefon: (06-72) 535-932, fax: (06-72) 535-931. E-mail: kuncz.adam@pte.hu
https://orcid.org/0000-0003-1246-653X

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Budapesten született, gyermekkorát az ostromlott fővárosban, majd később Veszprémben töltötte. A veszprémi Lovassy László Gimnáziumban végezte középiskolai tanulmányait, és érettségizett 1958-ban. A Pécsi Orvostudományi Egyetemen (POTE) szerzett általános orvosi diplomát 1964-ben, ahol számos iskolateremtő professzor oktatta, köztük Romhányi György és Környey István, akik élete során példaképül szolgáltak.

A diploma megszerzését követően a POTE Igazságügyi Orvostani Intézetében dolgozott négy évig, majd megtiszteltetésnek számító gyakornoki állást kapott a Környey István vezette Ideg- és Elmegyógyászati Klinikán, ahol az idegsebészet is helyet kapott. Környey prof. a neurológiai képzés során nagy hangsúlyt fektetett a neuropatológiára, ami Bobest Mátyás szemléletét pályája során alapvetően befolyásolta. A neurológiai szakvizsga megszerzését és az Idegsebészeti Klinika önállóvá válását követően (1972) teljes energiájával az idegsebészet felé fordult. Mestere és főnöke, az innovatív és keménykezű Mérei F. Tibor mellett széles látókörű, határozott és „harcedzett” idegsebésszé vált, aki a szakmai problémákat szakszerűen és gondosan megoldotta. Pécsi évei alatt kezdetben az akkor újdonságnak számító echoencefalográfiával foglalkozott, majd figyelme a koponyabázis-sebészet, a hypophysisdaganatok, a koponyaalapi törések speciális ellátása felé irányult[1]. Az 1970-es évek második felében egy évet a duisburgi Idegsebészeti Klinikán töltött, ahol lehetősége volt a német idegsebészeti szemléletet elsajátítani, valamint az akkor felfutóban lévő, a nyaki gerinc degeneratív betegségeit célzó elülső beavatkozások terén is nagy gyakorlatot szerzett.

1980-ban a Vas megyei Markusovszky Kórház önálló idegsebészeti osztályt hozott létre, aminek vezetésére felkérték Bobest Mátyás egyetemi adjunktust (**1. ábra**). A felkérésnek örömest tett eleget, és hamarosan ütőképes orvoscsapatot (Alpár Balázs, Réthly András, Szabó János, Baranyi Miklós) és egy nagyszerű nővérgárdát (osztályvezető főnővér: Peitli Ottóné, Zsuzsa) alakított ki. Kiemelten foglalkozott azzal, hogy a társszakmákkal jó legyen az együttműködés, kiszélesítette a betegutakat, színesebbé tette a műtéti palettát. Kitűnő szakmai kapcsolat alakult ki gyermekgyógyászokkal, fül-orr-

1. ábra. *Bobest Mátyás (1940–2019)*

gégészekkel, szemészekkel, radiológusokkal és neurológusokkal. A rutin idegsebészeti beavatkozások mellé bekerültek a nagy felkészültséget igénylő transnasalis-transsphenoidalis hypophysis-, az orbitát érintő és a gyermek-idegsebészeti műtétek. A gerincfolyamatok diagnosztikájában az akkor újdonságnak számító, a C. I–II. lateralis punctión keresztül végzett myelographiát az országban az elsők között vezette be. A neurológusokkal közösen tartott folyóirat-referátumok és „agyszeánszok" (neuropatológiai megbeszélések) a folyamatos tanulást és továbbképzést szolgálták. (Ez utóbbiak megszervezésében jó partnerekre talált a Környey-féle neuropatológiai szemlélettel „megfertőzött" neurológusokban, Baltavári Lászlóban és utódjában, Garzuly Ferencben.) A szombathelyi idegsebészet pár éven belül országosan elismert idegsebészeti centrummá vált, amit az is bizonyított, hogy a szakma Bobest Mátyást az idegsebészeti szakmai szervezetek vezetőségi tagjainak sorába választotta.

Munkájában igényes és lelkiismeretes volt, és ezt minden munkatársától is elvárta. Addig, amíg beosztottjai nem tudták azt az ellátási szintet nyújtani, amit ő kívánatosnak tartott, hosszabb időre nem hagyta el Szombathelyt, így az első négy évben szabadságra sem ment. Munkája során mind elméleti, mind gyakorlati tudását megosztotta mindenkivel, tanult és tanított, dicsért és kritikus volt.

Úgy vélte, egy megyei kórházban olyan klinikai kutatásokat kell végezni, amihez bőven van beteganyag, ezért a KFKI kísérletes MRI laborjával együttműködve a porckorong-degeneráció in vitro MR-vizsgálatával foglalkozott akkor, amikor az MR-diagnosztika még nem volt elérhető[2, 3]. A probléma további kutatásában a porcos határlemez scanning elektronmikroszkópos vizsgálata szerepelt.

Bobest Mátyás 23 éves osztályvezetői működése során (1980–2003) számos idegsebészt indított el szakmai útján, még több kollégát képzett tovább, tanított alázatra a szakma, a segítő szakszemélyzet és nem utolsósorban a betegek iránt.

Munkáját a Markusovszky Kórház és Vas megye is nagyra becsülte és elismerte: 2005-ben a Vas Megye Önkormányzata Szolgálatáért Egészségügyi Tagozata kitüntetést, 2010-ben a Vas Megye Közgyűlése Elnökének Emlékplakettjét és a kórház Pető Ernő-emlékérmét kapta.

Bobest Mátyás halálával olyan idegsebész távozott közülünk, aki szemtanúja és aktív résztvevője volt a magyarországi idegsebészet önállóvá válásának, a mikrosebészet elterjedésének és a neuroradiológiai diagnosztika paradigmaváltásának. Személyisége, felkészültsége, vezetői képessége által szakmailag európai szinten működő idegsebészeti osztályt hozott létre Szombathelyen.

Az osztály fennállásának harmadik évfordulóján rendezett idegsebészeti tudományos szimpóziumra korábbi főnökét, Mérei F. Tibort hívta díszvendégül, aki köszöntőjében Bobest Mátyás munkájának elismeréséül Ady Endre *A tűz csiholója* című versét idézte. Ezzel az idézettel búcsúzunk Tőle.

„Csak akkor születtek nagy dolgok,
Ha bátrak voltak, akik mertek
S ha százszor tudtak bátrak lenni,
Százszor bátrak és viharvertek."

IRODALOM

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ATTITUDE OF SPINE SURGEONS TOWARDS THE APPLICATION OF 3D TECHNOLOGIES – A SURVEY OF AOSPINE MEMBERS

Péter Endre ÉLTES[1, 2], László KISS[1, 2], Márton BARTOS[3], Zsolt EÖSZE[1]; Zsolt SZÖVÉRFI[1], Péter Pál VARGA[1], Áron LAZÁRY[1]

[1]National Center for Spinal Disorders, Budapest
[2]Semmelweis University School of PHD studies, Budapest
[3]DO3D Innovations Ltd., Budapest

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Background – 3D technologies (3D virtual and physical model, 3D printing, computer aided engineering, finite element analysis based simulations) play an important role in personalized spine surgery.
Objective – In collaboration with AOSpine a global, online survey-based study was performed in order to determine the acceptance rate and the factors which stand against the wider spread of 3D technologies.
Methods – A survey containing 21 questions was developed and divided into five pages, every page corresponding to one chapter. Our analysis is based on the responses of 282 spine surgeons from 57 countries. To interpret our results in a global context, we used the Human Development Index of the respondent's countries in comparisons.
Results – Significant difference between the AOSpine regions ($p \leq 0.05$) was found, with the highest acceptance in Asia-Pacific region. There was no significant difference in acceptance score according to the field of spine surgery, or the surgical experience in years ($p=0.77$, and $p=0.19$). In the case of public practice, we found significantly higher acceptance compared to private and mixed (public and private) surgical practice ($p \leq 0.05$). The acceptance of the technology varied based on the respondent's resident country's Human Development Index and was significantly different between „Medium" vs "Very high" ($p = 0.0005$) and „High" vs „Very high" ($p=0.019$) category. Significant positive correlation was found between the acceptance score and the HDI score (Spearman test, $\rho = 0.37$, $p = 0.007$). The main limitation factor was identified as the lack of information.

GERINCSEBÉSZEK VISZONYULÁSA A 3D TECHNOLÓGIÁK ALKALMAZÁSÁHOZ – AOSPINE-TAGOK KÖRÉBEN VÉGZETT FELMÉRÉS

Éltes PE, MD; Kiss L, MD; Bartos M; Eösze Zs; Szövérfi Zs, MD, PhD; Varga PP, MD; Lazáry Á, MD, PhD

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Bevezetés – A 3D technológiák (háromdimenziós virtuális és fizikai modellek, háromdimenziós nyomtatás, mérnöki digitális tervezés, végeselem-analízisre épülő szimuláció) kulcsszerepet játszanak az egyénre szabott gerincsebészeti beavatkozások megvalósításában.
Célkitűzés – A 3D technológiák klinikai alkalmazását elősegítő és limitáló tényezők meghatározása érdekében nemzetközi, online felmérést végeztünk az AOSpine közreműködésével.
Módszer – Kifejlesztettünk egy 21 kérdésből álló kérdőívet. A vizsgálat során 57 ország 282 gerincsebésze által kitöltött kérdőíveket használtunk fel. A kérdőívek számszerűsítve mérték az elfogódottságot különböző paraméterek mellett. Az adatok értékelésében a válaszadók származási országainak megfelelő humán fejlettségi indexet is figyelembe vettük.
Eredmények – A 3D technológiák elfogadottsága az AOSpine-régiók között szignifikánsan eltért ($p \leq 0,05$), a legnagyobb elfogadottságot az Ázsia/Csendes-óceáni régió mutatta. A gerincsebészeten belüli szakterület, illetve a gerincsebészként eltöltött évek szerint történő csoportosítás esetén nem találtunk szignifikáns különbséget ($p = 0,77$, illetve $p = 0,19$). A finanszírozást figyelembe véve, a 3D technológiák elfogadottsága szignifikánsan magasabb a kizárólag közfinanszírozott ellátásban dolgozó gerincsebészek esetén, a privát vagy mindkét (közfinanszírozott és privát) ellátáshoz viszonyítva ($p \leq 0,05$). Az elfogadottság a humán fejlettségi index értéke alapján eltérő volt: szignifikáns különbséget találtunk a „Közepes" vs. „Nagyon magas" ($p = 0,0005$) és a „Magas" vs. „Nagyon magas" ($p = 0,019$) csoportba tartozó válaszadók közt;

Correspondent: Dr. Áron LAZÁRY, National Center for Spinal Disorders;
1126 Budapest, Királyhágó u. 1–3. Phone: (+36) 1 887-7900, fax: (+36) 1 887-7987,
e-mail: aron.lazary@bhc.hu (corresponding author)
https://orcid.org/0000-0002-0157-719X

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Conclusion – There is high interest among spine surgeons towards the incorporation of 3D technologies into the clinical practice. Education, the healthcare system, and the economic environment plays a major role in acceptance. Our results provide the basis of a strategy to promote the application of 3D technologies.

Keywords: *spine, surgery, health care technology, education, human development*

továbbá szignifikáns, pozitív korrelációt igazoltunk a technológia elfogadottsága és a humán fejlettségi index értéke közt (Spearman-teszt, $\rho = 0,37$, $p = 0,007$). A legfontosabb limitáló tényezőnek az ismerethiány bizonyult.
Következtetés – Vizsgálatunk a 3D technológiák széles körű elfogadottságát bizonyítja. Az eredmény alátámasztja az oktatás, a gazdasági környezet, valamint a klinikai környezet/az egészségügy általános helyzetének szerepét. Vizsgálatunk alapul szolgálhat a 3D technológiák fejlesztésével és terjedésével kapcsolatos fő feladatok meghatározására.

Kulcsszavak: *gerinc, sebészet, orvosi technológia, oktatás, emberi fejlettség*

The emergence of patient focused, holistic medicine generated new technological challenges for medicine that resulted in a new discipline, "in silico medicine". This new approach places the studying of the human body, thus the biomechanics of the musculoskeletal system into a new context. In silico medicine, including finite-element analysis (FEA) based simulation technologies and three-dimensional printing (3DP), plays a crucial role in the realization of individualized treatments, surgeries[1–3]. 3DP allows the fast, relatively cheap and accessible production of unique complex geometries. The benefit of the patients and clinicians is based on the application of FEA simulations in presurgical planning, and the preparation of surgeons aided by the 3D printed models in case of highly customized procedures[4–8].

The first biomechanical application of the FEA was published by *Brekelmans* et al in 1972[9], who demonstrated that this method is suitable for analysis of stresses and strains of complex constructions such as the femur under a variety of load situations. In 2002, *Fagan* et al[7] reviewed the FEA contribution to our understanding of the spine and its components and its behavior in healthy, diseased or damaged conditions. In Fagans' conclusion the method reduces our dependence on animal and cadaveric experiments and is a valuable complement to clinical studies[7]. In 2014, *Viceconti* discussed the role of contemporary biomechanics in the applications and the development of the so-called *Virtual Physiological Human* technologies for physiology-based *in silico* medicine[1]. In Viceconti's vision computer models can reliably predict certain quantitative changes in health status of a given patient, based on the existing biology and physiology knowledge after it is formulated as a quantitative hypothesis, which can be expressed in mathematical terms[1].

However it is important to emphasize that new scientific and technological results or methods in the medicine cannot be widespread if the knowledge of the "end users"– spine surgeons in this case – is insufficient. So far no study has been published about the global perspective of the need, knowledge, and acceptance of 3D technologies in spine surgery. To fill this gap, an online survey research had been conducted in the AOSpine community assessing the level of knowledge and attitude of spine surgeons about the 3D printing and modeling technologies. The global context of the results was supported by the use of the Human Development Index (HDI), an indicator of the human well-being[10], which is based on life expectancy, education and per capita income. Countries of the world are categorized into very high HD, high HD, medium HD, low HD groups, where the higher HDI shows the greater prosperity. Based on our results, we have determined the information gaps and restricting factors of the development of 3D technologies, whereas the effective knowledge transfer may hold the key to widespread approval.

ABBREVIATIONS

3D: three-dimensional
3DP: three-dimensional printing
CT: computer tomography
FEA: finite element analysis
HDI: Human Development Index
R&D: Research and Development
SPSS: Statistical Package for the Social Sciences

Methods

In October 2016, an online survey was sent out a single time to all AOSpine members on the mailing list. The survey was open for two months and a single answer was permitted per email address. The

questionnaire included 21 multiple choice or ordinal scale questions, being divided on thematic chapters (one page each) as follows: (I.) question I/1-6 we collected demographic data of the respondents (country of residence, details of spine surgical practice, basic knowledge of 3D technologies); (II.) questions II/1-3 focused on the personal use of 3D printed or virtual 3D models; (III.) questions III/1-5 focused on the use and attitude towards 3D technologies in surgical navigation; (IV.) questions IV/1-5 investigated the advanced manufactured (3DP) and patient-specific implants; in chapter (V.) we raised questions V/1-2 about the future and limitations of 3D technologies. Answers to ordinal scale questions (I/6, II/1, II/2, III/1, III/4, IV/1, IV/2, V/1) have been scored with the summed score (range: 0-28) representing the plausible level of acceptance (acceptance score) of 3D technologies in spine surgery. The influence of geographical location (AOSpine region), spine surgical practice, experience, etc. on the acceptance score was analyzed statistically. Participants of our survey were grouped based on the HDI of their country of residence and survey results were analyzed in the context of this parameter too. For statistical analyses, Spearman correlation, non-parametric tests, and Chi-square tests were applied depending on the nature of the variables. Statistical tests were performed using SPSS and $p<0.05$ was considered as significant.

Results

283 AOSpine members from the six AO regions completed the online survey. **Table 1** shows the demography of the participants. The most responders were from Europe (35.7%); 24,4% of the responders were from Latin America; 19,8% from Asia-Pacific; 9,2% from North America; 0,6% from Middle East. Only one person completed the questionnaire from AOSpine Africa region, so this region and this participant were excluded from further analysis. The study population was grouped into three subgroups based on the HDI of the country of the participants. More than half of the subjects (56.0%) have been from a very high HDI country, while 30.5% of the responders have come from a country with high HDI and 13.5% from a country with medium HDI. There has been nobody among the responders in the low HDI group. Most of the surgeons do surgeries in the public system (44.1%), while 36.3% of them have got a mixed practice and 19.6% work only in the private practice. Regarding the specialties, 83.7% of the surgeons do degenerative cases, 50.4% of them have got trauma and 39.4% have got deformity practice. 27.7% of the responders operate on spinal tumors. The majority of the study population has had an experience of 3 to 10 years in spine surgery (33.5%). 26.7% of the responders have had an experience of 10 to 20 years while 23.5% have been more experienced surgeons (more than 20 years in spine surgery). Young surgeons (0 to 3 years' experience) represented the 16.4% of the population.

Table 1. *Demographics of survey respondents*

Characteristic	N (%)
AO Spine region	*283*
Africa*	1 (0.4)
Asia Pacific	56 (19.8)
Europe	101 (35.7)
Latin America	69 (24.4)
Middle East	30 (10.6)
North America	26 (9.2)
Human Development Index (HDI)	*282*
Very high	158 (56.0)
High	86 (30.5)
Medium	38 (13.5)
Low	0 (0.0)
Practice where you do spine surgeries	*281*
Public	124 (44.1)
Private	55 (19.6)
Both	102 (36.3)
*Your common practice in spine surgery***	*282*
Degenerative	236 (83.7)
Deformity	111 (39.4)
Tumor	78 (27.7)
Trauma	142 (50.4)
Years of experience in spine surgery	*281*
0-3	46 (16.4)
3-10	94 (33.5)
10-20	75 (26.7)
> 20	66 (23.5)
What percentage of your cases are complex. challenging surgeries?	*281*
0-20%	102 (36.3)
20-40%	100 (35.6)
40-60%	57 (20.3)
more than 60%	22 (7.8)

*Note: The single respondent from AoSpine region Africa was excluded from the survey
**Note: multiple choice

Table 2 summarizes the questions and the distribution of the answers related to the acceptance of 3D technologies. 17% of the participants have not had any specific knowledge about the 3D technologies, while a similar rate of the subjects (18%) had already used these techniques. Most of the participants (41.5%) have had some information only from the media, and a further 23% of the responders

Table 2. *Questions related to the acceptance of 3D technology*

Characteristic	score	N (%)
I/6: Are you familiar with the concept and the benefits of 3D printing/modelling technologies?		*282*
I don't have any specific knowledge	0	48 (17.0)
I have some general information from news, advertisements	1	117 (41.5)
I have read scientific papers/conference talks in the topic	2	65 (23.0)
I have already used some of these technologies	3	52 (18.4)
II/1: Have you ever used any 3D technology for education (or demonstration) for medical students, residents, colleagues?		*282*
never	0	130 (46.1)
occasionally, 3D virtual models	1	89 (31.6)
occasionally, 3D printed models	2	43 (15.2)
frequently, 3D virtual or printed models	3	20 (7.1)
II/2: Have you ever used 3D virtual models or printed models for surgical planning or for the development of a surgical technique (e.g. by demonstrating the difficult anatomical situation or the challenging surgical steps)?		*282*
never	0	172 (61.0)
occasionally	2	90 (31.9)
frequently	3	20 (7.1)
*III/1: Intraoperative 3D navigation systems can reduce the complications and the morbidity of spinal surgeries. Do you use any 3D navigation system or tool in your clinical practice? **		*282*
not at al	0	127 (45.0)
occasionally (CT or fluoro based system)	1	84 (29.8)
regularly (CT or fluoro based system)	2	60 (21.3)
occasionally (3D printed surgical guide)	3	13 (4.6)
regularly (3D printed surgical guide)	4	5 (1.8)
III/4: Have you ever experienced or felt that a specific, unique surgical instrument (e.g. a particular chisel, curette or screwdriver) would have helped the surgery?		*282*
no	0	44 (15.6)
occasionally	1	159 (56.4)
frequently	2	79 (28.0)
IV/1: Have you ever used any advanced manufactured (3D printed) implant?		*280*
never	0	227 (81.1)
occasionally	2	44 (15.7)
frequently	3	9 (3.2)
IV/2: Where do you see the possible advantage of the use of advanced manufactured implants?		*279*
all implanted surgeries because a general or patient-specific advanced manufactured implant can provide better clinical outcome even in case of a standard pathology	4	45 (16.1)
challenging surgeries (e.g. tumor resection) and compromised anatomy or biology	3	113 (40.5)
only in complex cases where patient-specific implant would be required	2	113 (40.5)
none of the spinal surgeries	0	8 (2.9)
V/1: What do you think about the role of 3D printing/modelling technologies in spinal surgery?		*281*
no real future – too complicated and expensive	0	6 (2.1)
an option only for very limited applications, individual cases	2	123 (43.8)
a promising, feasible option for the near future	3	118 (42.0)
revolutionary	4	34 (12.1)

*Note: multiple choice

had learned about 3D technologies on scientific forums.

Only 7.1% of the clinicians use regularly 3D virtual or printed models for education or demonstration, while 46.1% of the surgeons have never used them. 3D models can play a significant role in the surgical planning[11, 12] or in the development process of a new surgical method, but 61% of the respondents have never used such a model for that purpose. Only 7.1% is the rate of the regular users.

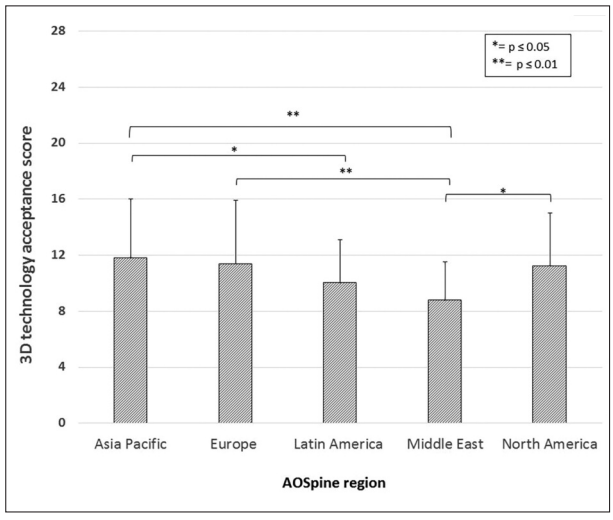

Figure 1. *3D technology acceptance score according to the AOSpine regions. The analysis found significant difference between the regions (* p ≤ 0.05, ** p ≤ 0.01)*

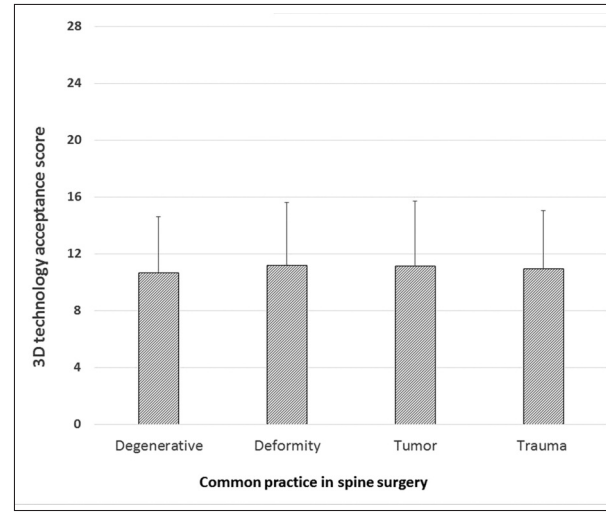

Figure 2. *The field of spine surgery does not significantly influence the acceptance score (p=0.77)*

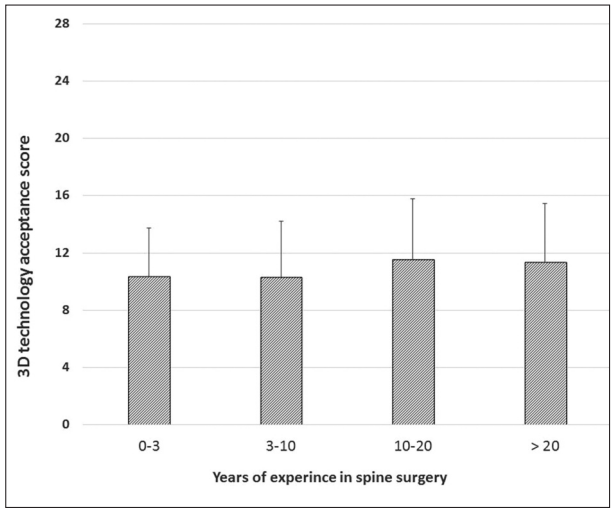

Figure 3. *The surgical experience does not significantly influence the 3D technology acceptance score (p=0.19)*

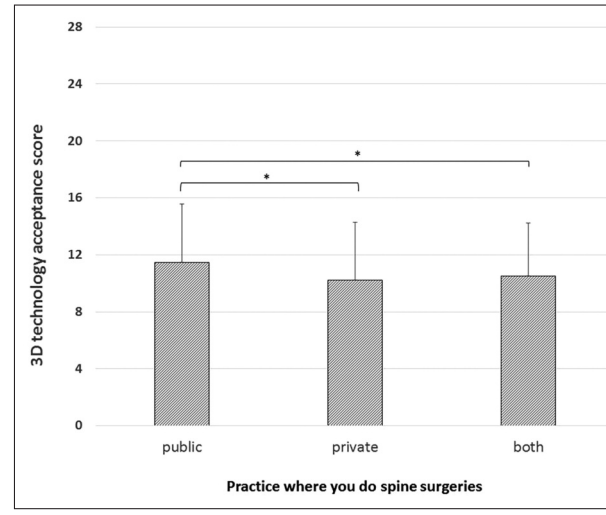

Figure 4. *The 3D technology acceptance score is significantly higher among surgeons who perform their clinical activity exclusively in the public sector (*p ≤ 0.05). In the public group, the mean is 11.4+4.1 compared to the group of surgeons working only in the private sector (10.2+4.1, p=0.026) and to those having shared praxis (10.5+3.8, p=0.036)*

Intraoperative 3D navigation can reduce the intraoperative complications and morbidity[13]. More than half of the study participants (55%) use some type of navigation in their surgical practice, and the rate of regular or occasional users of 3D printed navigation guides is 1.8% and 4.6% respectively. One of the advantages of 3D technologies, especially 3DP is that unique devices, tools can be manufactured in a cost-effective way[14]. The claim for a specific, unique surgical instrument has been quite high in the survey population (28% of the surgeons would frequently need such a tool, while 56.4% of them would occasionally need a unique, individually manufactured instrument). Implants manufactured by an advanced technique (e.g. 3DP) are regularly used by a minority of the surgeons (3.2%), and most of them (81.1%) have never used such a spinal implant. 40.5%-40.5% of the responders have thought that these implants have got a possible advantage in challenging surgeries (e.g. tumor resections, special anatomical variations) and in individual, complex cases where patient-specific implants would be required. On the other hand, 16.1% of the surgeons would use advanced manu-

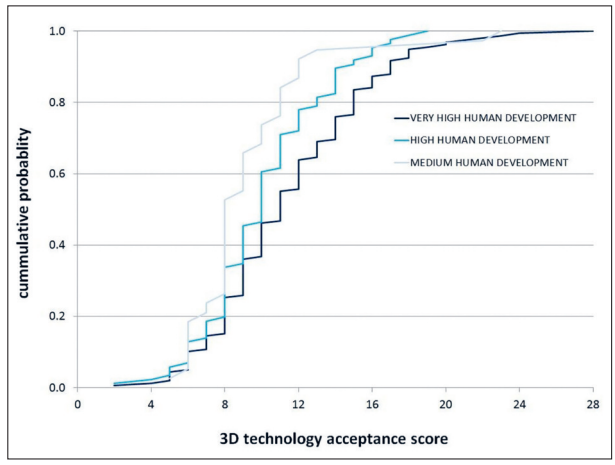

Figure 5. *The influence of the HDI index on the 3D technology acceptance score is represented on the cumulative probability plot. The scores were the lowest for the medium development group, the leftward shift in the cumulative probability plot showing an increasing interest in the 3D technologies in the higher developed countries. The difference reached the significance level for the medium vs very high and high vs very high HDI groups (posthoc test between medium vs very high HDI: p=0.0005, and high vs very high HDI: p=0.019)*

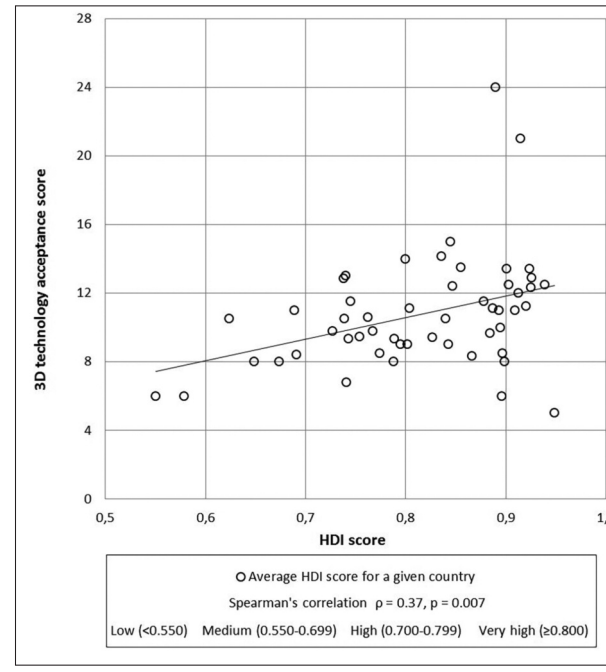

Figure 6. *Positive correlation was found between the 3D technology acceptance score and the survey respondents residence country's HDI values (Spearman test, ρ=0.37, p=0.007)*

factured implants in all instrumented spine surgeries providing a plausible better clinical outcome. Only 2.9% think that there is no need for such implants.

Over half of the spine surgery community believes that 3D technologies are a promising choice (42%) or will play a revolutionary (12.1%) role, based on the responses related to question V/1. However 43.8% of the respondents consider it as an option with limited applications in individual cases. It is important to underline that only 2.1% of the spine surgeons have answered that 3D technology has no real future because it is too complicated and expensive.

To understand the differing attitudes towards 3D technologies we investigated the acceptance score according to the AOSpine region affiliation, the field of spine surgery, experience in spine surgery (years of practice) and practice type (public, private, both). **Figure 1** represents the comparison between the AOSpine regions. The highest acceptance was observed in the Asia-Pacific region (Mean+SD: 11.8+4.2), which has not differed significantly from Europe (11.4+4.5) or North America (11.2+3.8) regions, but it was significantly higher compared to Latin America (10.0+3.1, *p=0.028*) and to Middle East (8.8+2.8, *p=0.002*). We found no significant difference (p=0.77) of the acceptance scores between the fields of spine surgery **(Figure 2)**; nor (p=0.19) when the subjects were grouped according to surgical experience in years **(Figure 3)**. However we revealed a significantly higher acceptance score among surgeons who perform their clinical activity exclusively in the public sector **(Figure 4)**. In this group, the mean score was 11.4+4.1 compared to the group of surgeons working only in the private sector (10.2+4.1, *p=0.026*) and to those having shared praxis (10.5+3.8, *p=0.036*).

The influence of the HDI index on the acceptance score is represented on **Figure 5** by a cumulative probability plot. The scores were the lowest for the medium development group, the leftward shift in the cumulative probability plot showing an increasing interest in the 3D technologies in the higher developed countries. However, the difference reached the significance level for the medium vs very high and high vs very high HDI groups (posthoc test between medium vs very high HDI: *p=0.0005*, and high vs very high HDI: *p=0.019*). In order to directly test this association, a correlation analysis was performed between acceptance score and the HDI values as shown in **Figure 6** (Spearman test, rho=0.37, *p=0.007*). **Table 3** represents the questions related to the limitations, main obstacles in the wider spreading of these technologies. Answers to multiple choice questions revealed that most of the subjects, regardless of the AO region believe costs, lack of access and insufficient

Table 3. *Limitations towards regular use of 3D technologies*

	Global	Asia/Pacific	Europe	Latin America	Middle East America	North	p**
		N (%)	N (%)	N (%)	N (%)	N (%)	
*II/3: What is the main barrier of the frequent use of such techniques in your clinical/educational practice?**							
no or limited knowledge about the possibilities and requirements	*98 (34.8)*	14 (25.0)	36 (35.6)	22 (31.9)	17 (56.7)	9 (34.6)	0.227
no or limited access to 3D modelling software	*116 (41.1)*	30 (53.6)	39 (38.6)	31 (44.9)	10 (33.3)	6 (23.1)	
no or limited access to 3D printing	*99 (35.1)*	16 (28.6)	42 (41.6)	24 (34.8)	11 (36.7)	6 (23.1)	
costs of 3D modelling/printing	*117 (41.5)*	23 (41.1)	43 (42.6)	26 (37.7)	13 (43.3)	12 (46.2)	
I am not interested in these technologies	*4 (1.4)*	1 (1.8)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	
other	*11 (3.9)*	3 (5.4)	8 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	
*III/2: If you are not using Intraoperative 3D navigation systems what is the reason?**							
lack of knowledge	*40 (14.2)*	3 (5.4)	7 (6.9)	18 (26.1)	10 (33.3)	2 (7.7)	0.0297
high purchasing price	*107 (37.9)*	22 (39.3)	30 (29.7)	35 (50.7)	15 (50.0)	6 (23.1)	
high maintaining costs	*55 (19.5)*	13 (23.2)	16 (15.8)	14 (20.3)	10 (33.3)	3 (11.5)	
too complicated to use (longer surgery, need of a technician, etc)	*53 (18.8)*	9 (16.1)	26 (25.7)	9 (13.0)	4 (13.3)	5 (19.2)	
lack of confidence	*11 (3.9)*	3 (5.4)	4 (4.0)	2 (2.9)	1 (3.3)	1 (3.8)	
I do not see its necessity in my practice	*32 (11.3)*	3 (5.4)	16 (15.8)	5 (7.2)	1 (3.3)	7 (26.9)	
other	*10 (3.5)*	1 (1.8)	7 (6.9)	1 (1.4)	0 (0.0)	1 (3.8)	
*IV/4: How do you see what is the main barrier of the spreading of advanced manufactured (3D printed) implants?**							
limited knowledge about the possibilities among the surgeons	*99 (35.1)*	13 (23.2)	38 (37.6)	21 (30.4)	14 (46.7)	12 (46.2)	0.327
limited access to 3D modelling and/or printing solutions	*144 (51.1)*	31 (55.4)	57 (56.4)	31 (44.9)	12 (40.0)	13 (50.0)	
high cost of modelling/printing	*162 (57.4)*	35 (62.5)	55 (54.5)	45 (65.2)	17 (56.7)	11 (42.3)	
unclear regulations	*53 (18.8)*	10 (17.9)	26 (25.7)	7 (10.1)	5 (16.7)	5 (19.2)	
lack of confidence, limited evidence	*54 (19.1)*	10 (17.9)	31 (30.7)	6 (8.7)	2 (6.7)	5 (19.2)	
other	*7 (2.5)*	1 (1.8)	6 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	
*V/2: What do you think what are the main barriers of the spreading of 3D printing/modelling technologies?**							
"distance" between engineers and surgeons	*85 (30.1)*	20 (35.7)	32 (31.7)	16 (23.2)	9 (30.0)	8 (30.8)	0.627
"distance" between the hospital and the printing/designing facility	*80 (28.4)*	19 (33.9)	31 (30.7)	22 (31.9)	5 (16.7)	3 (11.5)	
surgeons are not aware of the possibilities provided by 3D printing/ modelling	*116 (41.1)*	22 (39.3)	42 (41.6)	24 (34.8)	15 (50.0)	13 (50.0)	
expensive technology	*177 (62.8)*	36 (64.3)	56 (55.4)	48 (69.6)	20 (66.7)	17 (65.4)	
market are full with traditional solutions	*45 (16.0)*	7 (12.5)	24 (23.8)	10 (14.5)	2 (6.7)	2 (7.7)	
surgeons are not motivated to use advanced manufactured implants	*56 (19.9)*	15 (26.8)	20 (19.8)	11 (15.9)	8 (26.7)	2 (7.7)	
process of a patient-specific surgery are time-consuming	*64 (22.7)*	19 (33.9)	25 (24.8)	7 (10.1)	5 (16.7)	8 (30.8)	
other	*6 (2.1)*	3 (5.4)	6 (5.9)	3 (4.3)	1 (3.3)	1 (3.8)	

Note: *multiple choice, **Chi-square test with Yates' correction

knowledge/expertise are limiting the frequent use of 3D technology in clinical/educational practice. When spine surgeons were asked about the reason for not using 3D navigation technologies the answers were similar: high purchasing and maintenance price, prolonged surgery time and recruitment of extra personnel. However, in this case we found a significant difference (*p=0.03*) between the AO regions. In Latin America, Middle-East and Asia-Pacific the high purchasing and maintenance cost, whereas in Europe the high purchasing price and complicated usage, were considered as the main limiting factors. The answers of North Americans point to the redundancy of these 3D navigational technologies in their praxis among the high costs.

The majority of the spine surgeons identify the high cost of modeling/printing and limited access to 3D modeling and/or printing solutions as main obstacles in the extensive use of advanced manufactured (eg. 3D printed) implants. The insufficient knowledge and lack of confidence, little evidence about the possibilities of the 3D printing technologies were also selected as limiting factor. We found no significant difference in the proportion of answers according to the AO region affiliation of the respondents. Concerning the 3D technologies generally, the majority of the surgeons (62.8%) consider the technology too expensive and they are not well informed about its full potentials.

Conclusion

Our survey research reveals a genuine interest in 3D technologies among spine surgeons on a global scale, which is emphasized by answers to questions related to the role of these technologies. Only 2.1% of the responders chose the answer: „no real future – too complicated and expensive"; and related to limitations to frequent use only a small minority of 1.4% chose the option „I am not interested in these technologies". Although the high financial demand topped among the barriers in front of frequent use of 3D modeling/printing, navigation, and advanced manufactured implants, it is important to note that these services and the technology itself has recently become less and less expensive. The decline in costs is expected to continue due to the continuous and fast development[15–17].The appearance of several open-source softwares also reduces the required investments. Therefore, it is important to draw the attention of the global spine surgeon community that application of 3D technologies in everyday clinical practice or in education does not necessary require significant financial investment. In case of the intraoperative navigation, the 3D printed patient-specific surgical guides are accurate[18, 19] and can be more accessible as traditional CT or fluoro-based systems[20, 21].The lack of knowledge is an indisputable problem with several sources, so as the little use of these technologies in education, incomplete information from media reports, growing but "hidden" body of scientific evidence. In addition, selection of the option „no or limited access to 3D modeling software" in high ratio demonstrates the disinformation of the subjects since there are several user-friendly open-source or commercially available softwares. The use of these softwares requires some training, therefore establishing forums for surgeons is a necessity. These forums, educational events can also serve as an access platform to knowledge related to 3D technology and as an interaction platform with engineers for sharing the experience and starting collaborations.

The positive correlation between the attitude towards these technologies and the HDI of the country of origin highlights the role of education, economic environment and the developmental state of the healthcare system. The fact that the years of experience and specialty of spine surgeons does not influence the level of acceptance raises the possibility of applying the technology within the whole professional community.

Based on the result of the survey research we can delineate tasks that are crucial for the further development and for the large-scale spinal application of 3D technologies. The clarification of the clinical cost-effectiveness of the technology is fundamentally requiring further clinical research projects with the active participation of spine surgeons. Spine surgeons should take part in the whole process not only as end-users but they have to be involved in the R&D steps as well. An optimal interdisciplinary work between researchers, engineers, and clinicians in order to develop and deliver new treatment possibilities through innovation can be supported by research funds but also facilitated by the active involvement of the med-tech industry. Another important task is the education and know-how delivery which has to be successfully implemented through educational events. Since AOSpine's mission is to advance science and the spine care through research, education and community development we invite members to initiate projects focusing on the sharing of the know-how of 3D technologies, taking into account the regional needs and differences.

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RESTLESS LEG SYNDROME FREQUENCY IN HEALTH WORKERS

Ruhsen ÖCAL[1], Gizem ATGÜDEN[2], Çağrı AYCAN[2], Zeynep BALABAN[2], Seran SENAR[2], Sena YAVUZ[2]

[1]Baskent University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[2]Baskent University Faculty of Medicine, 3. Class Student, Ankara, Turkey

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Introduction – Restless Leg Syndrome (RLS) is a disease, primarily composed of sensational symptoms, caused by the urge to move lower extremities especially at night, and characterized by undesired feelings of the legs. Decreasing of the dopaminergic effect at night is thought to be responsible from these symptoms. RLS patients suffer from low quality of sleep affecting their daily life activities even causing socio-economic loss. Although RLS is a common and treatable disease, it can not be diagnosed easily due to the variability of symptoms.
Aim – The purpose of this study is to determine the frequency of RLS among health workers and to define the disease causing factors.
Method – A questionnaire was applied to 174 randomly selected health workers at Baskent University Medical Faculty (KA17/285). The demographic information, history of illnesses or usage of drugs, socioeconomic status, working hours and daytime sleepiness were questioned. Included in the questionnaire were diagnostic criteria for RLS, frequency assessment scale, and survey of sleep quality. We used "the diagnostic criteria of international RLS working group" for the diagnosis, and "Pittsburgh sleep quality index survey" to determine the quality of sleep. Reliability and validity studies were performed on both tests.
Results – A significant relationship between socio-economic status and RLS was found ($p<0.05$) as an increase of RLS frequency in parallel with decreased socio-economic status. RLS was found to be common among health workers. We suggest that health workers should be checked regularly, and they should be informed about the disease in order to raise an awareness and hence increase their quality of life.

Keywords: *restless leg syndrome, health workers, sleeping disorder*

A NYUGTALAN LÁB SZINDRÓMA FREKVENCIÁJA EGÉSZSÉGÜGYI DOLGOZÓK KÖRÉBEN

Öcal R, MD; Atgüden G; Aycan Ç; Balaban Z; Senar S; Yavuz S

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Bevezetés – A nyugtalan láb szindróma elsődlegesen érzékszervi tünetekkel kísért megbetegedés, ami az alsó végtagok különösen éjszaka jelentkező mozgáskényszerével és a lábakban jelentkező kellemetlen érzésekkel jár együtt. A feltételezések szerint a tünetek hátterében az éjszaka csökkenő dopaminszintek állnak. A betegek rossz éjszakai alvásminősége nappali aktivitásukra is negatívan hat, és társadalmi-gazdasági kárt okoz. Habár gyakori és kezelhető betegség, a tünetek változékonysága megnehezíti diagnosztizálását.
Cél – A vizsgálat célja annak megállapítása volt, hogy milyen gyakran jelentkezik a nyugtalan láb szindróma az egészségügyi dolgozók körében, és milyen okok vezetnek a betegség kialakulásához.
Módszer – A Baskent Egyetem Orvosi Karának véletlenszerűen kiválasztott 174 egészségügyi dolgozója töltötte ki a kérdőívet (KA17/285), amiben a demográfiai információk és a kórtörténet mellett rákérdeztünk a gyógyszerfogyasztásra, a szocioökonómiai státuszra, a munkaidő hosszára, illetve a napközben jelentkező álmosságra is. A kérdőív tartalmazta a nyugtalan láb szindróma diagnosztikai kritériumainak megfelelő, valamint a tünetgyakoriság és az alvásminőség megállapításához szükséges kérdéseket. A diagnózis felállításához a nemzetközi nyugtalan láb szindróma munkacsoport kritériumait, az alvásminőség megállapításához a Pittsburgh alvásminőség-index pontrendszerét használtuk; mindkét kérdéssor megbízhatóságát és validitását ellenőriztük.
Eredmények – Szignifikáns ($p < 0,05$) kapcsolatot találtunk a szocioökonómiai státusz és a nyugtalan láb szindróma jelentkezése között: a szocioökonómiai státusz romlásával párhuzamosan egyre gyakoribbá vált a kórkép, és nagy prevalenciával jelentkezett az egészségügyi dolgozók körében. Ezért az egészségügyi dolgozók rendszeres szűrővizsgálatát javasoljuk, hogy felhívjuk a figyelmüket erre a szindrómára, és következésképpen javulhasson az életminőségük.

Kulcsszavak: *nyugtalan láb szindróma, egészségügyi dolgozók, alvászavar*

Correspondent: Dr. Ruhsen ÖCAL, Baskent University Faculty of Medicine, Department of Neurology; Ankara, Turkey.
E-mail: ruhsenocal@yahoo.com, gsm: 05054423227

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RLS is a condition characterized by an irresistible need of moving the legs, dysesthesia and restlessness. These unpleasant feelings increase during rest, while motor activity provides relief from symptoms[1, 2]. Furthermore, RLS is a common cause of sleep disorders. Reduced sleep quality causes socio-economic loss by negatively affecting daily life activities of RLS patients[1].

RLS affect all age groups, although the prevalence increases with advancing age. RLS is more frequently reported in women[3–6].

Today the diagnostic criteria of RLS are determined by the International Restless Leg Syndrome Study Group (IRLSSG) and all of the five essential criteria should be present for the diagnosis[1, 7] **(Table 1)**.

For the treatment of RLS, the underlying secondary disease should be treated first. If there is no underlying disease (primary RLS), dopamine agonists are used[8].

RLS is classified according to the etiology as primary or secondary. The most common clinical presentation of the disease is primary RLS. Secondary RLS occurs during the course of iron-deficiency anemia, diabetes mellitus, peripheral polyneuropathy, renal failure, Parkinson's disease or during the use of some medications (antidepressants, antiepileptics, dopamine agonists ...)[8].

Dopaminergic system is thought to have an important role in RLS pathophysiology. Hence, it is believed that decreasing of the dopaminergic effect at night is responsible for the symptoms. As iron deficiency is found to be the most common cause of secondary RLS, it has been suggested that regulatory effect of iron on the dopaminergic pathway may also be a factor in the etiology of the disease[8].

RLS also has a genetic linkage. Family history and possible environmental factors are frequently investigated and found to have an important role in the etiology[9].

Materials and methods

This research was approved by the Medical and Health Sciences Ethics Committee of Baskent University (KA17/285) and supported by the Research Fund of Baskent University. 174 health professionals were randomly selected and the ones gave consent were surveyed. In the first part of the survey, demographic attributes, known diseases and history of drug use, levels of monthly income, wakefulness time, working time and daytime sleepiness were questioned. In the second part of the survey, diagnostic criteria of RLS were questioned along with sleep quality. Diagnostic criteria of IRLSSG[1] and Pittsburgh Sleep Quality Index was used to assess quality of sleep[10]. Reliability and validity of both tests were performed.

Statistical analysis

All analyzes were carried out by using the SPSS Statistical Package version 23. Evaluating the data, frequency distributions for categorical variables and descriptive statistics for numerical values (mean ± sd) were given. In order to be able to decide about the analyzes to be applied, primarily normality test was applied to numerical variables. Parametric tests were used when normality assumption was provided, and nonparametric tests were used when not. The Chi-square test was applied to assess the relationship between the categorical variables. The Kolmogorov-Smirnov test was used as the normal distribution test for the ordinal variables, and the Mann-Whitney U test was used to determine the relationships between the variables. Logistic regression analysis was performed to determine the possible risk factors of RLS. Statistical significance was accepted as $p < 0.05$.

Table 1. *Restless leg syndrome diagnostic criteria*

1	An urge to move the legs, usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs
2	The urge to move the legs and any accompanying unpleasant sensations beginning or worsening during periods of rest or inactivity
3	The urge to move the legs and any accompanying unpleasant sensations partially or totally relieved by movement
4	The urge to move or the unpleasant sensations are worsening in the evening or at night or occurring only in the evening or at night
5	The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

Table 2. *Participants' demographic information and study results*

	Age	Sex	Health Workers				Monthly income level (<2000TL)	Anxious-Depressive Personality	Working Hours	Fatique
			Doctor	Technician	Nurse	Health consultant				
With RLS	34.85 ±9.14	Female: 24 Male: 17	13 (31.7%)	17 (41.5%)	2 (4.9%)	9 (22 %)	19	22	9.12 ±0.9	30
Without RLS	38.59 ±9.22	Female: 88 Male: 45	65 (48.9%)	18 (13.5%)	21 (15.8%)	29 (21.8%)	18	26	8.76 ±0.9	65
P value	p>0.05	p>0.05	p<0.05				p<0.05	p<0.05	p<0.05	p<0.05

Results

Within the scope of our research, 112 (65%) women (mean age: 37.4±9.46) and 62 (35%) men (mean age: 38.10±9.04), a total of 174 health workers (mean age: 37.71±9.31) were surveyed. 41 (23%) (mean age: 34.85±9.14) of the participants were diagnosed with RLS; 24 (58.5%) of these cases were female and 17 (41.5%) were male **(Table 2)**. There was no statistically significant difference detected in terms of the factors including age, doing regular sports, gender, smoking, alcohol use, snoring and obstructive sleep apnea between participants who were diagnosed with RLS and who were not.

78 (45%) participants were doctors, 23 (13%) were nurses, 35 (20%) were operating room-laboratory technicians and 38 (22%) were health consultants. Among the professional groups, the RLS diagnosis was the highest in the operating room-laboratory technicians (17; 41.5%). This value was found to be statistically higher than in other professional groups. (p<0.05) **(Table 2)**.

Among all cases with RLS, 19 (46%) participants had 0-2000 TL monthly income (lowest monthly income level). When the group of participants with the lowest monthly income was compared with the higher income ones, RLS was significantly higher in the lowest income group (p<0.05).

Among the 48 participants who defined themselves as anxious-depressive, 22 (46%) had RLS, while only 19 (15%) of the 126 participants who defined themselves as calm and peaceful had RLS. That is to say, RLS was found to be significantly more frequent among participants with anxious-depressive personality (p<0.05).

When the group with a mean daily working time of 9.12±0,9 hours were compared to the group with 5.69±0.63 hours, the RLS was found to be significantly more frequent in the group with more working hours (p<0.05).

Among all cases diagnosed with RLS, 88% (n=36), stated to feel tired during the day. During the wakefulness period, 61% of the participants diagnosed with RLS had unintentional arm-leg movements detected by their relatives. Both daytime tiredness and unintentional arm-leg movements were found to be significantly more frequent in the group of participants with RLS (p<0.05).

Participants were questioned both with subjective and objective questions to determine their quality of sleep. Among cases with RLS, 35 (85%) awakened at night, and among them 19 (54%) could not fall asleep again; while 43 (32%) of the cases without RLS were awakening at night and only 16 (37%) of those stated they were not able to fall asleep again. Both awakening at night and not being able to fall asleep again were significantly more frequent in participants with diagnosis of RLS (p<0.05). There was no statistically significant difference in snoring during sleep or in the average sleeping and waking times among participants with and without RLS for the past month (p>0.05).

Participants who were diagnosed with RLS needed in average 20.9±15 minutes to fall asleep during the last month, whereas participants without RLS needed 13.9±12.2 minutes. Sleeping time of participants with RLS were 5.88±0.9 hours at night, while sleeping time of participants without RLS were 6.74±1.13 hours. The duration of sleep, separated from the duration of falling asleep, was found to be significantly higher in participants with RLS compared to those who weren't diagnosed with RLS (p<0.05).

The most frequent answer given to the question "How do you evaluate your sleep quality for the last month?" was 'quite good' (n=75; 56%) by the participants without RLS, while it was quite bad' (n=23; 56%) by the RLS-diagnosed participants.

Participants without RLS mostly answered to the question "To what extent did your sleep quality caused a problem at work" as "it did not cause any problems" (n=104; 78%), whereas participants with RLS most often responded as "it only created very few problems" (n=19, 46%). Participants with RLS had significantly worse sleep quality and more frequent daytime sleepiness and fatigue compared to those who weren't diagnosed with RLS ($p<0.05$).

RLS was found to be significantly higher in participants with low monthly income level, anxious personality structure, and high working hours. The sleep quality of the cases with RLS was bad at night, which was found to affect the functionality of them on the following day ($p<0.05$) **(Table 2)**.

All the questions in our study were evaluated by logistic regression analysis, and the "yes" answer to this question "Do you identify yourself as an anxious-depressive person?" was found to be an independent risk factor (OR: 9,812; 95% CI: 2,21-3,56).

Discussion

According to epidemiological studies, the prevalence of RLS in the population is 1-15%, whereas in our study this rate was higher[5, 6, 11]. There are many risk factors affecting the health of the health staff, especially those working in hospitals. These risk factors vary according to the work being done and the working conditions.

In a study conducted with 266 participants in our country, RLS was found to be 18.3% (n=39) among health personnel (11). In our study, we found higher RLS-rate among health professionals (23%, n=41). In our study, the incidence of RLS in operation-laboratory technicians (48%) was the highest among all health workers. Physicians were the group with the least risk of developing RLS among all the health professional groups, as 49% of the medical doctors were not previously diagnosed with RLS.

It was observed that the number of participants diagnosed with RLS increased in parallel with decreased monthly income level. The monthly income level of 49% of participants who were diagnosed with RLS was between 0-2000 TL. It was found that working hours and days was higher in cases with RLS. In our study we could not show any relationship between RLS and shift work; there are some publications that could and some that could not show such a relation[6].

There was no statistically significant relationship detected between participants who were diagnosed with RLS in terms of the factors including age, snoring and not snoring or making regular exercise or not.

Although some studies indicate that alcohol and cigarette use may affect the frequency of RLS, some do not. In one study, comorbid conditions were reported to be a contributing factor to the development of RLS, while in another one alcohol consumption, smoking, obesity and body mass index were not correlated with RLS[5, 12]. In our study we could not demonstrate any significant connection between smoking and alcohol use and the incidence of RLS.

In some studies depression was found to be 4 times higher in people with RLS than in normal population[13]. This was explained by RLS related sleeping disorders and decreased quality of life. Also, symptoms of RLS such as fatigue, difficulty of focusing can be interpreted as depression[3]. We did not evaluate depression in our study, but we questioned about personality traits. It has been detected in our study that having an anxious-depressive personality is an independent risk factor for RLS. The incidence of RLS was found 9.8 times higher in participants defining themselves as having anxious-depressive personality.

There are studies in the literature pointing out incidence of RLS being twice as much in women. Symptoms of RLS was reported to increase during pregnancy; therefore the number of births might be the cause of RLS being more frequent among women[13]. These features were also questioned in our study, but no significant relationship was found.

RLS affects the quality of life in many ways; the most affected one is the sleep quality. Patients with RLS can develop sleep disorders such as difficulty in sleeping and difficulty in maintaining sleep without interruption; causing increased daytime sleepiness and pathological fatigue. RLS can lead to insomnia or excessive daytime drowsiness, as well as to obstructive sleep apnea syndrome and narcolepsy. In a study evaluating the frequency of RLS, 52% of patients with risk of RLS were detected to have a high risk of obstructive sleep apnea also[5]. We used the Pittsburgh Sleep Quality Index to assess sleep quality in our study[10]. We found that RLS had a negative effect on sleep quality and there was a meaningful association in the cases where patients were diagnosed with RLS and were awake at night and unable to fall sleep again. A significant relationship between RLS and the mentioned sleep disorders has been shown in many other studies. Other studies have reported difficulty in falling asleep and maintaining sleep, and increased daytime sleepiness as our study[5, 6, 12, 13]. In our study, 88% of the cases diagnosed with RLS stated that they felt tired and exhausted during the day.

Conclusion

We found that the frequency of RLS in health workers was higher than in the normal population. We have determined that some modifiable working conditions can have an impact on this. Raising awareness ensures patients to get diagnosed and treatment can improve the daily life activities of the patients thus improving the quality of life.

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EFFECTS OF CHADS2 SCORE, ECHOCARDIOGRAPHIC AND HAEMATOLOGIC PARAMETERS ON STROKE SEVERITY AND PROGNOSIS IN PATIENTS WITH STROKE DUE TO NONVALVULAR ATRIAL FIBRILLATION

Ozer AYNACI[1], Aslan TEKATAŞ[1], Gülden AYNACI[2], Sezgin KEHAYA[1], Ufuk UTKU[1]

[1]Trakya University, Medical Faculty, Department of Neurology, Edirne, Turkey
[2]Trakya University, Health Science, Department of Obstetric & Gynecology. Edirne, Turkey

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Introduction – The aim of this study is to evaluate utility of CHADS2 score to estimate stroke severity and prognosis in patients with ischemic stroke due to non-valvular atrial fibrillation (AF) in addition to evaluate effects of hematologic and echocardiographic findings on stroke severity and prognosis.
Methods – This prospective study included 156 ischemic stroke cases due to non-valvular AF in neurology ward of Trakya University Medical School between March 2013-March 2015. National Institute of Health Stroke (NIHS) score was used to evaluate severity of stroke at admission. Carotid and vertebral Doppler ultrasonography findings, brain computed tomography (CT) and magnetic resonance imaging (MRI) of the cases were evaluated. Left atrial diameter and ejection fraction (EF) values were measured. CHADS2 score was calculated. Modified Rankin Scale was used to rate the degree of dependence. Effects of age and sex of the patients, presence of diabetes mellitus (DM), Congestive Heart Failure (CHF), Cerebrovascular Disease (CVD) and C-reactive protein (CRP) levels on CHADS2, NIHS, and mRS were evaluated.
Results – In patients with age ≥75, mean NIHS score was 3.3 points and mean mRS score was 1.02 points higher, than in patient below 75 years of age. Compared with the mild risk group, cases in the high risk group had older age, higher serum D-dimer, fibrinogen and CRP levels and lower EF. A positive relation was detected between stroke severity and Hemorrhagic Transformation (HT), previous CVD history, and presence of CHF. A significant association was found between increased stroke severity and Early Neurological Deterioration (END) development. Older age, higher serum fibrinogen, D-dimer, CRP and

A NEM BILLENTYŰ EREDETŰ PITVARFIBRILLÁCIÓ KÖVETKEZTÉBEN KIALAKULÓ AGYVÉRZÉS SÚLYOSSÁGÁNAK ELŐREJELZÉSE

Aynacı O, MD, PhD; Tekataş A, MD, PhD; Aynacı G, MD, PhD; Kehaya S, MD, PhD; Utku U, MD, PhD

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Bevezetés – A vizsgálat célja az volt, hogy felmérjük a CHADS2-skála, valamint a hematológiai és echokardiográfiai paraméterek használhatóságát a nem billentyű eredetű pitvarfibrilláció következtében kialakuló ischaemiás agyvérzés súlyosságának és prognózisának előrejelzésében.
Módszerek – A prospektív vizsgálatba 156, nem billentyű eredetű pitvarfibrilláció következtében kialakuló ischaemiás agyvérzésben szenvedő beteget vontunk be. A betegeket a Trakya Egyetem Orvostudományi Iskolájának neurológiai osztályára vették fel 2013 március és 2015 március között. Az agyvérzés súlyosságát a felvételkor a National Institute of Health Stroke (NIHS) skála segítségével állapították meg. Carotis- és vertebralis Doppler-ultrahang, agyi CT- és MRI-leletek kerültek rögzítésre. Mérték a bal pitvar átmérőjét és az ejectiós frakciót (EF), kiszámolták a CHADS2-pontszámot. Az összefüggés mértékét módosított Rankin-skálával állapították meg. Értékelték az életkor, a nem, a diabetes, a congestiv szívelégtelenség (CHF), a cerebrovascularis betegség (CVD) és a C-reaktív protein szint hatását a CHADS2-, a NIHS-, valamint az mRS-pontszámokra.
Eredmények – A 75 éves vagy idősebb betegek csoportjában a NIHS- és az mRS-pontszámok mediánja 3,3, illetve 1,02 ponttal volt magasabb, mint a 75 évesnél fiatalabbak csoportjában. A CHADS2-pontszám szerinti alacsonyabb kockázatú csoporttal összehasonlítva, a nagyobb kockázatú csoportban magasabb volt az életkor, a szérum D-dimer-, fibrinogén- és CRP-szintje, továbbá alacsonyabb az EF értéke. Pozitív összefüggés derült ki az agyvérzés súlyossága, valamint a haemorrhagiás transzformáció (HT), a CHF, továbbá a kórtörténetben szereplő

Correspondent: Ozer AYNACI, MD, PhD, Trakya University, Medical Faculty Department of Neurology; Edirne, Turkey.
Phone: +90 507 979 9506, e-mail: guldenaynaci@hotmail.com

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lower EF values were associated with poor prognosis. History of CVD and presence of CHF were associated with poor prognosis. END development was found to be associated with poor prognosis. In the high-risk group, 30.3% (n = 33) had END. Among those in the high-risk group according to the CHADS2 score, END development rate was found to be significantly higher than in the moderate risk group ($p < 0.05$). There was a strong positive correlation between CHADS2 and NIHS scores. mRS score increased with increasing CHADS2 score and there was a strong correlation between them. Effect of stroke severity on prognosis was assessed and a positive correlation was found between NIHS score and mRS value.
Discussion – Our study demonstrated the importance of CHADS2 score, haemostatic activation and echocardiographic findings to assess stroke severity and prognosis. Knowing factors which affect stroke severity and prognosis in patients with ischemic stroke may be directive to decide primary prevention and stroke management.

Keywords: *CHADS2 score, stroke severity, ischemic stroke*

CVD között. Szignifikáns összefüggést lehetett kimutatni az agyvérzés súlyossága és a korai neurológiai állapotromlás (END) kialakulása között. Az idősebb életkor, a magasabb szérum-D-dimer-, -fibrinogén- és -CRP-szint, továbbá az alacsonyabb EF-érték, a CHF, a kórtörténetben szereplő CVD és az END kialakulása rosszabb prognózissal járt együtt. A nagyobb kockázatú csoportban 33 fő esetén (30,3%), és szignifikánsan gyakrabban alakult ki END, mint a mérsékelt kockázattal bíró csoportban ($p < 0,05$). Erős pozitív összefüggés derült ki a CHADS2- és a NIHS-pontszámok között. A növekvő mRS-pontszámokkal párhuzamosan a CHADS2-pontérték is növekedett. Pozitív összefüggés derült ki a NIHS-pontszámok és az mRS-értékek között.
Megbeszélés – A CHADS2-pontszám, a haemostaticus aktiváció és az echokardiográfiás leletek alkalmasak az agyvérzés súlyosságának és prognózisának előrejelzésére. Az agyvérzés súlyosságát és prognózisát befolyásoló ismert faktorok segíthetnek a primer prevenció és az agyvérzés-terápia tervezésében.

Kulcsszavak: *CHADS2-pontszám, az agyvérzés súlyossága, ischaemiás stroke*

Cardio-embolic stroke forms 15-25% of all strokes and AF is the underlying cause in 45% of the cases[1–3]. Stroke risk classifications are used when deciding to initiate oral anticoagulant treatment in patients with AF and one of them is CHADS2 scoring system. (CHADS2= congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke [double weight]). The aim of the scoring systems is to estimate risk of stroke in patients with AF[4, 5]. Previous studies have indicated that CHADS2 score was also closely associated with severity and prognosis of stroke. Some other authors suggest that further research is warranted on this topic[6, 7].

Factors that affect severity of stroke and prognosis in AF patients with stroke are not known exactly[7]. CHADS2 scoring parameters do not include echocardiographic parameters. Left atrial enlargement and low EF were demonstrated to be independent risk factors for stroke in several studies[8, 9]. Hematologic parameters that are measured after stroke were reported to be used to evaluate stroke severity and prognosis[10, 11]. The aim of this study is to evaluate utility of CHADS2 score to estimate stroke severity and prognosis in patients with ischemic stroke due to non-valvular AF. In addition, the study wants to evaluate effects of hematologic markers and echocardiographic findings on stroke severity and prognosis. Decrease in morbidity and mortality may be achieved by early estimation of prognosis which leads to more effective stroke management and prevention strategies.

Methods

This study included 156 ischemic stroke cases due to non-valvular AF in neurology ward of Trakya University Medical School between March 2013-March 2015. Our study was planned as a prospective study. The study was approved by the Ethics Committee for Clinical Investigations of the Faculty of Medicine of Trakya University (2013/57, 06/05). Each patient signed the informed consent form. Age, sex, history for diabetes mellitus (DM), CVD, CHF, 12-lead electrocardiography findings, and neurological examination findings of the patients included in this study were recorded. NIHS score[12] was used to evaluate severity of stroke at admission. Serum fibrinogen, CRP, D-dimer values were measured at first 12-24 hours and recorded. Carotid and vertebral Doppler ultrasonography findings, brain CT and cranial MRI of the cases were evaluated. Left atrial diameter and EF values measured with transthoracic echocardiography were recorded and left atrial diameter >40 mm was accepted as large. Cut-off values were 0.5 mg/dL for CRP, 0.5 mg/mL for D-dimer, and 400 mg/dL for fibrinogen. Based on a previous study, patients were divided into three subgroups depending on the NIH score[3]. A score ≤ 7 was classified as mild, $>7 \leq 16$ was classified as moderate, and > 16 was classified as severe stroke.

CHADS2 score was calculated in our study as defined in the original article. One point was given for the presence of CHF, HT, DM, and age over 75

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

Parameters	Male (n=92)	Female (n=65)	P
NIHSS	9.39 ± 5.83	12.17±6.62	p<0.05
mRS	2.84 ± 1.74	3.63 ± 1.7	p<0.05
HT	88.5%	89.5%	
DM	34.6%	34.6%	
CHF	48.1%	49.1%	
CVD/TIA history	50%	50%	
Age (years):			
Means: 74.1±11.4	58.9%	41.1%	p<0.05
p<0.05			
≥75	NIHSS: 12.39 ± 6.33	NIHSS:9.09±6.07	
<75	mRS: 3.72 ± 1.69	mRS: 2.70 ± 1.67	
Left atrial diameter			
Means: 43.39±11.4 (mm)			
>40	53.2%	46.8%	
≤40			
Fibrinogen (mg/dL)	64.7%	35.3%	
Means: 462.2±130.4			
>400			
≤400			
D-dimer (mg/mL)	69.9%	30.1%	
Means: 1.4±2.4			
>0.5			
≤0.5			
CRP (mg/dL)	75.6%	24.4%	
Means: 1.8±2.7			
>0.5			
≤0.5			

years and 2 points were given for the history of ischemic stroke or transient ischemic attack or thromboembolic event[4]. Since patients with ischemic stroke were included, CHADS score was at least 2. Patients with CHADS2 score of 2-3 were defined as moderate risk group and 4 were defined as high risk group. Prognoses of the cases were evaluated at third week. Modified Rankin Scale which has a score range of 0-6 points was used to rate the degree of dependence and to evaluate functional improvement[14]. mRS score equal to or lower than 2 was defined as good prognosis, and equal to or above 3 was defined as poor prognosis.

During the follow-up the deterioration of neurological symptoms with a 1 or more points increase in NIHS score was defined as Early Neurological Deterioration (END)[5]. Reasons of END included haemorrhagic transformation, cerebral herniation, systemic causes (infection, metabolic dysfunctions, myocardial infarction (MI), etc.), infarct extension and recurrent stroke. Brain imaging was ordered to determine haemorrhagic transformation and cerebral herniation. Physical examination was performed and routine blood work up (CRP, Troponin I-T, blood urea nitrogen, creatinine, serum electrolytes, and liver function tests) and chest X-rays were evaluated in END cases due to systemic factors. To detect END due to infarct extension and recurrent stroke, diffusion MRI and brain CT were assessed.

Correlations of CHADS2 score with NIHS and mRS scores were assessed. Effects of age and sex of the patients, presence of DM, CHF, and CVD, large left atrial diameter, EF value, and serum fibrinogen, D-dimer, and CRP levels on CHADS2, NIHS, and mRS scores were evaluated. Risk factors for development of END were investigated.

Statistica 7.0 (Lisence no: 31N6YUCV38) package program was used for statistical analyses. In addition to descriptive statistical methods (mean, standard deviation, frequency) comparisons for quantitative variables were also performed for statistical evaluation. The results were reported as mean ± standard deviation or percentage. Mann-Whitney U test was used to compare means and Chi-Square test was used to compare frequencies. The results were evaluated with a 95% confidence interval and $p<0.05$ significance value.

Table 2. *Clinical features of the cases*

Parameters	Values	Prognosis/ Risks	P
NIHSS Mean (SD): 11.03 ± 6.43	Mild 34% (n=53) Moderate 39.1% (n=61) Severe 26.9% (n=42)		
mRS Mean (SD): 3.31±1.75	0 /1 8.33% (n=13) 2 15.38% (n=24) 3 21.79% (n=34) 4 14.7% (n=23) 5 21.15% (n=33) 6 10.25% (n=16)	Good prognosis 32.1% (n=50) Poor prognosis 67.9% (n=106)	
Early Neurological Deterioration (+): 22.2% (n=33)	Haemorrhagic transformation: 7.1% (n=11) Cerebral herniation: 3.2% (n=5)	Due to systemic factors 7.1% (n=11) Infarct extension/ recurrent ischemic stroke 3.8% (n=6)	
CHADS2 Mean (SD): 4.17±1.01	2 2.56% (n=4) 3 27.56% (n=43) 4 28.21% (n=44) 5 33.97% (n=53) 6 7.69% (n=12)	Moderate risk 30.1% (n=47) 22 females/25 males High risk 69.9% (n=109) 70 females/39 males	p<0.05

Results

Demographic and clinical features of the cases in our study are summarized in **Table 1** and **2**. In patients with age 75, mean NIHS score was 3.3 points and mean mRS score was 1.02 points higher than in patient below 75 years of age. In females, NIHS score was 2.78 points and mRS score was 0.8 points higher than males (p<0.05). There was no difference in sex distribution in the moderate risk group, but female proportion was higher in the high risk group (p<0.05).

Serum D-dimer level and CRP level were higher in the moderate risk group according to NIHS score compared with the high risk group (p<0.01 and p<0.05, respectively). No significant difference was detected between groups in age, left atrial diameter, EF value, and serum fibrinogen level. Compared with the mild severity group, cases in the moderate severity group had higher serum D-dimer (p<0.01), fibrinogen (p<0.01), and CRP levels (p<0.01) and lower EF value (p<0.05). Age and left atrial diameter were not significantly different between the two groups. Compared with the mild risk group, cases in the high risk group had older age (p<0.01), higher serum D-dimer (p<0.01), fibrinogen (p<0.01) and CRP levels (p<0.01) and lower EF (p<0.05). No difference was detected between the groups in left atrial diameter.

Table 3 summarizes the differences between the groups according to stroke severity. Female sex was predominant in the groups with higher NIHS scores (p<0.05). A positive relation was detected between stroke severity and HT, previous CVD history, and presence of CHF (p<0.05). No significant difference was detected between the stroke severity groups in presence of DM and left atrial diameter. A significant association was found between increased stroke severity and END development (p<0.05). Cases with moderate to severe stroke risk were associated with poor prognosis and those with mild stroke risk were associated with good prognosis (p<0.05).

Table 3. *The differences between the groups according to stroke severity*

NIHSS	Mild Severity	Moderate Severity	High Severity	P
Female	49.1% (n=26)	55.7% (n=34)	76.2% (n=32)	<0.05
HT	81.1% (n=43)	86.9% (n=53)	100% (n=42)	<0.05
Previous CVD	20.8% (n=11)	59% (n=36)	73.8% (n=31)	<0.05
CHF	15.1% (n=8)	49.2% (n=30)	88.1% (n=37)	<0.05
DM	30.2% (n=16)	39.3% (n=24)	33.3% (n=14)	
Left atrial diameter	58.5%	54.1%	45.2%	
END	0% (n=0)	14.8% (n=9)	57.1% (n=24)	<0.05
mRS >2	88.7% (n=47)	95.1% (n=58)	100% (n=41)	<0.05

Table 4. *The groups according to prognosis*

mRS	Good prognosis (n=50)	Poor prognosis (n=106)	P
Age (years)	70.7±11.2	75.7±11.2	<0.05
Left atrial diameter (mm)	42.4±6.8	43.9±10.1	
EF	57.8±10.4	53.6±9.7	<0.05
Fibrinogen (mg/dL)	395.1±110.7	493.9±127.5	<0.05
D-dimer (mg/mL)	0.6±0.4	1.8±2,9	<0.05
CRP (mg/dL)	0.8±0.7	2.4±3,2	<0.05
Female	48% (n=24)	64.2% (n=68)	=0.08
HT	82% (n=41)	91.5% (n=97)	<0.05
DM	28% (n=14)	37.7% (n=40)	<0.05
Previous CVD	16% (n=8)	66% (n=70)	<0.05
CHF	18% (n=9)	62.3% (n=66)	<0.05
CHADS2			
Moderate risk	87.2% (n=41)	12.8% (n=6)	<0.05
High risk	8.3% (n=9)	91.7% (n=100)	<0.05

Table 4 summarizes the groups according to prognosis. Older age, higher serum fibrinogen, D-dimer, CRP and lower EF values were associated with poor prognosis ($p<0.05$). No significant difference was found between the good and poor prognosis groups according to left atrial diameter. No difference in sex was found in the good prognosis group but female sex was higher in the poor prognosis group ($p=0.08$). Presence of HT and DM did not affect prognosis. History of CVD and presence of CHF were associated with poor prognosis ($p<0.05$). Being in the moderate risk group was associated with good prognosis and being in the high risk group was associated with poor prognosis ($p<0.05$).

END was not detected in the good prognosis group and was detected in 31.1% of the poor prognosis group (n=33). END development was found to be associated with poor prognosis ($p<0.05$). Left atrial diameter, EF, and serum fibrinogen level were not different between cases that developed END or not. Age, NIHS score, serum D-dimer and CRP values were different between cases that developed END or not ($p<0.05$). The END ratios of the cases were divided into groups according to CHADS2 score. It was determined that there wasn't any END in the cases of the middle-risk group (n = 47). In the high-risk group, 30.3% (n = 33) had an END. Among those in the high-risk group according to the CHADS2 score, END development rate was found to be significantly higher than in the moderate risk group ($p <0.05$).

Differences between groups according to CHADS2 score are shown in **Table 5**. There was no significant difference between the groups in left atrial diameter and EF. Age, NIHS score, serum D-dimer, fibrinogen, CRP value, and mRS were higher in the high risk group than the low risk group according to CHADS 2 score ($p<0.05$).

Spearman's correlation analysis was performed to evaluate the relationship between CHADS2, NIHS score, and mRS. There was a strong positive correlation between CHADS2 and NIHS scores ($\rho=0.68$). mRS score increased with increasing CHADS2 score and there was a strong correlation between them ($\rho=0.7$). Effect of stroke severity on prognosis was assessed and a strong positive correlation was found between NIHS score and mRS ($\rho=0.92$).

Table 5. *Differences between groups according to CHADS2 score*

CHADS2	Moderate risk (n=47)	High risk (n=109)	p
Age (years)	69.4±11.7	76.1±10.7	<0.05
Left atrial diameter (mm)	42±6.7	44±9.9	
EF	59.1±8.8	53.1±10.1	
Fibrinogen (mg/dL)	400±101	489±133	<0.05
D-dimer (mg/mL)	0.7±0.5	1.7±2.9	<0.05
CRP (mg/dL)	0.9±0.8	2.3±3.2	<0.05
NIHS	4.7±3.1	13.7±5.5	<0.05
mRS	1.4±1.1	4.1±1.2	<0.05

Being in the moderate risk group was associated with good prognosis and being in the high risk group was associated with poor prognosis ($p<0.05$). There was a strong positive correlation between CHADS2 and NIHS score ($\rho=0.68$) and mRS ($\rho=0.7$).

Discussion

Although there are many novel treatment methods in acute ischemic stroke, primary prevention is still the most effective approach[15, 16]. There are different views regarding factors that affect stroke severity and prognosis in stroke due to AF[7, 17]. In our study effects of CHADS2 score, haematological markers, and echocardiographic findings on stroke severity and early prognosis were evaluated in patients with ischemic stroke due to nonvalvular AF.

Mean age was higher in cases with high severity and bad prognosis ($p<0.01$). Development of END was associated with advanced age. Although various cut-off values were used for advanced age in different studies its negative effect on stroke prognosis was generally accepted[18, 19]. *Hisayama* et al demonstrated that stroke over 65 years of age was associated with poor prognosis at early period[20]. *Kim* et al.[13] reported that stroke was more severe in patients above 75 years of age and prognoses at 3rd and 12th months were worse. CHADS2, NIHS score, and mRS were higher in females ($p<0.05$). Many studies demonstrated worse prognosis of CVD in females[21–23]. A study which included 1055 ischemic stroke patients found higher CHADS2, NIHS, and mRS scores in females[13]. Ways by which gender influences stroke severity and prognosis are not known. However there are also reports that suggest equal or worse stroke severity and prognosis in males[17, 24].

Kimura et al.[25] found mean NIHS score of 13.7 in patients with AF and mean NIHS score of 6.9 in patients without AF. Mean NIHS score was significantly higher (13.7 points) in the high risk group ($p<0.01$). *Hong* et al[5] demonstrated in 649 stroke patients associated with non-valvular AF that NIHS score was the highest in the high risk group, followed by the moderate risk group and was the lowest in the lowest risk group. A higher CHADS2 score was independently associated with stroke severity. In this study total infarct size was the highest in the highest risk group which partially explains increased stroke severity. Another study in AF patients demonstrated an association between infarct size and NIHS score. However, CHADS2 score was not shown to affect stroke severity and infarct size. This suggests that factors associated with stroke severity are different from the factors that contribute to stroke risk in AF[17].

In accordance with the literature a higher CHADS2 score was associated with increased stroke severity and worse prognosis[5, 6]. There was a strong positive correlation between NIHS score and mRS ($\rho=0.92$) as expected. Association of high NIHS score with poor prognosis is an expected finding[5, 24, 25]. Age, NIHS score, and mRS were higher in the high risk patients ($p<0.05$). Kim et al[6] also found higher values for age, NIHS score, and mRS in the highest risk group according to high CHADS2 score in 298 stroke patients with AF. They suggested that this result was due to higher vascular risk factors and vascular endothelial dysfunction in the group with higher CHADS2 score[6, 24]. In our study the rate of END was higher in the high risk group ($p<0.05$). A similar study also found an association between higher CHADS2 score and END[5]. We think that CHADS2 scoring may be used as a prognostic risk classification before and after stroke.

Similar to the previous studies[13, 25] advanced age and previous CVD history were found to be associated with increased stroke risk ($p<0.05$). There are various opinions about effects of DM, CHF, and HT on stroke severity and prognosis[17, 24, 26, 27]. In parallel with previous studies[28, 29] the presence of CHF and HT were detected to be associated with increased stroke risk ($p<0.05$).

CHF was found to be associated with poor prognosis ($p<0.05$) whereas no effect of HT on prognosis could be found. During the acute period there is a U type relationship between blood pressure and prognosis meaning that both low and high blood pressures lead to poor prognosis[30]. Also there are opinions that CHF and HT don't affect stroke severity and prognosis[24, 27, 31]. Presence of DM was not detected to be associated with stroke severity or prognosis ($p<0.05$). Hyperglycaemia in patients with ischemic stroke is associated with poor prognosis and increased mortality[32]. But there are various views about the effects of DM on stroke severity and prognosis[13, 24, 26]. *Hoshino* et al[31] found associations between high CHADS2 score and increased stroke severity, and poor prognosis in 153 stroke patients but couldn't find an association between prognosis and HT or DM.

Inflammatory response and haemostatic activation are known to occur after ischemic stroke and many studies have been performed on this topic[10, 33]. Haemostatic and inflammatory markers were reported to be used to estimate risk and prognosis before and after stroke. However they can't be

used in clinical practice because exact benefit of these markers are not known[16, 34]. In our study increased CRP level was associated with increased stroke risk, poor prognosis and END development ($p<0.05$). This is thought to be due to contribution of inflammation to brain damage initiated by ischemia during acute phase of stroke which increases stroke risk[35, 36]. *Smith* et al[11] detected that high post-stroke CRP level after ischemic stroke in 37 ischemic patients were associated with increased stroke severity and poor prognosis. Inflammatory markers were found to be directive for prognostic information and novel treatments in patients with acute ischemic stroke. CRP was suggested not to be informative about stroke severity and prognosis[37]. CRP evaluation is recommended at 12-24 hours after stroke. But there is not a common view about timing of the first CRP measurement during acute ischemic stroke and clinical cut-off point that predict prognosis. In addition, because CRP is affected by many factors such as infection, tissue damage, age, cigarette smoking, obesity, DM, and AF it is a nonspecific laboratory finding with a limited utility[36]. *Winbeck* et al[38] could not detect an association between CRP which is measured at admission and 12th hour and infarct size in 127 patients with ischemic stroke but high CRP at 48th hour was found to be associated with large infarct size. High CRP level at 12-24 hours after ischemic stroke was found to be associated with poor prognosis but high CRP level during first 12 hours after ischemic stroke was not associated with prognosis. Similar to our results *Lip* et al[39] found higher CRP values in the high risk group and they concluded that using CRP for future risk classifications would be beneficial.

Fibrinogen is an acute phase reactant formed as a response to inflammation; it contributes to atherosclerosis and plays a role in haemostatic activation[40]. Compared with other stroke subtypes, serum fibrinogen levels were found to be higher in cardioembolic strokes due to AF[33, 41]. Since patients with cardio-embolic stroke are evaluated in our study, higher fibrinogen levels could be found in most of the patients. There was a significant relationship between high serum fibrinogen level and increased stroke risk ($p<0.05$). Increased fibrinogen after stroke is thought to have a toxic effect on central nervous system and to affect apoptosis and neurodegeneration[42]. *Rallidis* et al[43] measured fibrinogen level at first 12 hours in 231 stroke patients and high fibrinogen level was found to be associated with increased stroke severity and short term mortality. *Swarowska* et al.[44] found association between increased fibrinogen level and long term mortality in 737 patients with ischemic stroke but could not find a difference in NIHS score between patients with high or low fibrinogen levels. Different results found in the studies may be due to differences in stroke subtype and timing of fibrinogen measurement. However, timing of fibrinogen measurement and clinical cut-off point have not been exactly determined. Moreover, fibrinogen may be affected by factors such as smoking, age, hormone replacement therapy, and exercise[42]. High serum fibrinogen was associated with poor short-term prognosis ($p<0.05$). *Del Zoppo* et al.[45] found gradually increasing fibrinogen levels during the first 24 hours after stroke and found associations between high fibrinogen level and poor prognosis and mortality. *Di Napoli* et al.[40] measured serum fibrinogen and CRP levels at first 24 hours after ischemic stroke in 128 patients and evaluated 1 year prognosis; increased CRP was associated with poor prognosis but no effect of fibrinogen was found on prognosis. In the high risk group according to CHADS2 score, serum fibrinogen and D-dimer levels were higher ($p<0.05$). Since fibrinogen and D-dimer levels increase at an atherosclerotic basis and there are parameters included in CHADS2 score like HT, DM, and age which can increase their levels, increased fibrinogen and D-dimer level in patients with high CHADS2 scores is an expected result[42, 46].

Serum D-dimer levels increase in acute ischemic stroke and the increase is even higher in cardio-embolic stroke; however there are conflicting views on this topic. This may be due to the structure of the clot and increased D-dimer in patients with AF due to hypercoagulability[33, 47, 48]. High D-dimer level was associated with increased stroke severity ($p<0.01$). *Berge* et al.[47] detected that high D-dimer level was associated with increased stroke severity and poor short-term prognosis in 76 patients with ischemic stroke. D-dimer level was higher in the embolic group and increased stroke severity was due to embolic stroke mechanism. High D-dimer level was found to be associated with poor short-term prognosis and development of END ($p<0.05$). Association of serum D-dimer value with post-stroke clinical progression and poor prognosis in ischemic stroke patients was evaluated. High D-dimer level was an early predictor for ischemic progression and it was associated with poor short-term prognosis[49, 50]. *Rallidis* et al.[43] found associations between high fibrinogen levels measured at first 12 hours post-stroke and short-term mortality but no effect of D-dimer could be detected. All mechanisms that increase D-dimer value during acute stroke period are not known and the reason can't be found in every occasion. D-

dimer may reflect inflammation and systemic hypercoagulability may increase before stroke due to atherosclerosis, and may indicate formation of new thrombosis. D-dimer is a practical and safe method to exclude thromboembolic events[50]. It may also be used to evaluate stroke severity and prognosis.

Although left atrial enlargement is in general a controversial risk factor for stroke, studies with larger samples are needed[8, 9]. *Caplan* et al.[51] found larger left atrial diameter in stroke patients due to AF and recommended its use for evaluation of stroke risk. Left atrial diameter is affected from many factors such as cardiac diseases, body mass index, advanced age, HT, DM, and AF[52, 53]. In our study no effect of left atrial diameter was detected on stroke severity or prognosis. Low EF was found to be associated with increased stroke risk and poor prognosis ($p<0.05$). *Milionis* et al[54] reported that low EF was associated with increased stroke severity and poor prognosis. In 231 patients who had ischemic stroke due to AF, left atrial diameter did not affect infarct size but larger infarcts were found in patients with low EF values[17]. Left atrial diameter is not included in CHADS2 risk scoring. In our study larger left atrial diameters were found in more than half of the patients and we suggest that left atrial evaluation as an additional parameter will be helpful for risk classifications. Since there was not a control group in our study, we couldn't determine the contribution of left atrial diameter to stroke development, however we could not find a difference in distribution of EF and left atrial diameter between moderate and high risk groups. *Bouzas* et al.[8] reported increased stroke frequency only in females and Framingham study reported only in males with increasing left atrial diameter[9]. Previous research has shown an association between low EF and poor prognosis but these studies included all ischemic stroke subtypes. Since low EF is more common in the cardio-embolic group, more severe stroke with worse prognosis in patients with low EF value may be due to the mechanism of embolic stroke. In our study all patients had cardio-embolic strokes. *Byun* et al.[55] found associations between low EF and increased stroke severity and poor short-term prognosis in 437 patients with cardio-embolic stroke.

In conclusion, left atrial diameter and EF may affect risk and prognosis of ischemic stroke but controversies in these studies should be eliminated[56]. We suggest that the use of echocardiographic findings, especially EF will be helpful in stroke risk classification. Our study demonstrated the importance of CHADS2 score, haemostatic activation and echocardiographic findings to assess stroke severity and prognosis. Knowing factors which affect stroke severity and prognosis in patients with ischemic stroke may be directive to decide pre-stroke prevention and stroke management.

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INVESTIGATION OF RISK FACTORS, TOPOGRAPHIC LOCATION AND STROKE MECHANISMS OF UNILATERAL ISOLATED AND POSTERIOR CEREBRAL ARTERY THALAMIC INFARCTS

Elif GÖKÇAL, Yıldızhan ŞENGÜL, Ferda USLU

Bezmialem Foundation University Hospital, Department of Neurology, Istanbul, Turkey

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Aim – In this study, we aimed to examine the risk factors, topographic features and stroke mechanisms of acute ischemic unilateral infarcts of thalamus.
Methods – Patient with isolated thalamic infarct and those with posterior cerebral artery (PCA) infarction who were admitted to our hospital between January 2014 and January 2017 with acute unilateral thalamic infarction (TI) were included in this study (isolated thalamic infarction/ isolated TI; thalamic and posterior cerebral artery infarction/PCA+TI). Demographic characteristics and vascular risk factors of the patients were determined. Thalamic infarct areas were recorded topographically as anterior, posteromedial, ventrolateral, posterolateral, more than one area, and variant areas. Stroke mechanism was determined according to the criteria of „Trial of Org 10172 in Acute Stroke Treatment" (TOAST). Patients with isolated TI and PCA TI were compared according to risk factors, stroke mechanism and infarct topography.
Results – Forty-three patients with a mean age of 63.3 ± 14.5 years were included in the study. Twenty-eight patients (60.1%) were found to have isolated TI and the remaining 15 patients (34.9%) had PCA+TI. 32.1% of patients with isolated TI had sensory symptoms on presentation, and 60% of patients with PCA-TI had sensorimotor symptoms. The mean age, the mean score on National Institutes of Health Stroke Scale (NIHSS) and the mean frequency of atrial fibrillation were higher in PCA+TI patients than in isolated-TI patients (p: 0.04, p: 0.004, p: 0.02 respectively). 32.6% of the patients had ventrolateral, 30.2% had posteromedial involvement. Ventrolateral topography was seen in 46.7% of the PCA+TI patients, while posteromedial topography was seen in 39.3% of the isolated-TI patients. 53.6% of the isolated-TI had small

AZ EGYOLDALI IZOLÁLT ÉS HÁTSÓ AGYI ARTERIOLARIS THALAMICUS INFARKTUSOK KOCKÁZATI TÉNYEZŐINEK, TOPOGRÁFIAI ELHELYEZKEDÉSÉNEK ÉS STROKE-MECHANIZMUSAINAK VIZSGÁLATA
Gökçal E, MD; Şengül Y, MD; Uslu F, MD
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Cél – A thalamus egyoldali, akut ischaemiás infarktusainak mechanizmusát, rizikótényezőit és topográfiai jellemzőit vizsgáltuk.
Módszerek – A vizsgálatba a kórházunkba 2014 januárja és 2017 januárja között akut egyoldali thalamus infarktussal felvett betegek kerültek (a betegek vagy izolált thalamicus infarktusban/TI, vagy kombinált thalamicus infarktusban szenvedtek; a kombinált infarktusban a thalamuson kívül a posterior cerebralis artéria területe volt érintett: PCA + TI). Meghatároztuk a betegek demográfiai jellemzőit és vascularis rizikótényezőit. A thalamicus infarktusokat topográfiai szempontból anterior, posteromedialis, ventrolateralis, posterolateralis, egy területnél többre terjedő és variáns csoportokba osztottuk. A stroke- mechanizmust a „Trial of Org 10172 in Acute Stroke Treatment" (TOAST) kritériumai alapján állapítottuk meg. Az izolált TI és a PCA + TI betegek csoportját a kockázati tényezők, a stroke-mechanizmus és az infarktustopográfia alapján hasonlítottuk össze.
Eredmények – A vizsgálatba 43 beteget vontunk be (az életkor mediánja: 63,3 ± 14,5 év). 28 beteg (60,1%) izolált TI-ben, míg 15 beteg (34,9%) PCA + TI-ben szenvedett. A kórházi felvételkor az izolált TI-betegek 32,1%-a esetében jelentkeztek szenzoros tünetek, míg a PCA + TI betegek 60%-a szenzomotoros tünetektől szenvedett. A PCA + TI betegek körében magasabb volt az életkor, a National Institutes of Health Stroke Scale (NIHSS-) pontszám, valamint a pitvarfibrilláció gyakoriságának mediánja, mint az izolált TI-betegek csoportjában (p: 0,04, p: 0,004, p: 0,02). A betegek 32,6%-a ventrolateralis, 30,2%-a posteromedialis elhelyezkedésű infarktustól szenvedett. A PCA + TI betegek 46,7%-ára volt jellemző a ventrolateralis elhelyezkedés, míg az izolált TI-betegek 39,3%-ának infarktusa pos-

Correspondent: Dr. Elif GÖKÇAL, Bezmialem Foundation University Hospital, Department of Neurology; Adnan Menderes Bulvarı, Fatih/İstanbul Turkey. E-mail: elifdr99@gmail.com, phone: 05054927902

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vessel disease etiology, while 40% of the PCA+TI had cardioembolic etiology, and the other 40% had large artery atherosclerosis.
Conclusion – Our study showed that the most ommon stroke mechanism in patients with thalamic infarction is the small vessel disease. Isolated TI and PCA+TI patients differ in terms of etiologic mechanism and infarct topography. Variant territorial involvement and multiple area involvements can be quite common in thalamic infarcts.

Keywords: *thalamic infarct, isolated thalamic infarction, thalamic and posterior cerebral artery infarction, stroke mechanism, topography*

teromedialis elhelyezkedésű volt. Etiológia szempontjából az izolált TI-betegek 53,6%-a kisérbetegségben, míg a PCA + TI betegek 40%-a cardialis emboliában, 40%-a nagyartéria-atherosclerosisban szenvedett.
Következtetés – Vizsgálatunk szerint a thalamicus infarktus leggyakrabban kisérbetegség talaján alakul ki. Az izolált TI-betegek és a PCA + TI betegek esetében eltérő az infarktus etiológiája és topográfiája egyaránt. Thalamicus infarktus esetén gyakori, hogy számos különböző terület érintett.

Kulcsszavak: *thalamicus infarktus, izolált thalamicus infarktus, thalamicus és posterior cerebralis arteria infarktus, stroke-mechanizmus, topográfia*

Vascular diseases of thalamus are one of the uncommon stroke syndromes. Thalamic ischemic stroke may be isolated or be associated with posterior cerebral artery (PCA) infarcts, top of the basilar artery syndrome or other posterior circulation infarctions[1]. In addition to these anatomic differences of ischemic stroke of the thalamus, differences may also be seen in terms of stroke mechanisms and risk factors. However, only a few studies have examined this topic until today.

Diffusion-weighted magnetic resonance imaging (DWI-MRI) is a rapid and easily accessible imaging technique that can detect early ischemic infarction. The mechanism of ischemic stroke requires time-consuming diagnostic studies such as conventional MRI, vascular imaging, transthoracic echocardiography (TTE), and rhythm Holter electrocardiography (ECG). Early recognition of the stroke mechanism is important in the proper application of the secondary protection as well as in determination of the prognosis. In recent years, some studies reported that topography of the infarction seen on DWI-MRI can predict the stroke mechanism[2, 3].

The aim of this study was to compare the topography of infarcts according to DWI-MRG, risk factors and stroke mechanisms of patients with acute unilateral isolated thalamic infarct (isolated TI) and with thalamic infarcts and posterior cerebral artery infarction (PCA + TI).

Methods

Patients admitted to our emergency department and diagnosed with acute ischemic stroke between January 2014 and January 2017 were retrospectively analyzed. According to DWI-MRI findings, patients with isolated-TI and those patients with PCA + TI were identified. Of patients with acute thalamic infarcts, those having bilateral infarcts, top of the basilar syndrome or concomitant infarcts areas other than PCA vascular region were excluded.

Demographic characteristics, vascular risk factors, clinical, laboratory and neuroradiological data were collected from patients included into the study. The following criteria were considered for vascular risk factors: a history of hypertension (HT) or an observed arterial blood pressure >140/90 mm Hg; presence of a history of diabetes mellitus (DM) or a fasting glucose exceeding 126 mg/dl other than that measured during the acute phase; a positive history of hyperlipidemia (HL) or a fasting total cholesterol >200 mg/dl, low-density protein (LDL)>130 mg/dl, and/or a triglyceride (TG) >180 mg/dl. Data for the presence of coronary artery disease (CAD), smoking and previous history of stroke were retrieved from patients' medical records.

The National Institutes of Health Stroke Scale (NIHSS) was recorded according to the assessment on the first day of hospital admission. All patients underwent brain MRI (including DWI-MRI). Etiological workup including brain and cervical computed tomography angiography (CTA), MR Angiography and /or Doppler ultrasonography, transthoracic echocardiography (TTE), 24-hour Holter ECG monitoring and other investigations if needed were reviewed from the data performed in a 3-month period after the index stroke. Patients having insufficient etiological work-up were not included into the study.

Considering all variable data, etiological classification of stroke was made based on the criteria of TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification[4]. According to these criteria, patients were grouped as large artery atherosclerosis (LAA), small vessel disease (SVD), cardioembolic (CE), other causes and undetermined etiology.

Thalamic infarct topographies were evaluated by two independent neurologists with consensus using

DWI-MRI, T_1 sequence was used if there was inconsistency between the two raters. All of the infarctions were grouped into anterior, posteromedial, ventrolateral, and posterolateral groups based on previously published templates for arterial territories. According to these territories a) Anterior territory arise from polar or tuberothalamic artery, (b) Posteromedial territory arise from the thalamoperforating artery; (c) Ventrolateral territory arise from the thalamogeniculate artery; (d) Posterolateral territory arise from the posterior choroidal artery. Besides, the infarct topographies which did not match to classical territories (called as variant type) and those having more than one vascular territories were determined.

Patients were grouped as those with isolated-TI and those with PCA + TI. SPSS (Statistical Package for Social Sciences for Windows Version 23 software) was used for statistical evaluation. Mean, minimum, maximum and percentage values were determined by descriptive statistical analysis. The Shapiro-Wilk test was used to evaluate distribution of data. Pearson's chi-square test was used for comparison of categorical variables. Student t-test was used for normally distributed variables and Mann-Whitney U test for those without normal distribution. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 43 patients (60.5% male) with a mean age of 63.3 ± 14.5 (minimum-maximum: 20-87) were included in the study. The mean of NIHSS on admission was 2.6 ± 1.7. 72.1% of patients had HT, 27.9% HL, 37.2% CAD, 16.3% AF and 18.6% of all patients had stroke history. Twenty-five (58.1%) patients had right thalamic and 18 patients (41.9%) had left thalamic infarction. Twenty-eight patients (60.1%) were found to have isolated-TI, and the remaining 15 patients (34.9%) had PCA + TI.

The time from the onset of complaints until admission to the hospital was 16.5 ± 16.7 (1-72) hours. There was no statistically significant difference between patients with isolated-TI and PCA + TI in the time of admission to the hospital. In 32.1% of patients with isolated-TI, clinical presentation was reported only with sensory symptoms, 28.6% with dizziness and / or gait disturbance, 25% with sensorimotor symptoms, 14.3% with consciousness changes such as apathy and somnolence. In PCA-TI patients, 60% had sensorimotor symptoms, 20% had only sensory symptoms, and 20% had clinical presentation in the form of dysarthria and / or gait disturbance.

When the demographic and clinical features were compared between the two groups; the mean of age and NIHSS in PSA + TI patients were statistically higher than those in isolated-TI patients (p: 0.04, p: 0.004 respectively). There was no significant difference in sex, HT, DM, HL, CAD, and stroke history between the two groups. AF was more frequent in PCA-TI patients than in isolated-TI patients (p: 0.02).

When the patients were grouped into two groups according to age, isolated-TI was found in 85.7% of patients younger than 55, whereas in 57.1% of patients at the age of 55 or older (p: 0.04).

When classified according to thalamic topography, 14 (32.6%) patients had ventrolateral, 13 (30.2%) posteromedial, 5 (11.6%) posterolateral and 1 (2.3%) anterior territorial infarct. There were 5 (11.6%) patients with infarct area involving more than one territory. 11.6% of patients with central infarction did not have classical topography.

Thalamic infarct topographies seen in the isolated-TI and PCA + TI groups are given in **Table 1**. The most common topography in patients with isolated + TI was posteromedial (39.3%) whereas the most common topography in patients with PCA + TI was ventrolateral (46.7%) and posterolateral (33.3%). All of the 5 patients who had central topography were in the isolated –TI group (80% of infarcts with more than one area) (p: 0.005).

Table 1. *Topographic localisation of unilateral thalamic infarcts with isolated and posterior cerebral artery areas*

	Isolated-TI (N %)	PCA+TI (n, %)	p
Anterior	1, 3.6%	0, 0%	0.005
Posteromedial	11, 39.3%	2, 13.3%	
Ventrolateral	7, 25%	7, 46.7%	
Posterolateral	0, 0%	5, 33.3%	
Central	5, 17.9%	0, 0%	
More than one	4, 14.3%	1, 6.7%	

According to stroke mechanisms, 15 patients (34.9%) had SVD, 12 patients (27.9%) had CE and 7 patients (16.3%) had LAA. 9 (20.9%) patients were included in the undetermined etiology group in spite of adequate investigations. While the most common stroke mechanism in isolated-TI patients was SVD (53.6%), the most common stroke mechanisms in PCA-TI patients were CE (40%) and LAA (40%) **(Table 2)**.

The most common vascular territories in isolated-TI patients having SVD etiology were the posteromedial, ventrolateral, and central regions, while all isolated-TI patients having undetermined etiology had infarctions involving multiple areas. Major

Table 2. *Stroke mechanisms in unilateral thalamic infarcts with isolated and posterior cerebral artery area*

	Isolated-TI (n, %)	PCA+TI (N, %)	Total (n, %)	p
Major vessel disease	1, 3.6%	6, 40%	7, 16.3%	0.001
Small vessel disease	15, 53.6%	0, 0%	15, 34.9%	
Cardioembolic	6, 21.4%	6, 40%	12, 27.9%	
Undetermined	6, 21.4%	3, 20%	9, 20.9%	

vascular disease and cardioembolic etiologies in PCA-TI patients were most commonly found in ventrolateral and posterolateral topographies **(Table 3)**.

Discussion

The aim of this study was to investigate relationship between stroke mechanisms and infarct topographies in patients with isolated TI and PCA+TI.

The vascular supply of thalamus is fundamentally provided by 4 main thalamic arteries, polar artery of the posterior communicating artery supplies the anterior, posterior choroidal artery branching from the PCA supplies the posterior, thalamoperforated arteries separated from the P1 segment of the PCA supply the medial thalamus and those from the P2 segment of the PCA supply the lateral thalamus. In addition to this classical topography, variations can also be seen in the thalamus vasculature[6].

In our study, all infarcts considered as variant infarcts were found in the central topography and those were 11.6% of all the infarcts of the study population. In the literature, central thalamic infarct rate has been reported as 6%[7]. Moreover, all of the central thalamic infarcts were in the group of isolated-TI, and the etiologic mechanisms were classified as SVD in all. In the literature, the pathophysiological mechanism of variant infarcts has been attributed to the frequent variations in thalamus vascularisation or they have been considered as border zone infarcts developed by simultaneous microangiopathic changes in neighboring border zone areas[6, 7].

In our results, only 1 of 5 patients with multiple territorial infarcts had PCA-TI. This patient had a panthalamic infarct and an atherosclerotic thrombus in the right PCA. Of the remaining 4 patients with isolated-TI, the infarct involved the anterior and posteromedial regions in the case of two patients, 1 involved the ventrolateral and posteromedial regions and the other 1 patient had posterolateral and posteromedial regional infarcts. All those patients were included in the undetermined etiology group. Among the other 4 patients having undetermined etiology, 3 had PCA + TI and 1 had isolated-TI. The rate of undetermined etiology in patients with thalamic infarcts have been reported as 10.3%, this rate was higher in our study group (approximately 20%)[8].

In our study, the most commonly seen clinical presentations were sensory and sensorimotor symptoms as in the literature[9]. Cortical findings in the form of apathy, unconsciousness and aphasia were observed in 14.3% of the patients, and the topographic locations in these patients were found in the anterior and posteromedial areas as in the literature[10]. The frequency of vascular risk factors in our patients was found to be similar to the rates reported in all ischemic stroke patients[11]. Isolated-TI patients were younger and their NIHSS scores were higher than that of the PCA-TI patients. The more frequent occurrence of AF in PCA-TI patients may be attributed to an increase in the prevalence of AF with age[12].

As reported in many studies, the most common affected thalamic area in patients with PCA + TI were the ventrolateral and posteromedial areas, while posteromedial infarctions were the most common in patients with isolated-TI[13, 14]. In terms of the etiologic mechanism, our results were also similar to the previously published literature: SVD was seen more commonly in patients with isolated-TI, whereas CE and LAA etiologies were seen more commonly in patients with PCA + TI[1, 8].

There are conflicting results in terms of the relationship between etiologic mechanisms and thalamic infarct topography. No significant difference was found between the etiologic mechanisms and thalamic stroke topography in our study. Similar to our results, it has been reported that different etiologic mechanisms can be responsible for different infarct topographies of thalamus[8]. In a recent study, however, SVD was determined in 72% of ventrothalamic infarcts and most of the patients with LAA etiology had posteromedial thalamic infarct[1].

The retrospective nature and the small number of patients are the most important limitations of this study. Thalamus has a lot of functions such as memory, executive functions, emotional state, and the processing of sensory information[15]. This functional diversity of thalamus causes the diseases of thal-

Table 3. *Isolated-TI and PCA+TI distribution of thalamic topography according to stroke mechanism in patients*

		Ant	PM	VL	PL	Central	More than one
Isolated TI	MVD	1. 100%	0. 0.0%	0. 0.0%	0. 0.0%	0. 0.0%	0. 0.0%
	SVD	0. 0.0%	5. 33.3%	5. 33.3%	0. 0.0%	5. 33.3%	0. 0.0%
	CE	0. 0.0%	4. 66.7%	2. 33.3%	0. 0.0%	0. 0.0%	0. 0.0%
	Undetermined	0. 0.0%	2. 33.3%	0. 0.0%	0. 0.0%	0. 0.0%	4. 66.7%
PCA+TI	MVD	0. 0.0%	1. 16.7%	2. 33.3%	2. 33.3%	0. 0.0%	1. 16.7%
	SVD	0. 0.0%	0. 0.0%	0. 0.0%	0. 0.0%	0. 0.0%	0. 0.0%
	CE	0. 0.0%	0. 0.0%	4. 66.7%	2. 33.3%	0. 0.0%	0. 0.0%
	Undetermined	0. 0.0%	1. 33.3%	1. 33.3%	1. 33.3%	0. 0.0%	0. 0.0%

Ant: anterior, PM: posteromedial, VL: ventrolateral, PL: posterolateral, SVD: small vessel disease, MVD: major vessel disease, CE: cardioembolic

amus to present in a wide variety of clinical pictures. In our study, thalamic infarcts were also reviewed for risk factors, topographic features and stroke mechanisms.

In conclusion, our study showed that the most common stroke mechanism in patients with thalamic infarction is SVD and that the most common localization is ventrolateral and posteromedial. Isolated-TI and PCA + TI patients differ in terms of etiologic mechanism. SVD etiology is more common in patients with isolated-TI, while CE and LAA more common in patients with PCA + TI. In terms of infarct topography, the most common is posteromedial topography in isolated-TI, and ventrolateral in PCA + TI. Variant topographies and infarcts involving more than 1 topography can be seen quite commonly in thalamic infarcts.

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RELATIONSHIP BETWEEN STATUS EPILEPTICUS SEVERITY SCORE AND ETIOLOGY IN ADULT NCSE PATIENTS

Fatma GENÇ[1], Abidin ERDAL[1], Gizem AKÇA[1], Ertan KARAÇAY[1], Eylem Özaydın GÖKSU[1], Gülnihal KUTLU[2], Yasemin Biçer GÖMCELİ[1]

[1]Antalya Training and Research Hospital, Department of Neurology Antalya, Turkey
[2]Muğla Sıtkı Koçman University Faculty of Medicine Department of Neurology and Clinical Neurophysiology, Muğla, Turkey

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Purpose – Nonconvulsive status epilepticus (NCSE) is a heterogeneous, severe neurological disorder of different etiologies. In this study, the outcomes of NCSE episodes was assessed in a large series of adult patients. Our objective was to evaluate relationship between Status Epilepticus Severity Score (STESS) and etiology and the role of etiological factors on predicting the outcomes.
Method – In this retrospective study, the medical records of 95 patients over 18 years of age who were diagnosed with NCSE between June 2011 and December 2015 were reviewed. Their treatment and follow-up for NCSE was performed at the Epilepsy Unit in Department of Neurology, Antalya Research and Training Hospital. Etiological factors thought to be responsible for NCSE episodes as well as the prognostic data were retrieved. The etiological factors were classified into three groups as those with a known history of epilepsy (Group 1), primary neurological disorder (Group 2), or systemic/unknown etiology (Group 3). STESS was retrospectively applied to patients.
Results – There were 95 participants, 59 of whom were female. Group 1, Group 2, and Group 3 consisted of 11 (7 female), 54 (33 female), and 30 (19 female) patients, respectively. Of the 18 total deaths, 12 occurred in Group 2, and 6 in Group 3. The negative predictive value for a STESS score of ≤ 2 was 93.88% (+LR 2.05 95% CI: 1.44-2.9 and –LR 0.3 95% CI 0.10-0.84) in the overall study group. While the corresponding values for Group 1 (patients with epilepsy), Group 2 (patients with primary neurological disorder), and group 3 (patients with systemic or unknown etiology) were 100%, 92.59% (+LR 2.06 95%CI: 1.32-3.21 and –LR 0.28 95% CI 0.08-1.02) 83.33% (+LR 1.14 95%CI: 0.59-2.9 and –LR 0.80 95% CI 0.23-2.73).

A STATUS EPILEPTICUS SÚLYOSSÁGI PONTSZÁM ÉS A NONCONVULSIV STATUS EPILEPTICUS ETIOLÓGIÁJA KÖZÖTTI KAPCSOLAT FELNŐTT BETEGEK KÖRÉBEN

Genç F, MD; Erdal A, MD; Akça G, MD; Karaçay E, MD; Göksu EÖ, MD; Kutlu G, MD; Gömceli YB, MD

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Cél – A nonconvulsiv status epilepticus (NCSE) heterogén, különböző etiológiai faktorok következtében kialakuló, súlyos neurológiai betegség. A vizsgálat során NCSE-epizódok kimenetét elemeztük nagyszámú felnőtt beteg körében. A cél a Status Epilepticus Súlyossági Pontszám (STESS) és az etiológia közötti kapcsolat, valamint az etiológiai faktorok prediktív szerepének megállapítása volt.
Módszer – A retrospektív vizsgálat során áttekintettük annak a 95, 18 évesnél idősebb betegnek az orvosi dokumentációját, akiket 2011 júniusa és 2015 decembere között NCSE-vel diagnosztizáltak, majd az Antalya Kutatókórház Neurológiai Osztályának epilepsziarészlegén kezeltek. Összegyűjtöttük az NCSE-epizódok hátterében feltételezhető etiológiai faktorokat és a prognosztikus adatokat. Az etiológiai faktorokat három csoportba osztottuk: ismert epilepsziás kórtörténet (1. csoport), primer neurológiai betegség (2. csoport), szisztémás, illetve ismeretlen etiológia (3. csoport). A STESS megállapítása retrospektív módon történt.
Eredmények – A 95 résztvevőből 59 volt nő. Az 1-es, 2-es és 3-as csoportokba 11 (7 nő), 54 (33 nő) és 30 (19 nő) beteg került. Összesen 18-an haltak meg, 12-en a 2-es, 6-an a 3-as csoportban. A ≤ 2 STESS-pontszám negatív prediktív értéke 93,88%-nak bizonyult a teljes betegpopulációban (+LR 2,05 95% CI: 1,44–2,9 és –LR 0,3 95% CI: 0,10–0,84), 100%-nak az 1-es, 92,59%-nak a 2-es és 83,33%-nak a 3-as betegcsoportban (+LR 2,06 95% CI: 1,32–3,21 és –LR 0,28 95% CI: 0,08–1,02; valamint +LR 1,14 95% CI: 0,59–2,9 és –LR 0,80 95% CI: 0,23–2,73).
Következtetések – Az eddigi egyik legnagyobb NCSE-betegpopuláció esetében állapítottuk meg a STESS-pontszámokat. A STESS mint prediktív eszköz hasznosnak bizonyult a kedvező kimenet előrejelzésében az epilepsziás

Correspondent: Dr. Fatma GENÇ, Antalya Training and Research Hospital, Department of Neurology; Antalya, Turkey.
Phone: +90 242 249 4400, mail: sanivardr@yahoo.com

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Conclusions – This study included the one of the largest patients series ever reported in whom STESS, a clinical scoring system proposed for use in patients with status epilepticus, has been implemented. Although STESS appeared to be quite useful for predicting a favorable outcome in NCSE patients with epilepsy and primary neurological disorders, its predictive value in patients with systemic or unknown etiology was lower. Further prospective studies including larger NCSE samples are warranted.

Keywords: *epilepsy, nonconvulsive status epilepticus, status epilepticus severity score, etiology*

és a primer neurológiai betegcsoportban, míg kevésbé hasznosítható eredményt adott a szisztémás, illetve ismeretlen etiológiájú csoportban.
További, nagyobb betegcsoporton végzett prospektív vizsgálatokra van szükség.

Kulcsszavak: *epilepszia, nonconvulsiv status epilepticus, Status Epilepticus Súlyossági Pontszám, etiológia*

Nonconvulsive status epilepticus (NCSE) is an epileptic condition with reduced or altered consciousness and behavioral, vegetative, or merely subjective symptoms, such as auras, but without major convulsive movements, lasting for at least 10 min[1]. NCSE is frequently overlooked by the clinicians, precluding accurate incidence estimations[2]. Studies across Europe have reported an incidence rate between 2.6 to 7.8 per 100.000, depending on the definition of "convulsive"[3-5]. The prevalence of NCSE in comatose patients without clinical convulsions admitted to intensive care unit is around 8%[6]. Although NCSE requires prompt diagnosis and treatment, it does not exhibit specific clinical characteristics, leading to missed diagnosis or may be confused with a psychiatric condition[6]. In contrast with some studies reporting high mortality and morbidity, others have proposed that it may actually represent a relatively benign condition requiring no aggressive treatment. The mortality differences across studies regarding NCSE are due to its heterogeneous nature[1, 7, 8].

A clinical scoring system–the Status Epilepticus Severity Score (STESS) was developed to provide a method for predicting outcome, and to orient early treatment strategy[9, 10].

History of seizures, age, seizure type, and level of consciousness were determined at status epilepticus onset, in order to calculate STESS. Although STESS has been reported to be a reliable scoring system in patients with status epilepticus, there is only one published study specifically examining NCSE patients. In that study by *Power* et al, STESS was found to have a predictive value in prognostic estimations in a total of 39 patients[2].

In the current study, outcomes at hospital discharge were assessed in a large patient series of NCSE, in order to evaluate the predictive value of STESS score in mortality estimations in NCSE patients of different etiologies.

Materials and methods

In this retrospective study, the medical records of a total of 95 patients over 18 years of age who were diagnosed with NCSE and followed up at the Epilepsy Unit, Department of Neurology, Antalya Research and Training Hospital between June 2011 and December 2015 were reviewed.

In our clinical practice, electroencephalogram (EEG) assessments are routinely performed by a

Table 1. *Working clinical criteria for nonconvulsive status epilepticus*

Patients without known epileptic encephalopathy
EDs > 2.5 Hz, or
EDs ≤ 2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) and one of the following:
EEG and clinical improvement after IV AED*, or
Subtle clinical ictal phenomena during the EEG patterns mentioned above, typical spatiotemporal evolution**
Patients with known epileptic encephalopathy
Increase in prominence or frequency of the features mentioned above, when compared to baseline with observable change in clinical state
Improvement of clinical and EEG* features with IV AEDs

Modified from Kaplan (2007).
Eds: epileptiform discharges (spikes, polyspikes, sharp-waves, sharp-and-slow-wave complexes); IV AEDs: intravenous antiepileptic drugs.
*If EEG improvement occurs without clinical improvement, or if fluctuation occurs without definite evolution, this should be considered possible NCSE.
**Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency >1 Hz or change in location), or decrementing termination (voltage or frequency)[11].

team of three neurologists. Every patient with a suspicious epileptic activity in EEG recordings is assessed by the epilepsy unit with respect to clinical findings. If these clinical assessments suggest the presence of NCSE, a special patient file is generated, treatment is prescribed, probable etiologic causes are investigated, and the patient is placed under a clinical and EEG follow-up program. Thus, all patients included in our study went through the above-mentioned procedures.

Clinically, NCSE was defined as epileptic seizures lasting more than 10 min and without prominent motor symptoms and/or convulsions. Clinical findings that were suggestive of NCSE included acute confusional status, behavioral or cognitive change from baseline, apathy, drowsiness, and mental fluctuations.

The EEG evaluation was performed and analyzed at the same institution. The standard placement of 10-20 electrodes was used for the EEG recordings and the standard recording phase lasted 30 minutes. A neurologist and an EEG technician were present during the EEG recording. When the ictal pattern was noticed, the patient was evaluated by a neurologist. We used the specific electrographic criteria for NCSE as defined by *Beniczky* et al on NCSE[11] **(Table 1)**.

NCSE episodes initiated by a primary or secondary generalized tonic-clonic seizure (GTC) or following anoxic brain damage were excluded. Based on the data retrieved from patient files, neurological findings at presentation, etiological factors thought to be responsible for the NCSE episode, treatments administered, and outcome measures were determined. Etiological factors were divided into the following three sub-groups as follows, Group 1: a known history of epilepsy, Group 2: primary neurological disease, and Group 3: systemic causes (systemic infection, electrolyte disturbance, abnormal glucose metabolism, drug abuse), and those with an unknown etiology. In case of patients with more than one known risk factors, an acute event that was more likely to lead to NCSE was considered as the main causative factor. On the other hand, even in the presence of acute events, patients with a known history of epilepsy were included in Group 1. In patients with more than one NCSE, only the first NCSE was included in these analyses to avoid dependency between variables.

Although a standard treatment protocol was not administered, all patients had received at least one antiepileptic drug (AED). Clinical outcomes were classified as follows: complete recovery, partial recovery, treatment-resistant, and death. Complete recovery was defined as the return to pre-episode baseline status, while partial recovery was defined as the functional improvement in the level of consciousness and in at least some aspects of the daily activities of living.

Table 2. *Status epilepticus severity score (STESS)*

Variable	Feature	Score
Level of consciousness	Alert or somnolent or confused	0
	Stuporous or comatose	1
Type of SE	Simple partial, complex partial, myoclonic, absence	0
	Generalized convulsive	1
	Non convulsive SE in coma	2
Age in years	<65	0
	≥65	2
Past history of seizures	Yes	0
	No	1
	Total	0-6

The STESS was administered to all patients retrospectively. This scoring system is based on four predictive features **(Table 2)**, with a total score of 6 (0-6), in which a score of 0-2 is defined as favorable, indicating low risk of death. Extent of consciousness impairment was determined before start of treatment. In the original article, STESS's ability to predict survival was estimated through the negative predictive value for mortality, and we also followed the same methodology in our assessments[12].

The study was approved by the Ethical Committee of Antalya Education and Research Hospital. Study data were analyzed with SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) for Windows and MedCalc 12. Demographic and baseline characteristics were summarized as mean±SD for continuous variables and as percentage of the group for categorical variables. Non-normally distributed data are presented as medians (inter-quartile range). The normality analysis was performed with the Kolmogorov-Smirnov test. Fisher's exact or the Chi-square tests were used to compare the proportions. Kruskal-Wallis tests were conducted, as the variables were not distributed normally, whereas the Mann-Whitney U test was performed with the Bonferroni correction to test the significance of pairwise differences. For the results of the Mann-Whitney U test with Bonferroni correction, $p<0.05$ and $p<0.03$ were accepted as statistically significant.

Results

Ninety-five patients were included in the study: 59 female and 36 male. All patients presented altered mental status, and the major characteristic symp-

Table 3. *Etiological factors in Group 2 and Group 3*

Etiology	N
1. Group 2 (Patients with primary neurological disease)	54
Cerebral infarction	25
- Acute/subacute	22
- Chronic	3
Cerebral hemorrhage*	7
- Acute	4
- Chronic	3
Intracranial tumor**	7
Cerebral trauma	2
Cranial operation***	2
CNS infection†	9
Limbic encephalitis	2
2. Group 3 (Patients with systemic or unknown etiology)	30
Systemic infection	9
Electrolyte disturbance‡	5
Unknown	16

*Intracerebral hematoma or subarachnoid hemorrhage
**Primary or metastatic tumor
***Surgery of arteriovenous malformation
†Meningitis or encephalitis
‡Hyponatremia, hypocalcemia

toms were confusion and apathy. Presence of frequent or continuous focal electrographic seizures was shown in 88 patients (92.6%), and 7 patients (7.4%) were found to have frequent or continuous generalized spike-wave discharges.

Participants were divided into three groups based on the etiological factors: Group 1 (11.6%), patients with a known history of epilepsy, Group 2 (56.8%) patients with a primary neurological disorder (excluding epilepsy), and Group 3, those with systemic or unknown causes. In Group 1, there were 11 patients, 7 being female (63.6 %). The age range of these patients was 22-57 years (mean: 36.6 y). The 54 patients in Group 2 had an age range between 18 and 89 years (mean: 63.1 y), and 33 of them were female (61.1 %). In Group 3, there were 30 patients, of whom 19 were female (63.3%) and the age range was 19-91 years (mean: 64.2 y). The mean age of patients in Group 1 was lower than those in Group 2 and 3, while the latter two groups had no significant age difference. There were more female patients in all study groups. The major cause of NCSE in Group 1 was failure to comply with medication and intercurrent infections. No specific etiological factors could be defined in 16 patients (16.8%) despite comprehensive diagnostic work up. We did not find any patients with glucose metabolism impairment or drug abuse in the group 3 patients. Details regarding etiological factors in Group 2 and Group 3 are depicted in **Table 3**.

Prognostic status at discharge included full recovery: 69 (72.6%), partial recovery: 4 (4.2%), treatment-resistance: 4 (4.2%) and death in 18 (18.9%) patients. All patients in Group 1 had full recovery with treatment. **Table 4** summarizes the prognosis in Groups 1, 2, and 3. Eighteen patients were admitted to the intensive care unit, and of these 12 (66.7%) died.

STESS was administered to all patients. The negative predictive value of a STESS score of 2 for mortality, regardless of the study sub-group, was 93.88% (+LR 2.05 95% CI: 1.44-2.9 and –LR 0.3 95% CI 0.10-0.84). The median STESS in Group 1 (patients with epilepsy) was significantly lower compared to those in Groups 2 and 3 ($p < 0.001$, each). All patients in Group 1 had low STESS (0 to 2) and recovered fully, and the negative predictive value of a STESS of 2 was 100% in Group 1.

In Group 2 (primary neurological disease), the negative predictive value of a STESS of ≤ 2 for mortality was 92.59% (+LR 2.06 95% CI: 1.32-3.21 and –LR 0.28 95% CI 0.08-1.02), while the corresponding value in Group 3 (patients with systemic or unknown etiology) was 83.33% (+LR 1.14 95% CI: 0.59-2.9 and –LR 0.80 95% CI 0.23-2.73). There were no deaths in Group 1, and the two other groups were comparable with regard to mortality rates ($p > 0.001$) **(Table 5)**.

Table 4. *Prognosis in Groups 1, 2 and 3*

Patients	Full recovery n=69	Partial recovery n=4	Unresponsive n=4	Death n=18
Group 1 (n=11) (Patients with epilepsy	11	–	–	–
Group 2 (n=54) (Patients with primary neurological disease)	38	2	2	12
Group 3 (n=30) (Patients with systemic or unknown etiology)	20	2	2	6

Table 5. *STESS score and mortality*

Patients STESS				
		≤ 2 Favourable	>2 Unfavourable	Total
Group 1 (n=11)	Alive	11	–	11
(Patients with epilepsy)	Death	–	–	–
Group 2 (n=54)	Alive	25	17	42
(Patients with primary neurological disease)	Death	2	10	12
Group 3 (n=30)	Alive	10	14	24
(Patients with systemic or unknown etiology)	Death	2	4	6

Discussion

Diagnosis of NCSE represents a major challenge in the practice of neurology due to a number of reasons including the controversy surrounding the classification and therapeutic approaches, potential sequela, and diagnostic challenges[13]. Early diagnosis and treatment of NCSE is of utmost importance because brain activity associated with increased cerebral blood flow, cytotoxic edema, cerebral vasoconstriction leading to cerebral ischemia, increased metabolic demand may lead to brain damage[14–16]. On the other hand, in the presence of cerebrovascular disease, head trauma, or cerebral hypoxia, it may be challenging to confirm the presence of persistent brain injury caused by epileptic activity[17–19].

NCSE occurs more frequently among the elderly, with a reported rate between 4 and 43 per every 100.000 elderly. This state is significantly higher compared to the situation reported for all age groups combined (1.5 per 100.000)[7].

NCSE is more common in elderly women than in elderly men, due to unknown factors[20]. Similar to previous reports, in our study NCSE was found to be more common in women 60 years of age.

Etiological factors associated with NCSE displays a wide range of variability between different age groups. In addition to direct insults on the central nervous system (CNS) such as acute or previous ischemic stroke, intracerebral hemorrhage, brain tumor, traumatic brain injury, indirect factors such as CNS infections, as well as electrolyte and metabolic disorders and systemic infections may be associated with NCSE. Also, NCSE is more common among critically ill and comatose patients[14, 21].

In our patients in Group 1 (epilepsy patients) the most common cause of NCSE was incompliance to medication and intercurrent infections, while ischemic stroke and systemic infections represented the leading causes of NCSE among patients in Group 2 and 3.

Prognosis in this condition appears to be dependent on the underlying causes[22]. In a study involving a total of 100 patients with NCSE, the reported mortality rate was 18%[23], similar to the figure in our study, i.e. 18.9%.

In contrast with many treatment protocols used for status epilepticus, optimum therapeutic strategy in NCSE remains controversial and increasing number of medications may be associated with treatment associated side effects[13].

Therefore, parameters predicting the outcome at the time of diagnosis may allow to design treatments. In this regard, STESS represents a practical and reproducible clinical bedside scoring system with the 4 variables assessed. The STESS was developed to provide a method for predicting outcome, and to orient early aggressive AED treatment strategy but not for etiological treatment. It has been validated by the same investigators in a prospective cohort of 35 patients with SE and in a multicenter study of 154 patients[12].

Although it has been reported to be a reliable scoring system, in the only study that specifically looked at its role in NCSE patients by *Power* and colleagues, the test was administered retrospectively. In that study, a lower score was associated with a better outcome and STESS had a negative predictive value of 96% for severe sequelae and death combined[2]. In our study, STESS could be readily administered using complete medical records. When all patients were combined (n=95) STESS had a negative predictive value of 93.8%. Previously reported etiological factors mainly included symptomatic and remote symptomatic factors. Conversely, in the current study etiological factors were classified as follows: epilepsy, primary neurological disease, and systemic or unknown etiology. While there was no mortality in the epilepsy group, two other groups were statistically similar in terms of the mortality rates. STESS was found to have value in predicting the outcome in patients with epilepsy (NPP: 100) and in primary neurolog-

ical disease groups (NPP: 92.59%), while this could not be demonstrated in the systemic or unknown etiology group (NPP: 83.33%).

The reported mortality rates in NCSE associated with epilepsy (3%) was lower compared to those with acute medical disorders (27%) or cryptogenic group (18%)[23]. In line with these reports, there was no death among our epilepsy patients, all subjects in this group fully recovered. Of our overall patient group, 18 were admitted to and followed up at the intensive care unit with 12 consequent deaths (66.7%). The increased rate of mortality in the elderly may be related with underlying conditions or with the complications of the treatment[24, 25].

Limitations: Classification of the patients by etiology (in particular, specifying the "main" factor) has significant limitations. In our practice, we found many patients with multiple etiology of NCSE: seizures in medical history, a primary neurological disorder as the cause of seizures, metabolic complication, systemic infections etc. In these cases we interpret NCSE as net result of the above-mentioned factors because the actual biological impact of them cannot be estimated in exact way. Merging patients with systemic and unknown etiologies into one group, and analysis of mixed groups can lead to confusion in the results and can cause vague conclusion.

Conclusions

Although NCSE can be readily managed when properly diagnosed, unfortunately neither the diagnosis nor the therapeutic strategies have been as well defined as those in status epilepticus. Outcome predictions may assist in determining the degree of insistence on therapy. In this study, although STESS was found to have a value in predicting favorable outcome in patients with epilepsy or primary neurological disease, its value was lower in those with systemic or unknown etiology. Further prospective studies with NCSE patients are warranted.

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ALVÁSI SZOKÁSOK ÉS ALVÁSMINŐSÉG ÓVODÁS- ÉS ISKOLÁSKORÚ GYERMEKEK KÖRÉBEN

FUSZ Katalin[1], RITECZ Bernadett[2], BALOGH Brigitta[2], TAKÁCS Krisztina[2], SOMLAI Eszter[2], RAPOSA L. Bence[3], OLÁH András[2]

[1]Pécsi Tudományegyetem, Általános Orvostudományi Kar, Élettani Intézet, Pécs
[2]Pécsi Tudományegyetem, Egészségtudományi Kar, Ápolástudományi, Alapozó Egészségtudományi és Védőnői Intézet, Pécs
[3]Pécsi Tudományegyetem, Egészségtudományi Kar, Alapozó Egészségtudományi és Analitikai Laboratóriumi Kutatóközpont, Pécs

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Célkitűzés – Célunk felmérni az alvási szokásokat, az alvásminőséget és befolyásoló tényezőit óvodás- és iskoláskorúak körében.
Vizsgálati módszer – Két kérdőíves adatfelvétel történt. Az 1. felmérés csecsemő- és óvodáskori altatási szokásokkal, szoptatással és egészségmagatartással kapcsolatos kérdéseket, valamint a Children's Sleep Habits Questionnaire-ből átvett kérdéseket tartalmaz.
A 2. kérdőív kérdései az egészség-magatartásra és az alváshigiénés szabályok alkalmazására vonatkoznak, valamint az Athén Insomnia Skálát tartalmazza.
A vizsgálat alanyai – Összesen 1063 kérdőívet értékeltünk: 516 óvodáskorú gyermek szülője vett részt online felmérésünkben Magyarország egész területén; 547 általános és középiskolás vett részt a 2. kérdőíves felmérésben Szolnokon.
Eredmények – A szülők megfigyelése szerint az óvodáskorúak átlagos éjszakai alvásideje hétköznap 10 óra 20 perc, hétvégén 10 óra 36 perc. A legnépszerűbb altatási szokások óvodáskorban: meseolvasás (65,1%) és együttalvás (42,8%). A szülők gyermekük csecsemőkorában a szoptatást (50,4%) és a ringatást (43,2%) alkalmazták leggyakrabban elalvás előtt. Az együttalvás pozitívan befolyásolja a szoptatás hosszát. Az óvodáskori altatási szokások közül a meseolvasás számos pozitív hatását bizonyítottuk, míg a tévénézés káros hatásaira világítottunk rá. Az iskoláskorúak alvásminősége az Athén Insomnia Skála szerint: 6,11 pont (SD: 4,11), 19% insomniásnak számít. Alvásidejük hétköznap 7 óra 31 perc, hétvégén 9 óra 30 perc. A helyes egészség-magatartás és alváshigiénés szokások alkalmazása pozitívan befolyásolják az alvásminőséget és alváshosszt.

SLEEP HABITS AMONG PRESCHOOL- AND SCHOOLCHILDREN

Fusz K, PhD; Ritecz B; Balogh B; Takács K, PhD; Somlai E; Raposa LB, PhD; Oláh A, PhD habil
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Objective – Our aim is to evaluate sleep habits, sleep quality and influencing factors among preschool- and schoolchildren.
Method – Two questionnaires were recorded. Questionnaire 1 dealt with sleeping habits, breastfeeding and health behavior of preschool children and infant, and it contained the abbreviated version of the Children's Sleep Habits Questionnaire. Questionnaire 2 dealt with health behavior and the application of sleep hygiene rules, as well as it contained the Athens Insomnia Scale.
Subjects – We assessed a total of 1063 questionnaires: 516 kindergarten children participated in our online survey across the country; 547 primary and secondary school students participated in the 2nd questionnaire survey in Szolnok.
Results – Parents' observation shows that the average nighttime sleeping time of kindergarten children is 10 hours 20 minutes on weekdays and 10 hours 36 minutes on weekends. The most popular sleeping habits in kindergarten age: teal reading (65.1%) and co-sleeping (42.8%). Parents of infants used breastfeeding (50.4%) and rocking (43.2%) most frequently before sleep. Co-sleeping has a positive influence on the length of lactation. Among the preschool sleeping habits we have proved a number of positive effects of teal reading, while watching television have negative effects. The sleep quality of school-age children according to the Athens Insomnia Scale is 6.11 points (SD: 4.11), 19% of the children are insomniac. Their sleep time is 7 hours 31 minutes on weekdays and 9 hours 30 minutes on weekends. The usage of good health behavior and sleep hygiene rules positively influence sleep quality and sleep duration.

Levelező szerző (correspondent): Dr. FUSZ Katalin, Pécsi Tudományegyetem, Általános Orvostudományi Kar, Élettani Intézet; 7621 Pécs, Szigeti út 12. Telefon: (06-72) 513-670, e-mail: katalin.fusz@aok.pte.hu

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Következtetések – Eredményeinkkel szeretnénk felhívni a gyermekek és a szülők figyelmét az alvás fontosságára, az alváshigiénés szabályok betartására.

Kulcsszavak: *alvási szokások, alvásminőség, alvásmennyiség*

Conclusions – With our results, we would like to draw the attention of children and parents to the importance of sleeping and using sleep hygiene rules.

Keywords: *sleep habits, sleep quality, sleep duration*

Az alvás során tudjuk kipihenni az ébrenlét során szerzett fizikai és mentális fáradtságot, annak tehát fontos a szerepe szervezetünk fizikai és pszichés regenerációjában. A megfelelő minőségű és mennyiségű alvás fontosságát számos kutatás hangsúlyozza[1–4]. Egyre nagyobb jelentőséget tulajdonítanak a gyermekkori alvás időtartamának és minőségének a jövőbeli egészségre és teljesítményre való hatása miatt[5]. A gyermekek alvásmennyisége folyamatosan csökken az utóbbi évtizedekben[6]. A csökkent alváshossznak számos egészségre káros hatása ismert: fokozódó nappali álmosság, a koncentrálóképesség csökkenése, hangulati instabilitás, alacsonyabb iskolai teljesítmény, fokozott hajlam az addikciók kialakulására, illetve az öngyilkosságra[7–9]. Az alvási problémák többsége megelőzhető és kezelhető lenne megfelelő alvási szokásokkal és edukációval[10, 11]. A szülők magatartása és altatási szokásai nagyban befolyásolják a gyermekek alvás-ébrenlét ciklusának beállítását[12, 13]. A csecsemők alvása, altatása terén többféle nézet él, például az együttalvás, a „suttogó módszer" és a „hagyd sírni módszer"[14–17]. A gyermekek más alvó környezetben való elhelyezésének gyakorlata viszonylag új szokás, amely nagyrészt a nyugati iparosodott társadalmakra jellemző. Fontos szem előtt tartani, hogy az együttalvás (bed-sharing) definíciója változáson ment keresztül az évek során. Egyes kultúrákban a szülők a gyermekkel ugyanabban az ágyban, máshol külön alvófelületen, de egy helyiségben, 'kartávolságon belül' alszanak. Néhány kutató a szobamegosztás (room-sharing) gyakorlatát is az együttalvás fogalma alá rendelte[18].

A jelen közleményben két felmérésünket mutatjuk be, amelyekkel a gyermekkori alvászavarokra szeretnénk felhívni a figyelmet. Az „Óvodáskorú gyermekek alvási szokásai" című felmérésünkben a 3–6 éves óvodáskorú gyermekek alvását monitoroztuk. Célunk volt feltérképezni a magyarországi altatási szokásokat és az ezeket befolyásoló tényezőket. Összehasonlítottuk a 0–3 éves és a 3–6 éves gyermekekkel kapcsolatos altatási szokásokat, valamint az együttalvási módszer használatát. Az „Alvási szokások általános és középiskolások körében" című kutatásunk célja az alváshigiénés szabályok alkalmazásának, az alvásminőségnek, az alvás időtartamának, a lefekvés és az ébredés időpontjának felmérése volt iskoláskorúak csoportjában.

Módszer

MINTA

Keresztmetszeti, kvantitatív, leíró jellegű kérdőíves felmérést végeztünk kutatásunk során (etikai engedély száma: 7383.-2018.PTE). Összesen 1063 gyermek adatait elemeztük. Mivel az életkori sajátosságokat figyelembe vettük, más kérdőívet alkalmaztunk az óvodások és az iskolások esetén, tehát két felmérést végeztünk.

A felmérés résztvevői: 516 óvodáskorú (3–6 éves) gyermek szülője vett részt az „Óvodáskorú gyermekek alvási szokásai" című online felmérésünkben (egy közösségi oldal segítségével) Magyarország egész területén, valamint 547 általános (n = 146) és középiskolás (n = 401) vett részt az „Alvási szokások általános és középiskolások körében" című kérdőíves felmérésben Szolnokon (a Chiovini Ferenc Kolping Katolikus Általános Iskola, Alapfokú Művészeti Iskolában, a Varga Katalin Gimnáziumban és a Szolnoki Szolgáltatási Szakképzési Centrumban).

MÉRŐESZKÖZÖK

Az 1. felmérésben alkalmazott kérdőív kérdéscsoportjai: szociodemográfiai adatok (szülőé és gyermeké), a csecsemő- és óvodáskori altatási szokásokkal, a szoptatással, és az egészség-magatartással kapcsolatos kérdések.

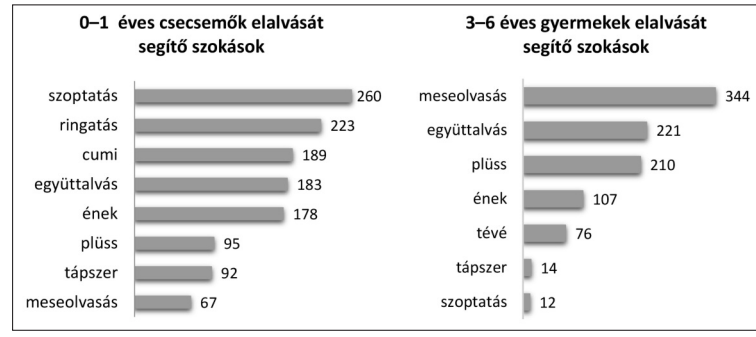
Kérdéseket vettünk át a Children's Sleep Habits Questionnaire, azaz a „Gyermekek Alvási Szokásai Kérdőívből" (CSQ, Owens, 2000)[19], amelyek a gyermekek alvási szokásait és az alvás esetleges nehézségeit mérik fel az elmúlt hétre vonatkozóan. A lefekvés idejére vonatkozólag kilenc állítást, az alvásmagatartással kapcsolatban hét, az éjszakai ébredések felmérésére két és a reggeli ébredésre négy állítást tartalmaz a kérdőív. A kérdéseket magyarra fordítottuk, majd az alábbi pontozást alkalmaztuk: a szülők 5 fokozatú Likert-skálákon értékelték gyermekük alvási szokásait. 'Soha' válasz esetén, egy átlagos héten egyáltalán nem fordul elő az állítás (0 pont), 'Ritka' válasznál heti 1-szer (1 pont), 'Néha' válasznál 2–4 esetben fordult elő (2 pont), 'Általában' esetén 5-6-szor (3 pont), 'Mindig' válasznál a hét minden napján előfordult

az állítás a gyermek altatásakor (4 pont).

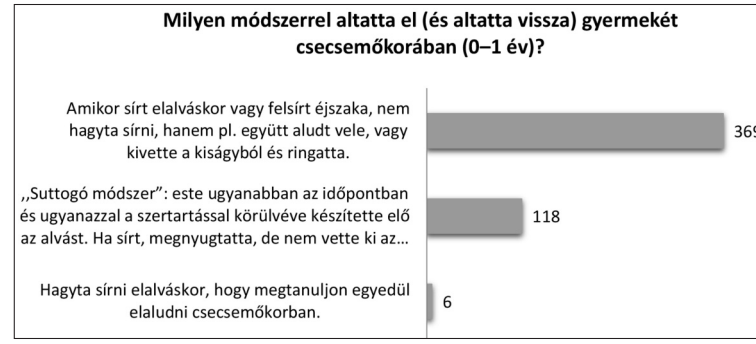
A 2. felmérésben alkalmazott kérdőív kérdéscsoportjai: szociodemográfiai adatok (életkor, nem, iskola típusa, tanulmányi eredmények, megye), egészség-magatartás és egészségi állapot (táplálkozás, fizikai aktivitás, testmagasság, testsúly, krónikus betegségek jelenléte). A saját szerkesztésű kérdések utolsó csoportja az alvási szokásokra, az alváshigiénés szabályok ismeretére és az alvásminőségre tér ki.

Az alváshigiénés szabályok betartásának felmérésére a tanulók 1-től (egyáltalán nem) 10-ig (teljes mértékben) jelölték egy táblázatban, hogy a felsorolt állítások milyen mértékben jellemzőek rájuk.

Alvási elégtelenség (insomnia) esetén az elalvás és/vagy az alvás fenntartása zavart szenved, és nappali panaszokkal jár. Az Athén Insomnia Skála (Athens Insomnia Scale, AIS – Soldatos, 2000)[20, 21] egy egyszerű kérdőív, ami epidemiológiai tanulmányokban az insomnia hasznos mérőeszköze. A nyolc kérdésből álló skála első öt kérdése az éjszakai tüneteket méri fel (elalvási és átalvási nehézség, korai felébredés), a többi a megzavart alvás nappali következményeire kérdez rá. Minél magasabb a pont, annál rosszabb az alvásminőség (maximum 8-szor 3 pont, azaz 24 pont kapható). Ha a kitöltő eléri a 10 pontot, az a skála alapján insomniára utal.



1. ábra. *Altatási szokások csecsemő- és kisgyermekkorban (n = 516)*



2. ábra. *Altatási módszerek alkalmazása csecsemőkorban (n = 516)*

STATISZTIKAI ELEMZÉS

A statisztikai elemzéseket az SPSS 23.0 programcsomaggal végeztük (SPSS, Chicago, IL). Az adatokat χ^2-próbával, kétmintás t-próbával, lineáris regresszióval, Mann–Whitney- és Kruskal–Wallis-teszttel elemeztük. Az eredményeket mindegyik teszt esetén $p < 0,05$-nél tekintettük szignifikánsnak.

Eredmények

ÓVODÁSKORÚ GYERMEKEK ALVÁSI SZOKÁSAI

Szociodemográfiai adatok

Az országos online felmérésben 516 gyermek alvásának körülményeit elemeztük. Átlagéletkoruk 4,21 év (SD: 1,11), 49,6% fiú (n = 256) és 50,4% lány (n = 260). A szülők átlagéletkora 34,52 év (SD: 5,1); 97,1%-uk nő, legtöbben házastársi kapcsolatban élnek (71,7%). A szülők nagy része (n = 270; 52,3%) főiskolai vagy egyetemi diplomával rendelkezik. Magyarország 18 megyéjéből érkezett kitöltött kérdőív, Baranya megyéből a legtöbb (47,1%). A válaszadók 41,5%-a városban él, 60,3% családi házban, 20,3% panellakásban és 19% társasházban. A legtöbb gyermeknek egy testvére van (n = 258; 50%); átlagosan két gyermek van egy családban (minimum: 1, maximum: 6). A legtöbb esetben (47,9%) külön szobája van a gyermeknek; 35,5%-ban közös szobában vannak a gyerekek, míg 16,7% esetén a szülőkkel egy szobában alszanak.

ALTATÁSI SZOKÁSOK ÉS ALVÁSMINŐSÉG CSECSEMŐ- ÉS KISGYERMEKKORBAN

Felmértük, hogy a szülőknek milyen esti altatási szokásaik voltak. A legtöbben (50,4%; n = 260) szoptatták gyermeküket elalvás előtt, 43,2% (n = 223) ringatta, 36,6% (n = 189) cumival altatta csecsemőjét, míg hat szülő a tévénézést jelölte meg **(1. ábra)**.

Óvodáskorban változtak a szokások, ugyanis a legtöbb szülő (66,7%; n = 344) mesét olvasott, 42,8% (n = 221) összebújt gyermekével, amíg az elaludt, vagy együtt aludtak. A harmadik legnépszerűbb szokás a plüssállat alkalmazása (40,7%; n = 210) volt, ezt követte az éneklés (20,7%; n = 107) és a tévénézés (14,7%; n = 76) **(1. ábra)**.

1. táblázat. *A „Gyermekek Alvási Szokásai Kérdőív” (rövidített) – Children’s Sleep Habits Questionnaire – eredményei (n = 516)*

Lefekvésre, alvásmagatartásra, éjszakai felébredésre, felkelésre vonatkozó állítások	Mindig (n)	Általában (n)	Néha (n)	Ritkán (n)	Soha (n)	Pontátlag (n)	SD (n)
1. A gyermek ugyanabban az időben megy aludni.	190	251	66	8	1	4,20	0,73
2. A gyermek 20 percen belül elalszik lefekvés után.	181	167	119	37	12	3,91	1,03
3. A gyermek egyedül alszik el a saját ágyában.	193	67	62	59	135	3,24	1,65
4. A gyermek a szülő vagy testvér ágyában alszik el.	91	33	35	86	271	1,2	1,54
5. A gyermek ringatásra vagy ritmusos mozgásra alszik el.	4	7	19	42	444	0,22	0,65
6. A gyermeknek szüksége van valamilyen különleges tárgyra az elalváshoz (baba, különleges takaró, plüssállat stb.).	254	69	66	47	80	2,71	1,51
7. A gyermeknek szüksége van a szülőre az elalváshoz.	204	75	81	71	85	2,46	1,51
8. A gyermek ellenáll a lefekvési időben.	22	40	101	160	193	1,1	1,12
9. A gyermek fél sötétben aludni.	57	65	99	82	213	1,36	1,4
10. A gyermek mindennap körülbelül ugyannyit alszik.	133	317	62	2	2	4,12	0,64
11. A gyermek nyughatatlan és sokat mozog alvás közben.	9	56	131	210	110	1,3	0,98
12. A gyermek éjszaka átmegy másvalaki ágyába (szülő, testvér stb.).	21	35	58	119	283	0,82	1,12
13. A gyermek csikorgatja a fogait alvás közben (a fogorvos beszámolhat erről).	9	22	36	77	372	0,48	0,92
14. A gyermek hangosan horkol.	12	20	52	159	273	0,71	0,95
15. A gyermek éjszaka felébred és izzad, sikoltozik és vigasztalhatatlan.	1	5	23	95	392	0,31	0,62
16. A gyermek napközben szundikál.	137	109	91	71	108	2,18	1,48
17. A gyermek egyszer kel fel az éjszaka folyamán.	24	64	80	175	173	2,79	1,16
18. A gyermek egynél többször kel fel éjszaka.	9	17	31	102	357	0,48	0,88
19. A gyermek magától ébred fel.	179	148	152	31	6	3,89	0,99
20. A gyermek reggel nagyon korán kel fel (vagy korábban, mint szükséges vagy kívánatos).	25	40	108	158	185	1,15	1,13
21. A gyermek fáradtnak tűnik napközben.	2	23	81	199	211	0,84	0,87
22. A gyermek elalszik tevékenységek közben.	0	2	3	18	493	0,05	0,29
Alvással kapcsolatos időpontok, időtartamok	Átlag			SD		Átlagos alváshossz	
felkelés időpontja hétköznap	6:40			1:05		hétköznap 10 óra 20 perc	
lefekvés időpontja hétköznap	20:20			0:29			
felkelés időpontja hétvégén	7:15			1:20		hétvégén 10 óra 36 perc	
lefekvés időpontja hétvégén	20:39			0:49			
szülők által becsült átlagos alváshossz	10,164			1,439		10 óra 10 perc	

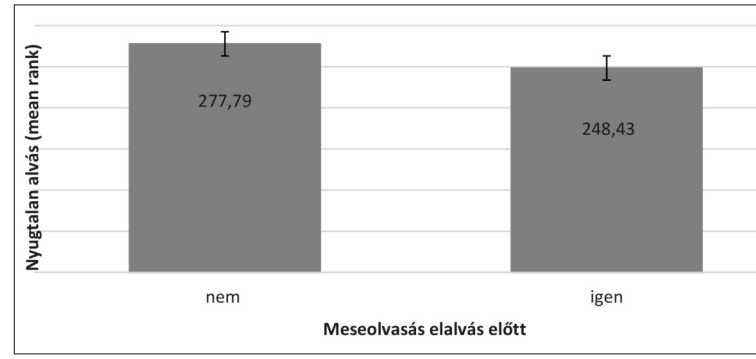
Felsoroltunk három altatási módszert, és felmértük, melyiket alkalmazták a gyermekek csecsemőkorában. A szülők 71,5%-a ha sírt a gyermek elalváskor vagy felsírt éjszaka, nem hagyta sírni, hanem például együtt aludt vele, vagy kivette a kiságyból és ringatta. A (Tracy Hogg nevéhez köt-

hető) „suttogó módszert” 22,9% alkalmazta, ennek lényege, hogy este ugyanabban az időpontban és ugyanazzal a szertartással körülvéve készítette elő az alvást, valamint ha sírt, megnyugtatta, de nem vette ki az ágyból. Csak 6 szülő válaszolta azt, hogy hagyta sírni gyermekét elalváskor, hogy megtanuljon egyedül elaludni csecsemőkorban **(2. ábra)**.

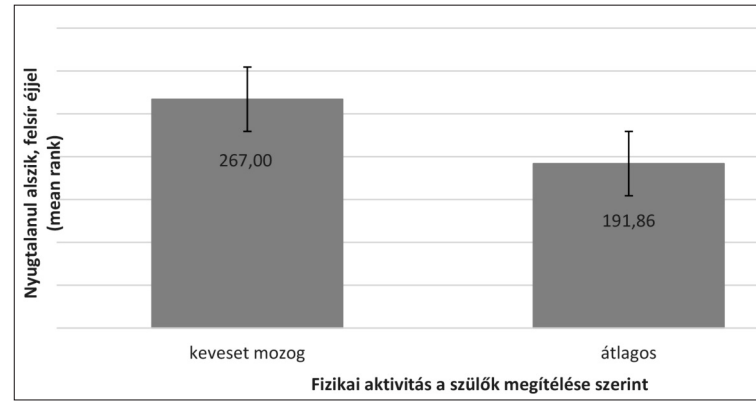
A szülők 50,6%-a (n = 261) válaszolta, hogy alkalmanként együttalszik gyermekével, 37%-a (n = 191) rendszeresen alkalmazza ezt a módszert, és 12,4%-a (n = 64) soha sem alszik egy ágyban gyermekével. Akik az első évben együtt aludtak csecsemőjükkel, hosszabb ideig szoptattak (n = 122; átlag: 13,18 hónap; SD: 11,1), mint akik külön ágyban aludtak (n = 216; átlag: 9,88 hónap; SD: 8,6; t = –3,04; p = 0,003).

Felmérésünk során felhasználtuk a Children’s Sleep Habits Questionnaire 22, általunk magyarra fordított kérdését. A lefekvéssel kapcsolatos kilenc kérdés közül a legmagasabb átlagpontot (4,20; SD: 0,73) az alábbi állítás kapta: a gyermek ugyanabban az időben megy aludni, azaz a legtöbben a „mindig” (36,8%) és az „általában” (48,6%) választ jelölték meg. Az alvásmagatartásra vonatkozó hét kérdés közül a legmagasabb átlagpontot (4,12; SD: 0,64) az alábbi állítás kapta: a gyermek mindennap körülbelül ugyanannyit alszik. Arra vonatkozólag, hogy a gyermek csikorgatja-e a fogát alvás közben kilencen (1,7%) válaszolták, hogy mindig megtörténik, 372-en (72,1%) pedig egyáltalán nem tapasztalták. Egy fő (0,2%) jelezte, hogy gyermeke mindig izzad vagy sikoltozik alvás közben, és 392 (76%) gyermekkel ez soha nem szokott előfordulni. Az éjszakai ébredésekre vonatkozó két kérdés esetén tapasztaltuk, hogy 24 (4,7%) gyermek minden éjjel felébred egyszer; kilenc (1,7%) gyermek pedig mindig egynél többször ébred fel. A reggeli felkelésre vonatkozó négy kérdés közül a legjellemzőbb, hogy reggelente a gyermek magától ébred fel (3,89; SD: 0,99). Hétköznapokon átlagosan 20:20-kor kerülnek ágyba, hétvégéken pedig 20:39-kor. Hétköznapokon átlagosan 6:40-kor kelnek fel, míg hétvégén 7:15-kor. A szokásos alvásmennyiség hétköznapokon 10 óra 20 perc, hétvégén 10 óra 36 perc, a szülők pedig 10 óra 10 percet becsültek átlagos alváshossznak **(1. táblázat)**.

Azok a gyermekek, akiknek mesét olvasnak elalvás előtt (n = 344), általában ugyanabban az időben fekszenek le (p < 0,001), gyakran a szülő ágyában alszanak el (p < 0,001), kevésbé állnak ellen lefekvési időben (p = 0,012), minden nap körülbelül ugyanannyit alszanak (p = 0,001), nem nyugtalanok alvás közben (p = 0,026) **(3. ábra)**, éjszaka nem kelnek fel (p = 0,006) és napközben nem tűnnek fáradtnak (p = 0,006) szemben azokkal a gyermekekkel, akiknek nem olvasnak mesét elalvás előtt (n = 172).



3. ábra. *A nyugtalan alvás és az esti meseolvasás elmaradásának kapcsolata (n = 516)*



4. ábra. *A csökkent fizikai aktivitás és a nyugtalan alvás kapcsolata (n = 387)*

Akik tévét néznek elalvás előtt (n = 76), nem ugyanakkor mennek aludni (p < 0,001), nem alszanak el 20 percen belül (p < 0,001); ellenállnak lefekvési időben (p = 0,003), kevesebbet alszanak, mint akik nem tévéznek elalvás előtt (p = 0,028), továbbá nem ugyanannyit alszanak minden nap (p = 0,004).

Az egészség-magatartás és az alvásminőség kapcsolata

A táplálkozási szokások felméréséből kiderült, hogy 10,9% (n = 56) nem fogyaszt zöldséget/gyümölcsöt, 8,5% (n = 44) sok édességet fogyaszt és 78,1% (n = 403) változatosan táplálkozik a szülők

2. táblázat. *Alváshigiénés szabályok alkalmazása (n = 547)*

Alváshigiénés szabályok	Átlag	SD
Napirendje rendszerezett (például lefekvés, felkelés, étkezés)	6,954	2,467
Délután nem szokott aludni	4,998	3,725
Lefekvés előtt nem szokott túl sok és nehezen emészthető ételt fogyasztani	5,486	3,016
Lefekvés előtt nem szokott élénkítő ételt/italt fogyasztani (csokoládé, tea, kóla, kávé, energiaital)	5,059	3,253
Rendszeresen végez testmozgást	6,642	2,998
A hálószoba, az ágy az alvást szolgálja, nincs televízió és/vagy számítógép a közelben	4,446	3,627
A nyugodt alvás érdekében kényelmes, jó minőségű a matraca	7,909	2,671
Megfelelő a hálószoba hőmérséklete	8,444	2,218
Alváskor megfelelő a fényerősség	8,556	2,301
Lefekvés előtt stresszcsökkentő módszereket alkalmaz, megnyugtató tevékenységeket végez (például meditáció, ima)	2,596	2,857
Akkor fekszik le, amikor tényleg álmosnak érzi magát	6,552	3,070
Összesített pont	*67,642*	*13,703*

3. táblázat. *Alvással kapcsolatos időpontok, időtartamok (n = 547)*

A lefekvés-felkelés ideje	Átlag	SD	Átlagos alváshossz
A felkelés időpontja hétköznap	5:56	0:38	hétköznap 7 óra 31 perc
A lefekvés időpontja hétköznap	20:41	4:57	
A felkelés időpontja hétvégén	9:13	1:32	hétvégén 9 óra 30 perc
A lefekvés időpontja hétvégén	23:45	10:33	

állítása szerint. A kitöltők 72,9%-a (n = 376) átlagosnak ítélte gyermeke fizikai aktivitását, 25,2%-a (n = 130) a kortársakhoz mérten többre értékelte, míg 1,9% (n = 10) kevesebbnek ítélte a gyermek aktivitását. A gyerekek 1%-a (n = 5) egyáltalán nem, 14,7%-a (n = 76) ritkán, 47,5%-a (n = 245) naponta egyszer, míg 36,8% (n = 190) naponta többször használ szórakoztató elektronikai eszközöket (például tévé, laptop).

Az egészségesen táplálkozó gyermekek általában 20 percen belül elalszanak ($p < 0,001$), a saját ágyukban alszanak el ($p = 0,03$), és napközben nem tűnnek fáradtnak ($p = 0,001$) szemben az egészségtelenül táplálkozókkal.

A keveset mozgó gyermekek gyakrabban alszanak nyugtalanul, sikoltozva, mint az átlagos ($p = 0,02$) **(4. ábra)** és nagy mozgásigényű gyermekek ($p = 0,047$), valamint napközben fáradtabbak ($p = 0,041$).

AZ ALVÁSI SZOKÁSOK ÁLTALÁNOS ÉS KÖZÉPISKOLÁSOK KÖRÉBEN

Szociodemográfiai adatok

A Szolnokon végzett felmérésben részt vevő 547 tanuló átlagéletkora 15,426 év (SD = 2,740; minimum: 9; maximum: 22; medián: 16); 409 fő (75%) nő, 138 fő (25%) férfi. Tanulmányait 146 fő (27%) általános iskolában, 60 fő (11%) gimnáziumban, 315 fő (58%) szakközépiskolában és 26 fő (5%) szakmunkásképzőben vagy szakiskolában végzi. Jó vagy jeles eredménye 385 főnek (70%), közepes eredménye 142 főnek (26%) és elégséges tanulmányi eredménye 20 főnek (4%) van.

Alvási szokások, alvásmennyiség és alvásminőség

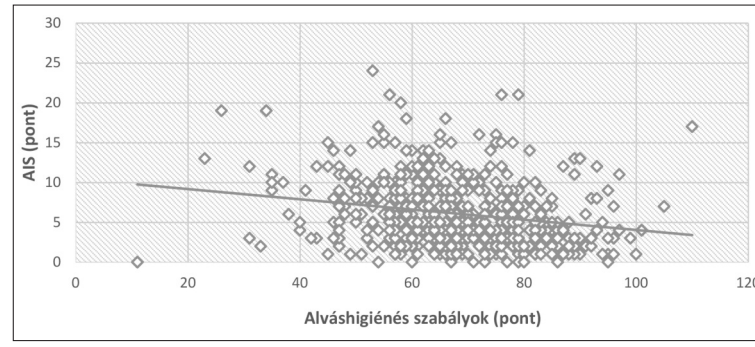
Az alváshigiénés szabályok alkalmazását egy 11 kérdéses kérdőívvel mértük fel. A 10 pontos Likert-skálák esetén 1 pont járt, ha egyáltalán nem jellemző a kitöltőre az állítás, és 10 pont, ha teljes mértékben jellemző. Az alváshigiénés szabályok kérdőív összesített pontszámának átlaga 67,642 pont volt (SD: 13,703; minimum: 11, maximum: 110; medián: 67). A legtöbb átlagpontot a megfelelő fényerősség (8,556; SD: 2,301) kapta. A „Lefekvés előtt stresszcsökkentő módszereket, megnyugtató tevékenységeket végez (például meditáció, ima)” állítás jellemző legkevésbé a résztvevőkre: 2,596 pont (SD = 2,857) **(2. táblázat)**.

Felmértük, hogy a tanulók mikor fekszenek le hétköznapokon (átlag: 20:41) és hétvégén (átlag: 23:45). Átlagosan 5:56-kor kelnek fel hétköznap, míg hétvégén 9:13-kor. Az alváshossz átlagosan 7 óra 31 perc és 9 óra 30 perc **(3. táblázat)**.

4. táblázat. *Athén Insomnia Skála eredményei (n = 547)*

AIS	0 pont (n)	1 pont (n)	2 pont (n)	3 pont (n)	Átlag	SD
Elalvás (a lámpaoltástól az elalvásig eltelt idő)	208	228	72	39	0,894	0,887
Éjszakai felébredés	278	192	62	15	0,660	0,785
Korai ébredés (reggel a kívánatosnál korábban ébredt)	284	200	44	19	0,631	0,776
Az alvás teljes időtartama	183	257	86	21	0,899	0,797
Az alvás átlagos minősége (függetlenül attól, hogy mennyi ideig aludt)	304	198	33	12	0,548	0,708
Nappali közérzet	292	202	31	22	0,603	0,771
Nappali (testi/szellemi teljesítmény)	290	219	29	9	0,556	0,673
Nappali álmosság	52	332	100	63	1,318	0,799

Az alváspanaszokat az Athén Insomnia Skálával (AIS) elemeztük: a skálán elért átlagpont 6,11 volt (SD: 4,11), a mintában 105 fő (19%) számított a skála alapján insomniásnak (10 pont feletti érték). A legmagasabb átlagpontot (1,318; SD: 0,799) a nappali álmosság kapta, azaz ez okoz a leggyakrabban panaszt **(4. táblázat)**.



5. ábra. *Alváshigiénés szabályok alkalmazásának hatása az alvásminőségre (n = 547)*

Az alváshigiénés szabályok betartása befolyásolja az alvásidőtartamot hétköznapokon ($r = 0{,}170$, $p < 0{,}001$) és hétvégéken ($r = 0{,}105$; $p = 0{,}014$), tehát az alváshigiénés szabályokra kapott magasabb átlagpont hosszabb alvásidőtartammal jár együtt.

Az alváshigiénés szabályok betartása pozitívan befolyásolja az alvásminőséget ($r = -0{,}214$; $p < 0{,}001$), azaz magasabb alváshigiénés átlagpont esetén alacsonyabb az AIS átlagpont **(5. ábra)**.

Az összesített AIS-pontszám szignifikánsan összefügg az alvásidőtartammal hétköznapokon ($r = -0{,}500$, $p < 0{,}001$) és hétvégéken ($r = -0{,}263$, $p < 0{,}001$) is, azaz az alvásminőség és -mennyiség összefügg egymással.

Az alvásidőtartam [hétköznapokon ($r = -0{,}218$, $p < 0{,}001$) és hétvégéken ($r = -0{,}145$, $p < 0{,}001$) is] szignifikánsan befolyásolja a testtömegindexet, lineáris regresszióval bizonyítottuk, hogy ha az alvásidőtartam hétköznapokon és hétvégéken növekszik, akkor a testtömegindex ezzel párhuzamosan csökken.

Megbeszélés

A szülők megfigyelése szerint az óvodáskorúak átlagos éjszakai alvásideje hétköznap 10 óra 20 perc, hétvégén 10 óra 36 perc. A National Sleep Foundation ajánlása szerint a 3–5 éves gyermekek napi alvásmennyisége 10-13 óra legyen, tehát az általunk vizsgált gyermekek alvásmennyisége megfelel az ajánlásnak, és ehhez még hozzáadódhat a délutáni alvás is[3]. A gyermekek 17%-a (n = 88) ébred fel egyszer éjjel (általában vagy mindig), míg egy angliai felmérésben az óvodáskorúak fele felébred egyszer éjszakánként[5]. A legnépszerűbb altatási szokások óvodáskorban a meseolvasás (65,1%) és az együttalvás (42,8%). A szülők gyermekük csecsemőkorában a szoptatást (50,4%) és a ringatást (43,2%) alkalmazták leggyakrabban elalvás előtt; *Sheuring* és munkatársai is hasonló eredményt kaptak 2015-ben[16]. Felmérésünk szerint az együttalvás pozitívan befolyásolja a szoptatás hosszát, *Ball* és munkatársai is ezt bizonyították angliai kutatásukban[22]. Hazánkban elsőként alkalmaztunk a Children's Sleep Habits Questionnaire-ből átvett kérdéseket[19]. A lefekvéssel kapcsolatos kérdések közül a legmagasabb átlagpontot „a gyermek ugyanabban az időben megy aludni" állítás kapta. Az alvásmagatartásra vonatkozó kérdések közül a legmagasabb átlagpontot az alábbi állítás kapta: a gyermek mindennap körülbelül ugyanannyit alszik. Az óvodáskori altatási szokások közül a meseolvasás számos

pozitív hatását bizonyítottuk, míg a tévénézés káros hatásaira világítottunk rá, ahogyan *Gradisar* és munkatársai is[23]. Az egészségesen táplálkozó gyermekek általában 20 percen belül elalszanak, a saját ágyukban alszanak el és napközben nem tűnnek fáradtnak, szemben az egészségtelenül táplálkozókkal. A keveset mozgó gyermekek gyakrabban alszanak nyugtalanul, sikoltozva, mint az átlagos és nagy mozgásigényű gyermekek; valamint napközben fáradtabbak. Tehát a helyes egészség-magatartás pozitívan befolyásolja az alvásminőséget.

Az iskoláskorúak (n = 547, átlagéletkor 15,43) alvásminősége az AIS szerint: 6,11 pont (SD: 4,11), 19%-uk insomniásnak számít. Egy 2015-ös hazai felmérésünkben a felnőttek esetén jobb eredményt kaptunk: 5,08 pont és 13% insomniás[24]. Az iskolások alvásideje hétköznap 7 óra 31 perc, hétvégén 9 óra 30 perc. *Sólyom* és munkatársai 2013-as felmérésükben magasabb értékeket kaptak (8,5 óra és 10,2 óra)[10]. A National Sleep Foundation a 6–13 éveseknek napi 9–11 óra alvást, míg a 14–17 éveseknek napi 8–10 órát javasolt, tehát a szolnoki iskoláskorúak kevesebbet alszanak az ajánlottnál[3]. Az alváshigiénés szabályok alkalmazását egy 11 kérdéses kérdőívvel mértük fel. A legtöbb átlagpontot a megfelelő fényerősség kapta, míg a „lefekvés előtt stresszcsökkentő módszereket, megnyugtató tevékenységeket végez" állítás jellemző legkevésbé a résztvevőkre. Az alváshigiénés szabályok betartása pozitívan befolyásolja az alvásidőtartamot és az alvásminőséget.

Eredményeinkkel szeretnénk felhívni a gyermekek és a szülők figyelmét az alvás fontosságára, az alváshigiénés szabályok betartására.

SZERZŐI MUNKAMEGOSZTÁS

F. K.: célkitűzések megfogalmazása, kérdőívcsomag készítése, statisztikai elemzés, a kézirat megszövegezése; R. B.: szakirodalmi áttekintés, a vizsgálatok lefolytatása, adatbázis készítése; B. B.: szakirodalmi áttekintés, a vizsgálatok lefolytatása, adatbázis készítése; T. K: szakirodalmi áttekintés, a kézirat megszövegezése; S. E.: a kézirat megszövegezése; R. L. B.: statisztikai elemzés; O. A.: célkitűzések megfogalmazása.

Nyilatkozunk arról, hogy a cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

ANYAGI TÁMOGATÁS

A közlemény megírása, illetve a kapcsolódó kutatómunka anyagi támogatásban nem részesült.

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CEREBRAL CAVERNOUS MALFORMATION TYPE 1 WITH RETINAL BLOOD VESSEL TORTUOSITY AND KRIT1 GENE MUTATION

Tibor KALMÁR[1], Zoltán MARÓTI[1], Árpád VADVÁRI[2], Ágnes HALMOSI[3], Ferenc KÁLOVITS[4, 5], Bernadette KÁLMÁN[5, 6]

[1]University of Szeged, Institute of Pediatrics and Pediatric Health Center, Szeged Hungary
[2]Markusovszky University Teaching Hospital, Department of Radiology, Szombathely
[3]Markusovszky University Teaching Hospital, Department of Ophthalmology, Szombathely
[4]Markusovszky University Teaching Hospital, Department of Neurosurgery, Szombathely
[5]University of Pécs, School of Medicine, School of Graduate Studies, Pécs
[6]Department of Molecular Pathology of the Markusovszky University Teaching Hospital, Szombathely

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Cerebral cavernous malformations (CCMs) represent a relatively rare and heterogeneous clinical entity with mutations identified in three genes. Both sporadic and familial forms have been reported. We present a young female patient with episodic paresthesia and headaches, but without acute neurological deficits. Her mother had a hemorrhaged cavernoma surgically removed 21 years ago. Cranial magnetic resonance imaging revealed multiple cavernous malformations in the size of a few millimeters and the ophthalmologic exam detected retinal blood vessel tortuosity in the proband. Targeted exome sequencing analysis identified a nonsense mutation in exon 16 of the KRIT1 gene, which resulted in a premature stop codon and a truncated protein underlying the abnormal development of cerebral and retinal blood vessels. This mutation with pathogenic significance has been reported before. Our case points to the importance of a thorough clinical and molecular work up despite the uncertain neurological complaints, since life style recommendations, imaging monitoring and genetic counseling may have major significance in the long term health of the patient.

Keywords: *cerebral cavernous malformations, retinal vascular tortuosity, MRI, KRIT1 gene*

1-ES TÍPUSÚ CEREBRALIS CAVERNOSUS MALFORMATIO RETINAÉR-TORTUOSITASSAL ÉS KRIT1 GÉN MUTÁCIÓVAL

Kalmár T, PhD; Maróti Z, PhD; Vadvári Á, MD; Halmosi Á, MD; Ferenc Kálovits F, MD; Kálmán B, MD, PhD, DSc, FAAN

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A cerebralis cavernosus malformatiók (CCM) viszonylag ritka és heterogén klinikai entitást képviselnek; a háttérben három génben találtak eddig mutációkat. Sporadikus és öröklődő formáit is leírták. Itt egy fiatal nőbeteg esetét mutatjuk be, aki epizodikus paraesthesia és fejfájás panaszával jelentkezett, de akut neurológiai tünetek nem voltak. Édesanyjának 21 évvel ezelőtt volt egy bevérzett cavernomája, amit sebészileg eltávolítottak. A koponya-MRI többszörös, néhány milliméteres cavernomatosus malformatiókat detektált, míg szemészeti vizsgálat során a retinalis erek tortuositasa derült ki. Kiválasztott gének exomszekvenálásának elemzése során egy nonsense mutációt azonosítottunk, ami a génátírás korai leállításához és egy csonkolt fehérje szintéziséhez vezetett, megmagyarázva az agyi és retinalis erek fejlődési zavarát. Ezt a patogén mutációt már leírták korábban. Esetünk rámutat az átfogó klinikai kivizsgálás és molekuláris elemzés fontosságára az enyhe és bizonytalan panaszok ellenére, mivel az életmódi tanácsadás, az MRI-monitorozás és a genetikai tanácsadás nagy jelentőséggel bírhat a beteg hosszú távú egészségmegőrzése tekintetében.

Kulcsszavak: *cerebralis cavernosus malformatiók, retinalis ér tortuositas, MRI, KRIT1 gén*

Correspondent: Prof. Bernadette KÁLMÁN, University of Pécs, Markusovszky University Teaching Hospital; 9700 Szombathely, Markusovszky u. 5. Phone: (06-94) 515-624, e-mail: Kalman.bernadett@markusovszky.hu
https://orcid.org/0000-0003-2592-3939

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Cerebral cavernous malformations (CCM) (OMIM 116860) are relatively rare venous capillary malformations in the central nervous system (CNS). Other organs such as the retina, skin or liver may also be affected. Both familial and sporadic cases have been reported since the early twentieth century[1–3].

Genetic linkage, cloning and sequence analyses revealed three affected genes underlying the majority of clinical phenotypes. CCM1 is caused by mutations in the *KRIT1* gene (OMIM 604214), while CCM2 by mutations in the *MGC4607* (OMIM 607929) and CCM3 by mutations in the *PDCD10* genes (OMIM 603285). Familial forms with autosomal dominant transmission patterns occur with the frequency of 1/2000 - 1/10,000[4].

Here we report a young female patient with recurrent headaches and episodic sensory disturbances on the face and head, in whom ophthalmological examination revealed severe vascular tortuosity in the retinae and MRI showed cavernous malformations in the brain. Genetic work up identified a heterozygous nonsense mutation in the *KRIT1* gene.

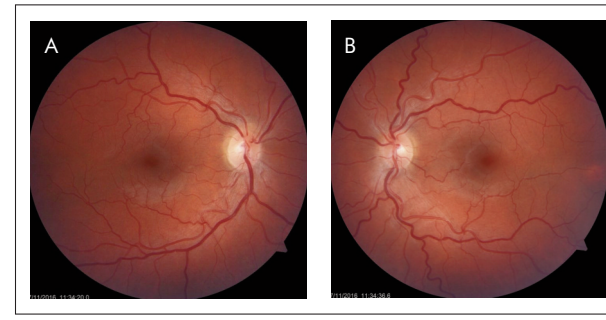

Figure 1. *Vascular malformations in the retinae. Photographs taken from the right* **(A)** *and left* **(B)** *retinae of the patient show vascular tortuosity (L>R) and cork screw-like venous malformations (L)*

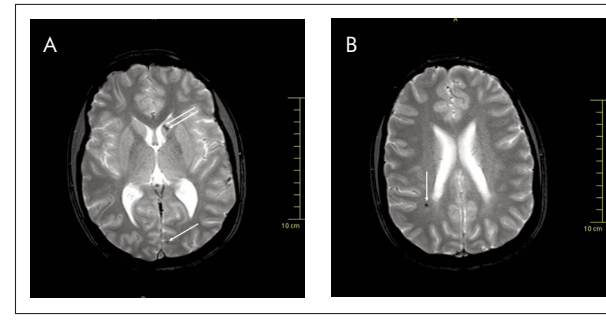

Figure 2. *Axial T2-weighted FFE MRI images of the brain.* **A** *shows two hypointense lesions (2-3 mm) within the head of left caudate nucleus, and one subcortical occipital lesion (3 mm);* **B** *shows one lesion (3 mm) in the right parietal region, behind the ventricular horn. These lesions are compatible with CCM*

Summary of the case

A 26 year old female patient presented to the Emergency Department three years ago because of a sudden onset numbness on the right side in her face, arm and leg, which gradually went away. Similar paresthesias have subsequently recurred multiple times, and each lasted for 2-3 days. Since the onset of the episodic numbness, she also had experienced burning episodic headaches, pain behind the eyes, tightness in her throat, dysphagia, cold extremities, fatigue, and hypersomnia.

She was born prematurely (in the 32nd week of pregnancy), and suffered of mild perinatal ischemia. Polycystic ovarian syndrome and insulin resistant glucose intolerance were diagnosed prior to the neurological presentation.

Her family history is notable for her mother who was diagnosed with cerebral cavernoma that blead at age 32 (21 years ago) and for an aunt on the father's side, who died of brain hemorrhage of hypertensive origin at age of 36 years.

On exam, the proband's skin was cool and sweaty, but without any sign of vascular or other lesions. Cranial nerves were normal. Slight muscle hypotrophy with slightly increased tone appeared in the right leg without paresis (likely related to the perinatal injury). Deep tendon reflexes were symmetric and 2+ throughout with no Babinski sign. Coordination of the trunk and extremities appeared normal. Sensorium showed no deficit. Her speech had a nasal quality, but was otherwise normal. Her cognition was within the normal range, but she expressed exaggerated anxiety.

Electrocardiogram and transthoracic cardiac echo showed normal results.

Electromyography revealed normal muscle activity, while electroneuronography showed normal conduction velocity and amplitudes.

Ophthalmology exam was significant for bilateral tortuosity of the retinal blood vessels (L>R), with cork-screw-like veins particularly on the L side, but no signs of hemorrhage **(Figure 1A, 1B)**. Myopia of minimal grade on both sides, and opacity of the vitreous body on the left side were also detected.

MRI of the brain: On T2-weighted fast field echo (FFE) and diffusion weighted images (DWI) hypointense lesions were visible within the left caudate nucleus (2 and 3 mm in diameter), the left occipital region (3 mm) and behind the ventricular horn

in the right parietal region (3 mm), which did not enhance gadolinium on T1-weighted sequences. These lesions were compatible with cerebral cavernous malformations **(Figure 2A, 2B)**.

Laboratory findings: Blood counts, chemistry, liver and kidney function tests showed normal results. Alpha-galactosidase activity was within the normal range excluding (along with the normal skin, and normal results of kidney and cardiac work up) Fabry's disease. A detailed hemostasis test also showed normal results. The anti-cardiolipin and anti-phospholipid antibodies were negative.

Genetic studies: Genomic DNA was obtained from peripheral blood cells. We performed Illumina TruSight One clinical-exome sequencing, restricting the analysis to genes related to Cerebral Autosomal Recessive and Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL and CADASIL, *HTRA1* 10q26.13; *NOTCH3* 19p13.12, respectively), Hereditary Angiopathy with nephropathy, aneurism and muscle cramp as well as cerebral small vessel disease (*COL4A1* 13q34 and *COL4A2* 13q34), Autosomal Dominant Retinal Angiopathy with Cerebral Leukodystrophy (*TREX1* 3p21.31) and CCM1, CCM2 and CCM3 (*KRIT1* 7q21.2; *MGC4607* or *C7ORF22* 7p13 and *PDCD10* 3q26.1, respectively). A heterozygous nonsense mutation in exon 16 of *KRIT1* was found: c.1815C>G resulting in a premature STOP codon p.Tyr605Ter. The identified mutation was confirmed by Sanger sequencing according to the standard protocol (BigDye® Terminator v3.1 Cycle Sequencing Kit, Applied Biosystems®).

The identified mutation was not listed in either The Genome Aggregation Database (gnomAD at http://gnomad.broadinstitute.org/ containing 123,136 exome sequences and 15,496 whole-genome sequences from unrelated individuals as of March 13, 2018), or in the ExAC database (more than 120,000 chromosomes from 60,706 unrelated individuals) or among 600 Hungarian population control chromosomes. This mutation was also absent from the Online Mendelian Inheritance of Man (OMIM, https://www.omim.org/) and the National Center for Biotechnology Information (NCBI) Clinical Variations and Single Nucleotide Polymorphism (SNP) databases (https://www.ncbi.nlm.nih.gov/ncbisearch/). However, it was listed as a pathogenic variant causing CCM1 in the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/) based on a publication by *Stahl* et al.[4] Unfortunately, the proband's mother refused to undergo either neurological examination, MRI follow up or genetic testing.

Discussion

We present a young patient with cerebral cavernous malformations and striking retinal blood vessel tortuosity. Her clinical complaints and symptoms have been mostly episodic headaches and paresthesias. Her family history revealed that 21 years ago a hemorrhaged cavernoma was discovered in her mother who has been well since the surgery.

CCM may be sporadic or inherited in an autosomal dominant manner. Clinically, it often presents with seizures, recurrent headaches and sudden neurological signs due to episodic bleeding. However, asymptomatic carriers are present in many families. CCM can be best detected by gradient echo and susceptibility weighted MRI sequences, although hypointense lesions are also visible to some degrees on T2- and T1-weighted images **(Figure 2)**. Calcification may develop in some lesions. CCMs are, however, undetectable by angiography. Vascular malformations in other organs such as the retinae, liver or the skin may co-occur[5].

Three CCM subtypes are distinguished based on mutations in three different genes named *KRIT1* (krev interaction trapped 1)*, MGC4607* (malcavernin) and *PDCD10* (programmed cell death protein 10). In familial forms, the inheritance follows autosomal dominant transmission pattern. *Craig* et al. reported that among non-Hispanic Caucasian kindreds, CCM1 occurred in 40%, CCM2 in 20% and CCM3 in 40%[6]. The penetrance of symptomatic disease among mutation carriers was 88% in CCM1, 100% in CCM2 and 63% in CCM3[6–9]. Not only the varying degrees of penetrance, but also the clinical heterogeneity associated with each of the mutations deserve attention. In sporadic cases, occurrence of *de novo* mutations or somatic mosaicism of mutations in these genes may play a role.

The mechanism of molecular pathogenesis has been best explored in CCM1. *Laberge-le Couteulx* et al. identified the first pathogenic mutations in the CCM1 gene, *KRIT1*[9]. All mutations resulted in truncated proteins lacking the RAP1 (Ras-related protein 1) - interacting site. *Zhang* et al. reported that the full length KRIT1 protein also interacted with the integrin cytoplasmic domain-associated protein-1 (ICAP-1) that binds to a specific site within the intracytoplasmic domain of beta-1 integrin (ITGB1)[10]. ITGB1 is involved in the regulation of cell adhesion and migration. Through the same binding sequence, ICAP-1 may bind to both KRIT1 and ITGB1, resulting in an equilibrated state among the three proteins under physiological conditions. When loss of function mutations eliminate the aforementioned binding site from the truncated KRIT1

protein, a shift in the molecular balance leads to disturbed angiogenesis. Further studies revealed, that KRIT1 expression co-localized with microtubules in endothelial cells, suggesting the involvement of KRIT1 in endothelial cell morphology and function, and explaining abnormal endothelial tube formation associated with the loss of interacting KRIT1 site from the truncated protein in CCM1[11]. Similar to the interactions of KRIT1/ITGB1 and KRIT1/ICAP1, interactions also have been described for KRIT1/CCM2[12]. Subsequent studies, however, revealed that a cooperative functional interaction among all three CCM gene products exists with key biological significance within the CCM1/CCM2/CCM3 complex[4]. Therefore, mutations in various members of the interacting / signaling complex may be responsible for the genetic heterogenity observed in clinical phenotypes of CCM.

The *KRIT1* gene (7q21-q22) has 19 exons the first three of which are non-coding[13]. As of today, over 150 pathogenic nonsense, splice-site and frame-shift insertion/deletion mutations with resultant truncated proteins have been reported and listed in the databases. Less frequently, loss of heterozygosity, haploinsufficiency and larger deletions and insertions affecting *KRIT1* have also been noted. Three quarters of the mutations were found in the C-terminal half of the gene, and affected mostly exons 13, 15 and 17[5, 14]. However, mutations in N-terminal exons as well as in other C-terminal exons have also been detected in other ethnic groups[4]. Because of the frequent occurrence of mutations causing premature stop codon in *KRIT1*, nonsense-mediated mRNA decay was proposed as a mechanism contributing to CCM1 pathogenesis. Besides inherited mutations, somatic mutations have also been identified in the lesion sites suggesting the Knudson two-hit mechanism consistent with the observation that complete loss of the KRIT1 function results in the development of cerebral cavernomas.

About half of mutation carriers seem to be asymptomatic in large pedigrees segregating pathogenic *KRIT1* mutations, but over 80% of these individuals have MRI-detected cavernous malformations in their brains[15].

Our patient had uncertain, non-localizing complaints and neurological presentation. MRI imaging identified small vascular lesions in her brain. Because of the suggestive familial recurrence, and the CCM-like MRI appearance of these lesions along with the retinal vessel abnormalities in the proband, we suspected genetic etiology of the problem. Targeted exome sequencing analysis then identified an already published nonsense mutation resulting in premature stop codon in the *KRIT1* gene, responsible for CCM1 pathogenesis[4]. Because of the multiple occurrence, small size and deep location of the vascular lesions, neurosurgical intervention was not indicated. A comprehensive counseling for imaging monitoring, blood pressure control and life style recommendations (e.g. avoiding head trauma and major physical exertion) for minimizing the risk of bleeding were undertaken by her neurologist. Finally, the patient was also informed about the *KRIT1* mutation in the context of formal genetic counseling including family planning. Implications of this genetic test result for other, potential career family members was emphasized. We have offered neurology and MRI studies as well as genetic testing for such family members.

Conclusion

We presented a case of CCM1 with neurological, ophthalmological and MRI presentations, related to a known pathogenic *KRIT1* mutation. We briefly discussed the typical CCM phenotypes and underlying genotypes along with the known mechanisms of pathogenesis. To identify the existing vascular abnormalities and the underlying genetic etiology in this young patient presenting with vague neurological complaints and signs, modern imaging and sequencing technologies were of invaluable utility. The correct diagnosis made it possible to provide the patient with appropriate recommendations for lifestyle and imaging monitoring, in case the vascular malformations grow in number and size over time.

ACKNOWLEDGEMENTS

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KOMPLEX REGIONÁLIS FÁJDALOM SZINDRÓMA AMITRIPTYLINKEZELÉSE

KOMOLY Sámuel

Pécsi Tudományegyetem, Neurológiai Klinika, Pécs

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Bevezetés – A komplex regionális fájdalom szindróma jelentős fájdalommal és trofikus zavarokkal jellemezhető, az életminőséget, sokszor a munkaképességet is negatívan befolyásoló, súlyos esetekben rokkantsághoz vezető állapot.
Esetbemutatás – Egy poszttraumás komplex regionális fájdalom szindrómában szenvedő beteg amitriptylinnel történt sikeres kezelését ismertetjük.
Diszkusszió – Az amitriptylinkezelés esetünkben nemcsak a fájdalom, de a kísérő autonóm és motoros tünetek kezelésében is eredményes volt.
Konklúzió – Megfigyelésünk kontrollált vizsgálatok végzését indokolhatja az amitriptylin hatékonyságának objektív megítélésére komplex regionális fájdalom szindrómában.

Kulcsszavak: *komplex regionális fájdalom szindróma, kezelés, amitriptylin*

TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME WITH AMITRIPTYLINE
Komoly S, MD, PhD
Ideggyogy Sz 2019;72(7–8):279–281.

Introduction – Complex regional pain syndrome is a distressing neuropathic pain condition without known etiology and evidence based treatment.
Case presentation – Here a posttraumatic severe case of complex regional pain syndrome is presented, successfully treated by amitriptyline monotherapy. Amitriptyline is one of the most effective evidence based treatments of peripheral diabetic neuropathic pain and other neuropathic pain syndromes.
Discussion – Amitriptyline seems to be effective to decrease pain, autonomic and motor symptoms in chronic regional pain syndrome.
Conclusion – Controlled trials may be warranted to test the effectiveness of amitriptyline in complex regional pain syndrome.

Keywords: *complex regional pain syndrome, treatment, amytriptilin*

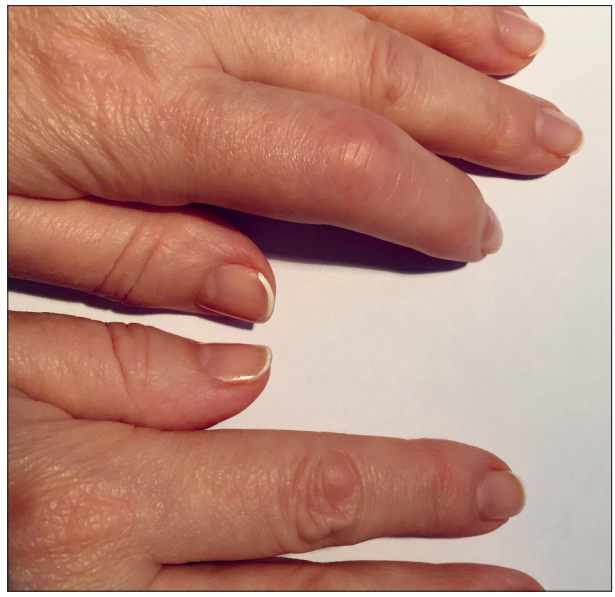
Levelezési cím (correspondence): Dr. KOMOLY Sámuel, Pécsi Tudományegyetem, Neurológiai Klinika; 7623 Pécs, Rét u. 2. Telefon: (06-72) 535-910, fax: (06-72) 535-911, e-mail: komoly.samuel@pte.hu
https://orcid.org/0000-0002-4800-556X

Érkezett: 2019. május 1. Elfogadva: 2019. május 12.

A korábban „Sudeck-atrófia”, „causalgia”, „reflex sympathicus dystrophia”, „kéz-váll szindróma”, és még számos egyéb elnevezéssel illetett kórképet egy nemzetközi ad hoc bizottság javaslata alapján 1995 óta, „complex regional pain syndrome”-nak nevezik[1]. Nőkben 5-ször gyakoribb, prevalenciájának csúcsa mindkét nemben a 25–50 életévek közé esik, az összes végtagtrauma mintegy 5%-a után kialakul, a legtöbb esetben enyhe, spontán remittál. Ha egy éven túl fennáll (ez az esetek 1-2%-a), akkor spontán remisszióra már nem lehet számítani[2].

Hagyományosan a komplex regionális fájdalom szindróma I-es és II-es típusát különböztetik meg. Az I-es típus nem korlátozódik egyetlen perifériás ideg területére. Sokszor banális trauma (például radiustörés, elesés kapcsán elszenvedett könyöktrauma, bokasérülés) előzi meg, kialakulhat továbbá stroke, szívinfarktus, az adott végtag tartós immobilizálása után, de vannak idiopathiás formái is.

Jellemzője égő, lüktető, szaggató fájdalom, allodynia (a finom tapintási ingerek igen heves fájdalomérzést provokálnak), amit vegetatív jelek (hyperhydrosis, a bőr kipirulása, oedemasodása) kísérnek **(1. ábra)**. Hosszabb fennállás után a bőr atrófiássá, pergamenszerűvé válik az érintett kézen. A trofikus zavarok következtében a csontok (elsősorban a kéz és a csukló csontjai) atrofizálódnak (Sudeck-atrófia). Több diagnosztikus rendszer ismert[3], a legelfogadottabb az utóbbi évtizedben validált „Budapest kritériumrendszer”[4] **(1. táblázat)**.



1. ábra. *Típusos elváltozások komplex regionális fájdalom szindrómában. A kép felső részén látható, hogy legkifejezettebben a bal kéz mutatóujja oedemás, felette a bőr „fényes”: atrófiás*

A komplex regionális fájdalom szindróma II-es típusa hátterében valamelyik nagy, felső vagy alsó végtagi ideg részleges (vágott, zúzott, lőtt) sérülése áll. Vezető tünete a causalgia (égő szaggató, nyilalló, vegetatív jelenségekkel kísért fájdalom), ami érintésre, a végtag mozdítására, de akár stresszre is aktiválódhat, és sokszor szinte elviselhetetlen szenvedést okoz a betegnek[3].

A komplex regionális fájdalom szindróma egyik formájának sincs bizonyítottan és biztosan hatékony terápiája. A szimpatikus ganglionok blokádja, α-receptor-blokkolók, szteroid, (triciklikus) antidepresszánsok, gabapentin, pregabalin adása megkísérelhető[1].

1. táblázat. *A komplex regionális fájdalom szindróma diagnosztikus kritériumai (klinikai diagnosztikus kritériumok a „Budapest- kritériumok”[4] után)*

1. Indokolatlanul tartósan fennálló, állandósult fájdalom, amit a kiváltó esemény súlyossága (természete) nem indokol (például típusos radiustörés).
2. Az alábbi négy tünetcsoportból legalább háromhoz tartozó tünetet panaszol a beteg és/vagy a betegvizsgálat során észlelhető:
– hyperaesthesia/allodynia (spontán neuropathiás fájdalom is lehet)
– vasomotoros eltérések (bőrpír és/vagy sápadtság)
– fokozott vagy csökkent verejtékezés, oedema
– bőr-, izom-, köröm-, csont- („Sudeck-”) atrófia (együtt vagy bármelyik a felsoroltak közül), motoros tünetek (izomgyengeség, tremor, dystonia)

Esetismertetés

Az 56 éves nőbeteg 2009. május 15-én autóbaleset érte, kirepült a hátsó ablakon. Bal vállát érte nagyobb ütés, a beteg ezt úgy mondja el, hogy a válla „összelapult”, a felkarján az izom „lecsúszott”; csonttörése nem volt. A baleset óta bal kezét kevésbé tudja használni, nem tud vele jól fogni.

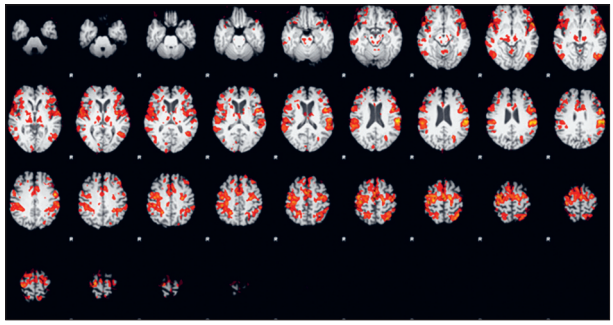
2009. október 6-án került felvételre a klinikánkra. Felvétele előtt két hónappal vette észre, hogy bal keze duzzadt és fájdalmas lett, időnként áramütésszerű érzése volt a kezében. A tapintási ingerek fájdalmat váltottak ki. A fájdalom csak karját függőlegesen felfelé tartva volt elviselhető, kezét lógatni nem tudta. A fájdalom nyugalomban is állandó volt, de az ujjak és a csukló mozgatására jelentősen felerősödött. A fájdalom vizuális analóg skálán 7–8-as értékkel volt jellemezhető. Felvételekor a bal keze duzzadt, bőre atrófiás volt, a fájdalom miatt a beteg ujjai, csuklójának mozgástartománya jelentős mértékben beszűkült, kezét gyakorlatilag nem tudta használni **(1. ábra)**. A beteg komplex regionális fájdalom szindrómájának kezelésére este 25 mg-mal kezdve, fokozatosan emelve 75 mg amitriptylint (Teperin) állítottunk be. Fájdalma, ujjainak oedemája mérséklődött, az ujjmozgások egyre kevesebb fájdalmat okoztak, 2010. július 8-i kontrollvizsgálatán (mintegy kilenc hónap Teperin-kezelés után) fájdalmát a vizuális analóg skálán 1–2-re értékelte, bal kezét a mindennapokban zavartalanul használta. A klinikai javulással összhangban funkcionális MR-vizsgálata is csökkent aktivitást mutatott **(2. A** és **B ábra)** (a vizsgálatok a GOP-1.1.1-07/1-2008-0072 támogatásával valósultak meg, az ábra illusztráció, a funkcionális MRI nem napi diagnosztikus eszköz).

Ez után az időpont után már nem jelentkezett klinikánkon kontrollra.

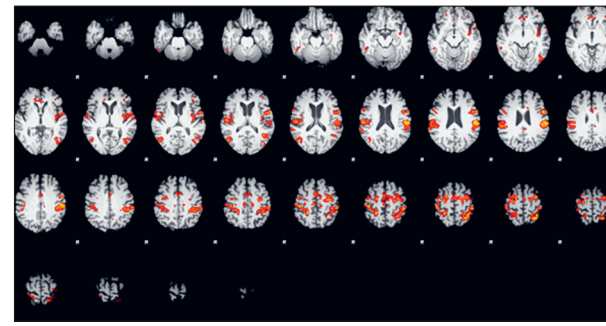
2019. április 23-án telefonon adott beszámolója alapján emlékezete szerint mintegy két év után a Teperint elhagyta, panaszai nem tértek vissza.

Megbeszélés

A komplex regionális fájdalom szindróma krónikus fájdalom, aminek kialakulásában autoimmun mechanizmusok, centrális és perifériás szenzitizáció, feltehetően genetikai tényezők is szerepet játszanak. Annak ellenére, hogy a komplex regionális fájdalom szindróma egy végtagot érint („egyoldali”), funkcionális vizsgálatokkal kétoldali változások (centrális szenzitizáció) mutathatók ki az agyban a szenzoros és motoros kérgi régiókban egyaránt[5, 6] **(2. A** és **B ábra)**.



2. A. ábra. *Funkcionális MR-aktivitás amitriptylinkezelés előtt. Hővel kiváltott fájdalomingerlés az érintett (bal) oldali csukló felszínén. Cluster-based thresholding Z > 2,3, p = 0,05*



2. B. ábra. *Funkcionális MR-aktivitás négy hét amitriptylinkezelés után. Hővel kiváltott fájdalomingerlés az érintett (bal) oldali csukló felszínén. Cluster-based thresholding Z > 2,3, p = 0,05*

Az amitriptylinről kimutatták, hogy perifériás neuropathiás fájdalommodellben hatékonyabb, mint a bupivacain[7], centrális fájdalomcsillapító hatása valószínűleg a periaqueductalis leszálló fájdalomgátló rendszer aktiválása útján magyarázható[8].

A szakirodalom egységes abban, hogy a neuropathiás fájdalom csökkentésében a triciklikus antidepresszánsok a leghatékonyabbak. „Number needed to treat" értékük 2–3, ami SNRI-szerek esetében 5–7, a pregabalin és a gabapentin esetében szintén 5–7. Amitriptylin esetében este 25 mg kezdő dózis ajánlott, amit mellékhatásoktól függően napok (néha hetek) alatt érdemes emelni, általában 75 mg-ig. A Teperin hosszú felezési idejének köszönhető az esti, egyszeri dozírozás lehetősége.

Nagy-Britannia 570 háziorvosi praxisából gyűjtött adatok alapján ellenőrizték az antidepresszánsok mellékhatásait több mint hatvanezer, 65–100 év közötti depressziós beteg körében. Elemezték többek között az összmortalitás, a hyponatraemia, a szívinfarktus, az öngyilkossági kísérletek, a közúti balesetek, az elesések, a csonttörések előfordulási arányát különönöző antidepresszánsok alkalmazása mellett. A betegek 54,7%-a SSRI-t, 31,6%-a triciklikus szert, 0,2%-a monoamin-oxidáz inhibitort, 13,5%-a nem részletezett hatásmechanizmusú, egyéb antidepreszszánst kapott. Legfontosabb eredménye a vizsgálatnak, hogy a „közvélekedéssel" szemben nem a triciklikus antidepresszánsok jelentették a legnagyobb mellékhatás-szövődmény kockázatot[9].

Következtetés

Az amitriptylin racionális választás lehet komplex regionális fájdalom szindróma kezelésében.

KÖSZÖNETNYILVÁNÍTÁS

A funkcionális MR-felvételek elkészítéséért Orsi Gergőt és Perlaki Gábort illeti köszönet. A beteg kezelésében dr. Deli Gabriella segítségét köszönöm.

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ISOLATED HYPOGLOSSAL NERVE PALSY DUE TO A JUGULAR FORAMEN SCHWANNOMA

Özgür ÖZTOP-ÇAKMAK[1], Ebru VANLI-YAVUZ[1], Serhat AYGÜN[2], Birgül BASTAN[3], Emrah EGEMEN[4], İhsan SOLAROĞLU[4], Yasemin GURSOY-OZDEMIR[1]

[1]Koç University Hospital, Departments of Neurology, İstanbul, Turkey
[2]Koç University Hospital, Departments of Radiology, İstanbul, Turkey
[3]Koç University Hospital, Departments of Neurosurgery, İstanbul, Turkey
[4]Haseki Hospital, Department of Neurology, İstanbul, Turkey

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Introduction – Although the involvement of the hypoglossal nerve together with other cranial nerves is common in several pathological conditions of the brain, particularly the brainstem, isolated hypoglossal nerve palsy is a rare condition and a diagnostic challenge.
Case presentation – The presented patient arrived to the hospital with a history of slurred speech and an uncomfortable sensation on his tongue. Neurological examination showed left-sided hemiatrophy of the tongue with fasciculations and deviation towards the left side during protrusion. Based on the clinical and MRI findings, a diagnosis of hypoglossal nerve schwannoma was made.
Discussion – Hypoglossal nerve palsy may arise from multiple causes such as trauma, infections, neoplasms, and endocrine, autoimmune and vascular pathologies. In our case, the isolated involvement of the hypoglossal nerve was at the skull base segment, where the damage to the hypoglossal nerve may occur mostly due to metastasis, nasopharyngeal carcinomas, nerve sheath tumors and glomus tumors.
Conclusion – Because of the complexity of the region's anatomy, the patient diagnosed with hypoglossal nerve schwannoma was referred for gamma knife radiosurgery.

Keywords: *isolated hypoglossal nerve palsy, schwannoma, radiosurgery*

A FORAMEN JUGULARE SCHWANNOMÁJA KÖVETKEZTÉBEN KIALAKULÓ IZOLÁLT NERVUS HYPOGLOSSUS BÉNULÁS

Öztop-Çakmak Ö, MD; Vanlı-Yavuz E, MD; Aygün S, Bastan B, MD; Egemen E, MD; Solaroğlu I, MD; Gursoy-Ozdemir Y, MD

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Bevezetés – Habár a nyelv alatti ideg más agyidegekkel együtt gyakran érintett a patológiás agyi, agytörzsi folyamatokban, az izolált nervus hypoglossus bénulás diagnosztikus kihívást jelentő, ritka betegség.
Esetbemutatás – A kórházunkba felvett beteg kórtörténetében elkent beszéd és a nyelvben jelentkező kellemetlen érzés szerepelt. A neurológiai kivizsgálás a nyelv bal oldali hemiatrophiáját és fasciculatióját, valamint protrusio közbeni bal oldali deviációját tárta fel. A klinikai kivizsgálás és az MRI-leletek alapján nervus hypoglossus schwannoma diagnózist állítottunk fel.
Diszkusszió – A nyelv alatti ideg bénulása számos ok miatt következhet be (például trauma, fertőzés, neoplasma, valamint endokrin, autoimmun és vascularis patológiák). A bemutatott esetben a beteg a koponyaalapi szegmenst érintő, izolált nervus hypoglossus bénulás tüneteivel jelentkezett osztályunkon; ez a típusú nervus hypoglossus károsodás leggyakrabban metasztázis, nasopharyngealis carcinoma, az ideg körüli szövetek tumora vagy glomustumor következtében alakul ki.
Konklúzió – A régió anatómiájának komplexitása miatt a nervus hypoglossus schwannomával diagnosztizált betegünket gammakéssel végzett radiosebészeti kezelésre utaltuk.

Kulcsszavak: *izolált nervus hypoglossus bénulás, schwannoma, radiosebészet*

Correspondent: Özgür ÖZTOP-ÇAKMAK, MD, Koç University Hospital, Departments of Neurology; Davutpaşa Caddesi No:4 34010 Topkapı, İstanbul, Turkey.
Phone: +90 850 250 8 250, email: ocakmak@kuh.ku.edu.tr
https://orcid.org/0000-0003-3413-0332

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Although the involvement of the hypoglossal nerve together with other cranial nerves is common in several pathological conditions of the brain, particularly the brainstem, isolated hypoglossal nerve palsy is a rare condition and remains a diagnostic challenge due to its varying etiologies. Herein, we present a case of isolated unilateral hypoglossal nerve palsy caused by a jugular foramen schwannoma encircling the 12th cranial nerve.

Case presentation

A 46-year-old male patient presented to the hospital with a 2-month history of slurred speech and an uncomfortable sensation on his tongue. He was otherwise healthy. Neurological examination showed left-sided hemiatrophy of the tongue with fasciculations and deviation towards the left side during protrusion, suggestive of a left hypoglossal nerve palsy **(Figure 1)**. Other findings were unremarkable.

Cranial and cervical magnetic resonance imaging (MRI) revealed a hyperintense lesion located at the left jugular foramen, obstructing the external orifice of the left hypoglossal canal **(Figure 2)**. Based on the clinical and MRI findings, a diagnosis of hypoglossal nerve schwannoma was made.

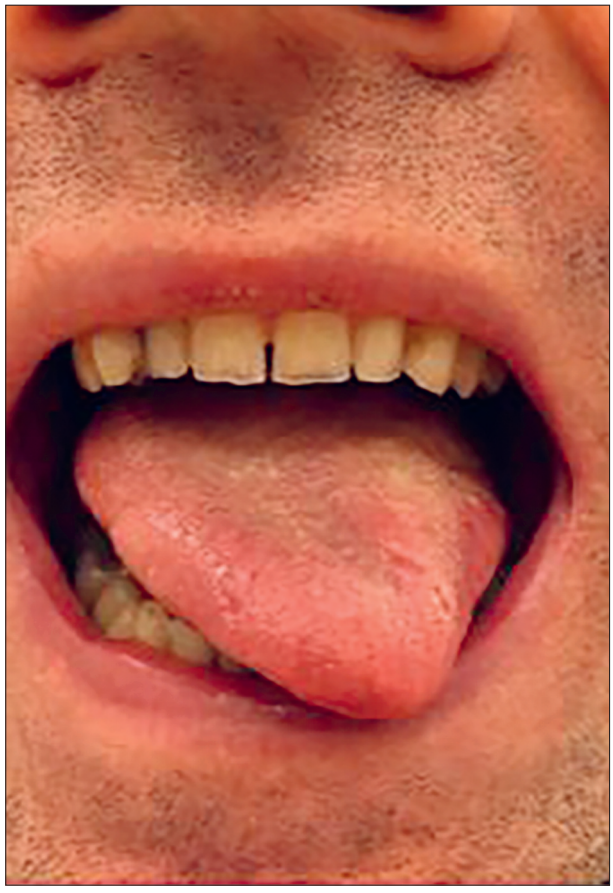

Figure 1. *Atrophy due to the hypoglossal nerve involvement on the left side of the tongue with a left-sided deviation on protrusion*

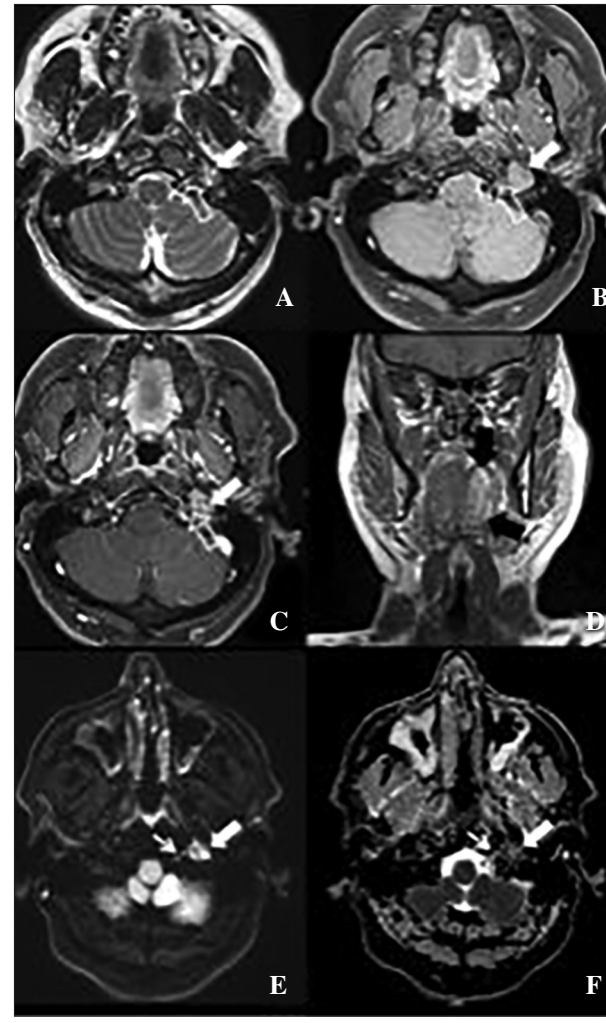

Figure 2. *Cranial MRI images of the patient.* **A:** *A T2-weighted image in the axial plane shows a hyperintense lesion (thick white arrow) on the left jugular foramen, obstructing the external orifice of the left hypoglossal canal (open arrow).* **B–C:** *Pre and postcontrast fat saturated axial plane T1-weighted images show a highly vascular lesion (thick white arrow).* **D:** *A coronal plane T2-weighted image shows denervation atrophy of the left lingular muscles (thick black arrow).* **E–F:** *A diffusion-weighted image and the ADC map show diffusion restriction of the lesion (thick white arrow) along with cytotoxic edema of the left hypoglossal nerve (thin white arrow) due to compression*

After a meticulous multidisciplinary assessment, surgical treatment was not considered due to the complexity of the region's anatomy and to avoid further complications. The patient was referred for gamma knife radiosurgery.

Discussion

The hypoglossal nerve contains only motor fibers that originate from the medulla oblongata and innervate the intrinsic and extrinsic muscles of the tongue except for the palatopharyngeus, which is supplied by the vagus nerve. The hypoglossal nerve can anatomically be divided into five segments, including the medullary segment, cisternal segment, skull base segment, extracranial segment, carotid space and anterior segment[1]. The hypoglossal nucleus is located in the hypoglossal eminence in the floor of the fourth ventricle in the dorsal medulla. The hypoglossal nerve fibers exit the brainstem at the ventrolateral sulcus between the olivary nucleus and the medullary pyramid in the cisternal segment, then enter the hypoglossal canal through the occipital bone to exit the skull base. The hypoglossal nerve travels close to the internal carotid artery and internal jugular vein and continues on to the tongue for innervation. During its course, the hypoglossal nerve is in contact with other cranial nerves such as the glossopharyngeal, vagal and spinal accessory nerves[2]. In our case, the involvement was at the skull base segment.

Hypoglossal nerve palsy may arise from multiple causes such as trauma, infections, neoplasms, and endocrine, autoimmune and vascular pathologies. Isolated hypoglossal nerve palsy may be associated with internal carotid or vertebral artery dissections, occipital condyle fractures, osteophytic changes in the atlanto-occipital joints, dural arteriovenous fistulas, enlarged emissary veins of the hypoglossal canal, aneurysm of the stump of the persistent hypoglossal artery, as well as hypoglossal schwannomas[3, 4]. An idiopathic etiology has also been reported[1, 5]. At the skull base segment, damage to the hypoglossal nerve may occur mostly due to metastasis, nasopharyngeal carcinomas, nerve sheath tumors and glomus tumors.

Schwannomas are benign tumors of the peripheral nerve sheath and may affect all cranial nerves, with vestibular schwannoma being the most common cranial nerve schwannoma[4]. They are usually diagnosed in middle-aged patients, with a predilection for females[5]. Isolated hypoglossal nerve palsy is a rare manifestation of schwannomas, resulting in ipsilateral hemiatrophy, deviation and fasciculation of the tongue and headache due to meningeal irritation.

An elaborative imaging study is the key to an accurate differential diagnosis, providing useful information for the identification of the exact etiology and treatment planning including surgical options. In our case, MRI revealed a schwannoma as the cause of the isolated hypoglossal nerve palsy, with compression of the fibers of the hypoglossal nerve on the left side at the level of the jugular foramen.

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A CASE REPORT OF MORVAN SYNDROME

Emrah AYTAÇ[1], Türkan ACAR[2]

[1]Fırat University, Departmant of Neurology, Elazığ, Turkey
[2]Sakarya University, Departmant of Neurology, Sakarya, Turkey

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Morvan syndrome is a rare disease characterized by peripheral nerve hyperexcitability, encephalopathy, dysautonomia and significant insomnia. The patient, who was included in the present study, was followed-up at our clinics for confusion, myokymia, hyperhidrosis, epileptic seizures, tachycardia, agitation, hypokalemia, and hyponatremia. The cranial MRI of the patient demonstrated hyperintensities at the T2 and FLAIR sections of the medial temporal lobe and insular lobes. Electromyography and neurotransmission examination results were concordant with peripheral nerve hyperreactivity. Contactin-associated protein-like 2 antibodies and leucine-rich glioma inactivated protein 1 antibodies were detected as positive. The patient was diagnosed with Morvan syndrome; intravenous immunoglobulin and corticosteroid treatment was started. Almost full remission was achieved. This very rare syndrome implies challenges in diagnosis and treatment; however, remission can be achieved during the follow-up. In addition, caution is needed in the long-term follow-up of these patients regarding the development of malignancies.

Keywords: *Morvan syndrome, protein-like antibodies, LGI1-Ab, CASPR2-Ab*

EGY MORVAN-SZINDRÓMÁS BETEG BEMUTATÁSA
Aytaç E, MD; Acar T, MD
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A Morvan-szindróma nagyfokú perifériás idegizgalommal, encephalopathiával, diszautonómiával és jelentős mértékű insomniával járó ritka kórkép. Az esetismertetésben bemutatott beteget zavartság, myokymia, hyperhidrosis, epilepsziás rohamok, tachycardia, agitatio, hypokalaemia és hyponatraemia miatt kezeltük klinikánkon. A beteg koponya-MR-vizsgálata a medialis temporalis és az insularis lebeny FLAIR-szekció- és T2-hiperintenzitását mutatta. Az elektromiográfia és az idegvezetési vizsgálatok a perifériás idegi hiperreaktivitással egybehangzó eredményt adtak. A Contactin-associated protein-like 2 és a leucine-rich glioma inactivated protein 1 antitestek vizsgálata pozitív eredményt adott. Morvan-szindróma diagnózisát állítottuk fel, intravénás immunoglobulin- és kortikoszteroid-kezelést indítottunk. Majdnem teljes remisszót értünk el. A szindróma diagnosztizálása és kezelése ritka előfordulása miatt kihívást jelent, mindazonáltal az utánkövetés során lehetséges remissziót elérni. A továbbiakban a hosszú távú utánkövetés során fontos annak ismerete, hogy Morvan-szindróma esetén megnő a malignitások gyakorisága.

Kulcsszavak: *Morvan-szindróma, fehérjeszerű antitestek, LGI1-Ab, CASPR2-Ab*

Correspondent: Türkan ACAR, MD, Sakarya University Departmant of Neurology, Sakarya, Turkey.
Phone: +905057948815, e-mail: tdeniz38@hotmail.com
https://orcid.org/0000-0003-2001-914X

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Morvan syndrome (MoS) was first described in 1890 by the French physician Augustin-Marie Morvan in five patients with irregular muscle contractions, painful cramps, itching, hyperhidrosis, delirium and hallucinations[1–3]. MoS is a rare autoimmune disease which can be defined by the sum of peripheral nerve hyperexcitability (myokymia, painful cramps, dysesthesias), autonomic instability (hyperhidrosis, urinary retention, constipation, disorders in blood pressure regulation and cardiac rhythm) and neuropsychiatric features (insomnia, hallucinations and delusions, mental decline, confusion), epileptic seizures[2–4]. Antibodies to voltage-gated potassium channels (VGKC-Ab) including contactin-associated protein-like 2 antibodies (CASPR2-Ab) and leucine-rich glioma inactivated

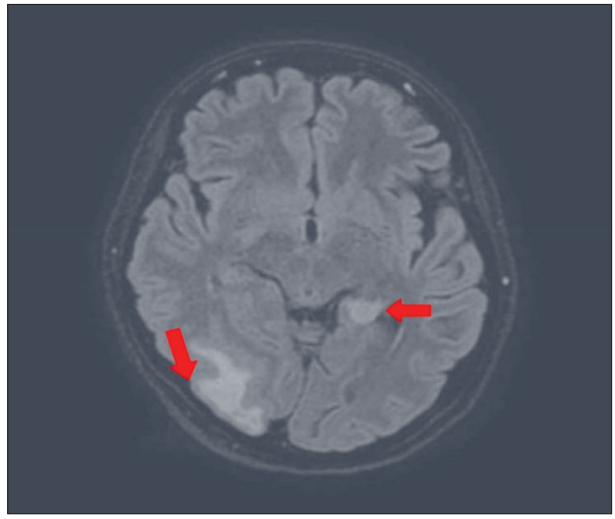

Figure 1. *Increased signal intensity in right occipital and bilateral medial temporal lobes on flair sequence MRI*

protein 1 antibodies (LGI1-Ab) were previously known for the potential association with this condition[4–6]. This rare case, which was diagnosed as Morvan Syndrome with the examination and imaging findings and with the presence of antibodies, is presented in the study.

Case

While the 41-year-old female patient was followed-up at the neurosurgery clinic due to coldness, numbness, and tingling complaints in both legs, which had started 15 days before, she was taken over by our clinic because of a recent onset of consciousness changes, hallucinations, memory losses, and insomnia. Brain computer tomography (CT) evaluated normal results, brain magnetic resonance imaging (MRI) FLAIR sections of the patient showed hyperintensities in both hippocampus and right occipital region **(Figure 1)**. Encephalopathic changes were observed in the electroencephalography (EEG). There were no signs of inflammation in the cerebrospinal fluid (CSF). Considering limbic encephalitis, the patient was treated with IVIG for 5 days (0.4 g/kg/day). On the last day of IVIG treatment, the patient had an epileptic seizure. In the follow-up, upon myokymia pain was detected in lower extremities, therefore electromyography was performed, which revealed significant spontaneous activity at rest **(Figure 2)**. As hyponatremia, hypokalemia, hyperhidrosis and tachycardia started, and as serum LGI1 and CASPR2 antibodies were positive, the patient was diagnosed with Morvan Syndrome (serum test in a cell based assay showed serum VGKC complex proteins (EUROIMMUN, Germany) - including CASPR2-Ab - positive (++) and LGI1-Ab positive (+), while cerebrospinal fluid (CSF) LGI1-Ab was negative). CT scan of the thorax and full abdominal CT scan were performed and the results were reported as being normal. Breast ultrasonography (USG) and suprapubic USG findings were normal.

The patient exhibited no significant improvement in her symptoms, so methylprednisolone 1000 mg/day and phenytoin 300 mg/day were administered for 7 days. Memory loss, myokymia, and confusion improved to almost normal levels. Control brain MRI showed minimal hyperintensities in the right occipital region **(Figure 3)**. Mirtazapine 30 mg/day was started due to insomnia. The patient was discharged on oral steroid treatment because of improvement in her complaints almost up to normal levels during follow-ups. The written informed consent form was received from the patient before the study.

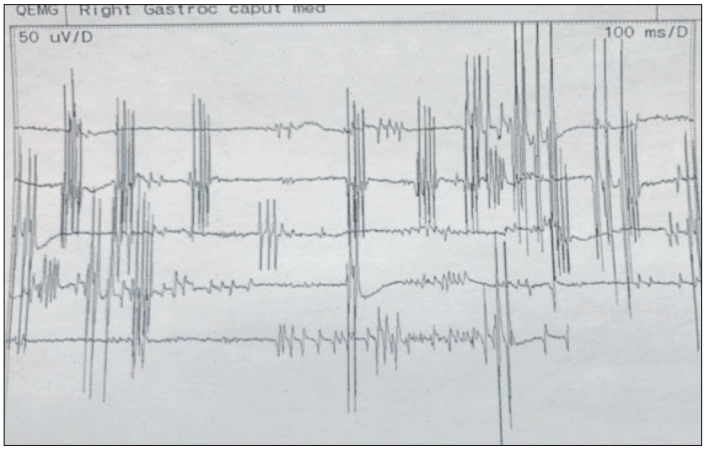

Figure 2. *EMG showing spontaneous discharges in right gastrocnemius muscle*

Discussion

The diagnosis of Morvan syndrome is based on the presence of encephalopathy, dysautonomia, and clinical and electrophysiological findings of myokymia together with hallucinations[3].

Neuropathic pain was present in 62.1% of the patients in a 29-patient series reported by *Irani* et al.[2]. Our patient, too, presented with neuropathic pain initially. Again, in the same study, 93.1% of the patients had autonomic dysfunctional findings such as hyperhidrosis, tachycardia, hypertension,

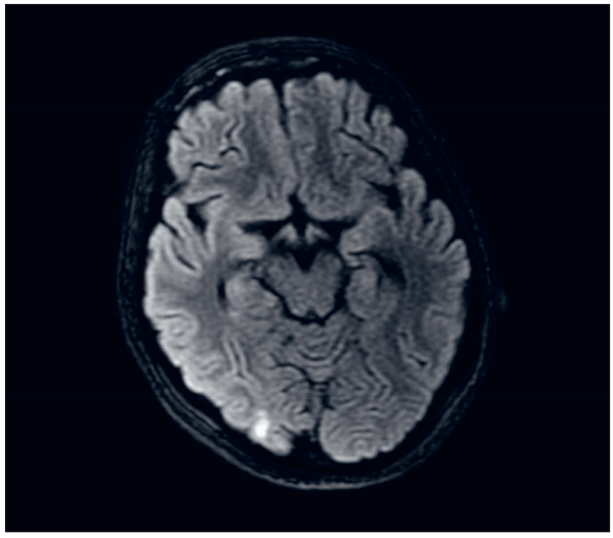

Figure 3. *Control brain MRI showed minimal hyperintensities in the right occipital region*

and constipation. Similarly, serious autonomic findings were also observed in our patient.

Many studies have shown close relationship between MoS and Voltage-Gated Potassium Channel Antibodies, contactin-associated protein-like 2 antibodies and leucine-rich glioma-inactivated protein 1 antibodies[4–6]. LGI1 is a secreted protein, mainly present in the hippocampus and the temporal cortex. CASPR2 is a membrane protein expressed in the central and peripheral nervous system. Its cytoplasmic domain is essential for potassium channel clustering at the juxtaparanodes of myelinated axons[7].

Anti-LGI1 antibodies are present in limbic encephalitis, while anti- CASPR2 antibodies may be associated with encephalitis, peripheral nerve hyperexcitability (also known as acquired neuromyotonia or Isaacs' syndrome), or a combination of both (Morvan syndrome). These 2 proteins are well characterised, and alterations in them provide the pathophysiological mechanism for the clinical symptoms of each type of autoimmune response[8].

LGI1 antibodies are more commonly associated with seizures, amnesia, confusion, hyponatremia and are predictive of better prognosis, while CASPR2 shows more peripheral nerve involvement and is associated with worse prognosis[4–6].

LGI1, a secreted neuronal protein, is a target antigen of limbic encephalitis. Moreover, mutations of LGI1 are the cause of autosomal dominant partial epilepsy with features, also called autosomal dominant lateral temporal lobe epilepsy. In contrast, CASPR2, a protein that is expressed in brain and peripheral nerve, clustering the VGKC at the juxtaparanodal regions of myelinated axons is the target antigen of encephalitis (Morvan's syndrome) and peripheral nerve hyperexcitability (Isaacs' syndrome). In our patient, too, both LGI1 and CASPR2 antibodies were positive, similar to the case report of *Zhang* et al.[9].

Morvan syndrome is an autoimmune disease and should be differentiated with limbic encephalitis, Isaacs' syndrome, Guillain Barre syndrome and familial fatal insomnia[10].

Compared with limbic encephalitis, hallucinations and agitation are more common in Morvan syndrome, although amnesia, confusion, or seizures as neuropsychiatric symptoms are less common. The presence of neuromyotonia, dysautonomia and neuropathic pain also help to diagnose Morvan syndrome[2].

In Morvan syndrome, normal cranial MRI findings were reported in the majority of patients. However, our patient had positive MRI findings with similar features to those of limbic encephalitis. In the study conducted with Irani et al.[2], 92% of the patients had normal cranial MRI values.

Limited EEG data have been reported in Morvan syndrome, and only one case was demonstrated with extensive slow wave abnormalities. In our patient, non-specific encephalopathic changes, which presented general slowing as the main EEG finding, were observed.

Malignancy screening should be performed in patients with Morvan syndrome and it is necessary to identify an antigenic source in these patients, especially regarding thymomas[11]. Malignancy was not detected in our patient. This situation might reflect a 5-year tumor-free window period prior to a paraneoplastic etiology according to the current guidelines[12].

Immunosuppressive therapies, including corticosteroids, azathioprine, methotrexate and more recently rituximab, constitute the main treatment. Other treatments include plasma exchange, IVIG, and thymectomy[2, 13]. As most patients with Morvan syndrome without neoplasms respond better to immunotherapy, including IVIG, plasma exchange, and corticosteroids, the prognosis is worse in cases with neoplasia[10]. Plasmapheresis is one of the most commonly used first line treatment option. IVIG, immunomodulatory therapy is preferred in case of urgent situation. Patients receiving IVIG (0.4 g/kg/day – for 5 days) should be reviewed regularly to ensure that the treatment remains appropriate. Dose should be in such a way that the lowest dose produces appropriate clinical outcome for each patient. The treatment helps to slow or modulate the unwanted response of the body and disease progression[14]. Antiepileptics may be used to alleviate the

symptoms in hyperexcitability developing in peripheral nerves[2, 5].

In our case, IVIG and pulse methylprednisolone treatment provided significant improvement and no relapses were observed in short-term follow-ups.

Conclusion: Similarly to others' opinion we also confirmed that Morvan syndrome can be considered as an autoimmune disease. In our case, Ig G antibodies were detected in the serum directed to LgI-1 and CASPR2.

PATIENT CONSENT

Written informed patient consent was obtained from the patient participating in this study.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

FINANCIAL DISCLOSURE

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

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