CLINICAL NEUROSCIENCE

70. ÉVFOLYAM 1–2. SZÁM • 2017. JANUÁR 30.

IDEGGYÓGYÁSZATI SZEMLE

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OFFICIAL JOURNAL
of the
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www.elitmed.hu

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Ideggyógyászati Szemle/Clinical Neuroscience
havonta megjelenő szakfolyóirat
Impakt faktor: 0,376 (2015)
ISSN 0019-1442

Mailing address • A szerkesztőség postacíme
H-6725 Szeged, Semmelweis u. 6.
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COMBINATION OF SEVERE FACIAL AND CERVICAL VASCULAR MALFORMATION WITH OBSTRUCTIVE SLEEP APNEA SYNDROME: DIAGNOSTIC AND THERAPEUTIC APPROACHES

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0007 | www.elitmed.hu

The combination of obstructive sleep apnea syndrome and vascular malformation within the head and neck region is a rare condition, and interestingly, only a few cases have recently been published. Propagation of the vascular mass to the larynx and pharynx can cause breathing and swallowing difficulties. Due to these sypmtoms, examination and initiation of appropriate therapy for such patients are indeed challenging.

We reviewed the literature available and present our case of a 64 year old woman emphasizing the complaints of sleep apnea syndrome and vascular malformation of the face and neck region. Polygraphic examination detected severe obstructive sleep apnea syndrome. The MR examination of the neck revealed extensive vascular mass narrowing the pharyngo-laryngeal region, thereby causing temporal bone destruction on the right side with intracranial propagation. ENT examination demonstrated significant narrowing of the pharyngeal lumen and the laryngeal aditus caused by multiple hemangiomas. CPAP titration showed the minimalization of the apnea-hypopnea index on the effective pressure level. Regular CPAP usage resulted in diminishing a majority of the patient's complaints.

Our examination clearly demonstrates, obstructive sleep apnea syndrome coupled with significantly obstructing vascular malformation in the head and neck region can be

A FEJ-NYAK RÉGIÓ VASCULARIS MALFORMÁCIÓJA ÉS AZ OBSTRUKTÍV ALVÁSI APNOE BETEGSÉG KOMBINÁCIÓJA: DIAGNOSZTIKAI ÉS TERÁPIÁS MEGKÖZELÍTÉSEK

Faludi B, MD; Imre M, MD; Büki A, MD; Komoly S, MD; Lujber L, MD
Ideggyogy Sz 2017;70(1–2):7–13.

Az obstruktív alvási apnoe betegség kialakulásában funkcionális és alkati okok mellett számos strukturális eltérés is szerepet játszik. Ilyenek például a nyakra és fejre lokalizálódó vascularis malformációk, melyek ritka kórállapotok, csak néhány esettanulmány található a szakirodalomban. A garat és gége irányába történő propagációjuk jelentős légzési nehezítettséget, esetenként alvásfüggő légzészavart eredményezhet. Tekintettel a szűkös ismeretanyagra, ilyen esetekben az alvásfüggő légzészavar kivizsgálása és megfelelő kezelése nagy kihívást jelent.

Az irodalmi adatok áttekintése mellett bemutatjuk egy 64 éves nőbeteg esetét, akinél a kifejezett nappali aluszékonyság mögött obstruktív alvási apnoe betegség igazolódott. Kialakulásában a fej-nyak régió vascularis malformációja játszik kulcsszerepet. Fül-orr-gégészeti és kontrasztos koponya-MR az arcon látható elváltozás mellett a vascularis malformáció kiterjedt pharingealis és laringealis szűkületét okozó propagációját jelezte, jobb temporalisan intracranialis terjedéssel. A CPAP-légsínterápia alkalmazása során az alvásfüggő légzészavar normalizálódását és a beteg panaszainak csökkenését tapasztaltuk.

Vizsgálataink azt bizonyították, hogy a fej-nyak régió vascularis malformációjával kombinálódott obstruktív alvási apnoe betegség biztonságosan kezelhető CPAP-légsínterápiával, amennyiben sebészeti megoldás nem lehetséges.

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Érkezett: 2015. december 19. Elfogadva: 2016. február 1.

effectively treated safely with a CPAP device, if surgical therapy is not possible.
We summarized our findings and the data available in the literature to set up recommendations for the appropriate examination and therapy (including mask fit, etc.) of vascular malformations and hemangiomas causing pharyngolaryngeal obstruction.

Keywords: *obstructive sleep apnoe syndrome, vascular malformation, CPAP, MR, fluid shift theory*

Az irodalmi adatok és saját esetünk kapcsán kivizsgálási és terápiás ajánlást fogalmazunk meg, mely tartalmazza a szükséges diagnosztikai eljárások mellett a hatékony CPAP és maszkhasználat lehetőségeit is.

Kulcsszavak: *obstruktív alvási apnoe betegség, vascularis malformáció, CPAP, MR, folyadékeltolódás-teória*

Obstructive sleep apnea syndrome is a well known disease with severe cardiovascular, cerebrovascular consequences, cognitive impairments and sleep alterations[1–3]. The background of the disease is the repetitive closure of the airway at the pharyngeal level, which is based on the functional consequence of the sleep related change of the muscle tone regulation precipitated by different additive factors such as obesity and different structural abnormalities of the head and neck region.

Soft tissue tumors of the head and neck region can mechanically compromise upper airways due to their mass effect. Vascular malformations and hemangiomas are benign richly vascularised soft tissue tumors, mostly localized within the head and neck region.

Combination of vascular malformation of the head and neck region with obstructive sleep apnea syndrome is a rare but yet a highly disabling condition. Due to the few cases presented in the literature since 1999[4–8], the knowledge regarding the proper examination and therapeutic approach is limited and beneficial guidance is not yet readily available.

To elucidate the known pathophysiological and therapeutic bacground, we performed a systematic review of the literature in reference to the combination sleep apnoe syndrome and vascular malformation.

Additionally, we specifically make reference to our case of a 64 year old woman with vascular malformation of the head and neck region combined with severe obstructive sleep apnea syndrome treated by CPAP.

Based on our examinations and published reports of patients with similar structural causes of sleep apnea syndrome, we plan to elucidate the appropriate examinations and therapeutic plan of patients by answering the following questions:

Is the CPAP/BiPAP device usage safe and tolerable for patients with hemangioma with mass effect in the pharyngeal region?

Can we define a strategy for proper examination and follow up procedures?

Are there any special aspects of the compliance enhancement (for example: mask type selection)?

Review of the former data

To review the literature in the field of sleep apnea syndrome based on vascular malformation, we performed a PubMed search using the key words: sleep apnea, vascular malformation, hemangioma and CPAP.

On the basis of our intensive and thorough PubMed search, we found only seven articles[4–10] in the field of sleep apnea combined with vascular malformation of the head and neck region.

Kimura and coworkers[8] reported three patients with hemangioma in the oral cavity. They concluded the usage of the CPAP/BiPAP device is safe and tolerable and regular follow-up examinations are important. All the patients adapted to the use of CPAP device. Clinically, the decrease of excessive daytime sleepiness, cease of snoring and the lack of apnea related sleep fragmentation was found.

Thong[6] reported a case with hemangioma on the uvula and sleep apnea which was effectively resolved following surgical excision.

Combination of vascular malformation, bilateral tonsillar enlargement and severe obstructive sleep apnea syndrome was presented by *Ramar*[9], highlighting the conclusion of safe and tolerable usage of CPAP therapy.

A case of a young girl was presented by *Walgama*[4]. Differentiation of hemangiomas and vascular malformation was written without any discussions in reference to possible therapeutic approach for the consequent sleep apnoe syndrome. The article, however discusses an important aspect of the position dependent filling of the vascular mass[4].

Irving and coworkers[7] reported several cases of Sturge-Weber syndrome, which is a vascular malformation of different degrees involving the leptomenings, face and eye. The syndrome can affect the airways resulting obstructive sleep apneas.

Morbidity related to the treatment was seen only in one case[10]. The patient developed severe headaches and hydrocephalus following BiPAP therapy. The authors concluded, the pressure support caused the swelling of the subcutaneous cervical and temporal hemangioma with the consequence of severe headaches.

The reviews and the case presentations contained only limited recommendations for the necessary examinations, about the appropriate CPAP/BiPAP device and mask usage for patients with hemangiomas or vascular malformations.

The MR examination of the affected region is substantial for the evaluation of the exact extent of the lesions. Based on the work of *Walgama*[4], the MR protocol should contain T1-weighed, fat saturated, T2-weighed or STIR and gadolinium enhanced T1-weighed sequences. The MR angiography is useful to determine the feeding arteries in case surgical treatment is planned.

Examination of sleep related complains (sleep related breathing disorders, sleep fragmentation, daytime sleepiness) is important if the vascular malformation or hemangioma affects the head and neck region. If the sleep study confirms obstructive sleep apnea syndrome, CPAP/BiPAP treatment can be applied following the extent of vascular mass and it's influence on the anatomy and the function of the laryngo-pharyngeal areas are carefully studied.

Case presentation

We examined a 64 year old woman with vascular malformation of the head and neck region and excessive daytime sleepiness. The vascular lesions were present from birth and characterized continuous growth. Multiple surgical interventions in the past resulted in slowing down and preventing the progression of the vascular masses.

The primary complaints of the patient were excessive daytime sleepiness with unexpected sleep attacks during the day, loud snoring, witnessed apneas and frequent awakenings during the night. Physical examination of the patient showed vascular mass on the right side of the face, the lips, tongue and soft palate (**Figure 1**). Based on the patient's history and physical examination, the vascular mass showed significant change in size influenced by posture (standing, laying position, bending forward) and strikingly, emotional conditions.

Physical neurological examination was within normal limits. BMI was 34.6 kg/m^2.

Based on the growth pattern of the vascular mass (visible at birth, continuous growing, absence of involution of the lesion) it should be classified as vascular malformation instead of hemangioma according to the classification system of *Mulliken* and *Glowacki*[11, 12].

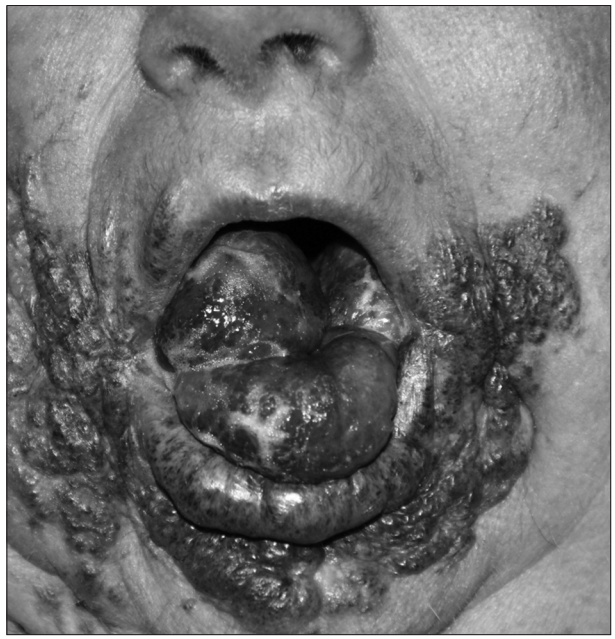

Figure 1. *Involvement of the tongue by vascular malformation on the same patient*

Due to visible structural abnormalities on the face, in the oral cavity, larynx and pharynx, MRI of the head and neck was done to elucidate the involvement of the upper airways and other areas otherwise considerably difficult to visualize. Instead of the commonly used MR angiography, which is the standard method to determine the blood supply of a vascular mass)[13], gadolinium contrast enhanced MRI was used to visualize the vascular structure and the detailed extension of the lesion.

The head and neck MR exhibited widespread involvement of the oral cavity, larynx and pharynx. Space occupying vascular malformation on the bucca, soft palate, tongue and in the masticator area, naso-meso-hypopharynx and supraglottis caused a significant narrowing of the airways. Besides the involvement of bilateral parotid gland, the temporal bone, zygomatic arch and pyramidal bone were also invaded, leading to intracranial propagation of the hemangioma into the epidural space (**Figures 2, 3**). The signal alteration of the affected regions was intermediate in T1 and T2 weighed sequences with intensive contrast enhancement in most parts of the lesion and hyperintense in diffusion TRACE sequence without any signs of parenchymal involvement of the brain.

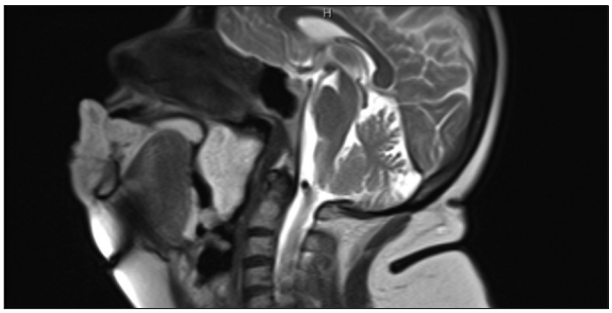

Figure 2. *Sagittal, T2-weighed MR image of the patient shows the vascular mass on the labial region and on the soft palate causing the narrowing of the airways*

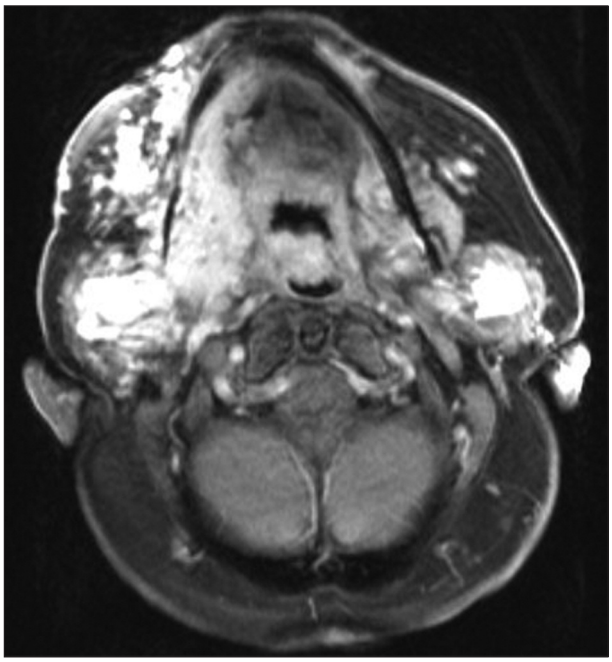

Figure 3. *Horizontal, T1-weighed, contrast enhanced MR of the patient showing the vascular laesion on both sides (buccal, parotid region, sublingual region) and the decreased antero-posterior pharyngeal diameter with a degree of dislocation*

Head CT scan (native and bone window) also revealed bony destruction of the right temporal bone **(Figure 4)** likely as the result of the direct pressure effect of the hemangioma mass.

The epidural propagation of the hemangioma can cause the chronic irritation of the temporal cortical area with the possible consequence of epileptic discharge. EEG examination with standard 21 leads showed normal brain electrical activity without the signs of epileptic discharge.

Neurosurgical examination of the patient revealed no immediate requirement for surgical intervention.

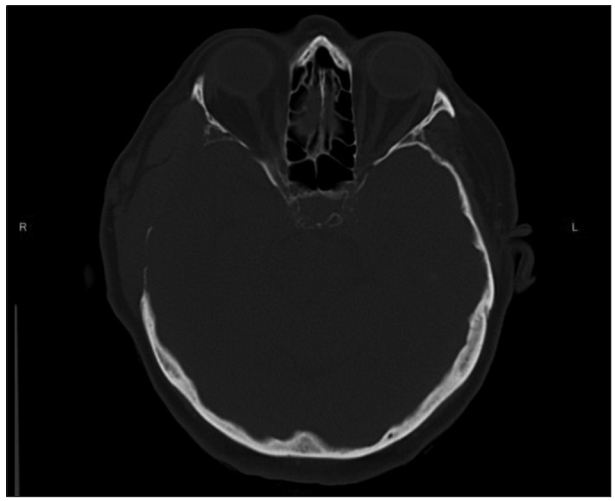

Figure 4. *Bone window CT scan proved the lack of temporal bone on the right side*

Obstructive apneas and the major structural anatomical changes in the head and neck region called for an ENT examination. Flexible nasal endoscopy verified the findings seen on the MRI, found the airways compromised to a degree and revealed posture dependent size change of the lesions. Endoscopic examination was repeated in various body positions (sitting up, laying on the back and side) in different time intervals (0-40 minutes). Lying flat on the back position caused significant narrowing of the pharyngeal diameter and the laryngeal entrance, which was even more prominent after 40 minutes. This may be the result of position dependent filling of the vessels and the effect of gravity on the vascular mass. Turning to right side, rotation of the laryngeal region was seen with some breathing improvement. Breathing difficulty caused by vascular malformation related ventil mechanism was not detected.

Due to the number of former unsuccessful surgeries, the high risk for bleeding and the extent of the lesion, surgery was not an option in this case, neither was the endovascular occlusion because of the high purported complication rate of the latter.

To determine the sleep related breathing abnormality, we performed a polygraphic examination, which substantiated our hypotheses, and proved in the diagnosis of a severe obstructive sleep apnea syndrome **(Figure 5)**. The apnea-hypopnea index was 73.4/h, the lowest oxygen level was 27% and the average oxygen level was 90%. The degree of daytime sleepiness was determined with Epworth Sleepiness Scale, which showed 18 points over 24.

Polysomnography controlled CPAP titration was accomplished. Recorded electrode montage covered the EEG channels (C3, C4, F3, F4, O1, O2 posi-

tion according to the international 10-20 system), eye movement; chin muscle EMG, nasal air flow, thoracic and abdominal breathing effort, ECG, pulse rate, oxygen saturation, limb EMG activity body position sensor and microphone for recording of snoring.

The effective pressure level to eliminate the obstructive breathing elements was 11 water centimeters. The apnea-hypopnea index reduced to 3.2/h and the average oxygen saturation level was 95% with the reorganization of the sleep architecture at this pressure level.

Consequently, due to the routine employment of the CPAP device, the patient reported the reduction of the daytime sleepiness and the ESS score declined to 4 points. Improvement of the cognitive functions and reduction of the night time complaints (snoring, sleep fragmentation) were also noticed.

Discussion

Several medical conditions may lead to structural anatomical changes including the consequences of sleep related repetitive upper airway obstruction. The most important characteristics are the tonsillar hypertrophy, tumors with mass effect, lymphoma of the upper airways, macroglossy, retrognathia and various craniofacial abnormalities. The hemangiomas and vascular malformations are rare structural causes of sleep apnea syndrome and therefore, our knowledge is limited regarding the proper therapy.

Surgical intervention is indicated in case of ulceration, bleeding, hearing and visual complication and in disfiguring facial deformities.

We presented a case of a 64 year old woman with excessive daytime sleepiness, snoring and space occupying vascular malformation within the head and neck region. Following a physical examination, head and neck MRI, otolaryngological, neurosurgical, polygraphic sleep examinations and polysomnography based CPAP titration, the patient implemented the use of the CPAP device. The results clearly demonstrate the CPAP therapy is safe and tolerable for our patient suffering from severe vascular malformation affecting the upper airways.

Vascular malformation versus hemangioma: terminological considerations

A majority of the case presentations and reviews within the literature we studied feature the terminology of "hemangioma" for the description of the patient's vascular lesions and the subjects were mostly adults at the time of the sleep study. In almost all cases, the vascular mass showed continuous growth despite any therapeutic approache (radiotherapy, surgery, etc.) without the sign of regression over the time. According to the classification of Mulliken and Glowacki[11, 12] **(Table 1)** a vascular birthmark with a continuous growing tendency and lack of involution, regression till the end of childhood is called "vascular malformation". On the contrary, "hemangiomas" are not present at birth, and they show rapid postnatal growth and slow involution during childhood[11].

The use of Doppler ultrasound is helpful to characterize the subtypes of vascular malformations on the base of blood flow patterns. Arterial and arteriovenous malformations are so called "high flow" lesions, while venous or lymphatic subtypes are "low flow" variations[4].

Despite the differences in characteristics of benign vascular tumors, they can cause similar complications such as ulceration, bleeding, infection, ocular propagation in addition to breathing and swallowing abnormalities due to the involvement of upper airways and pharyngeal regions.

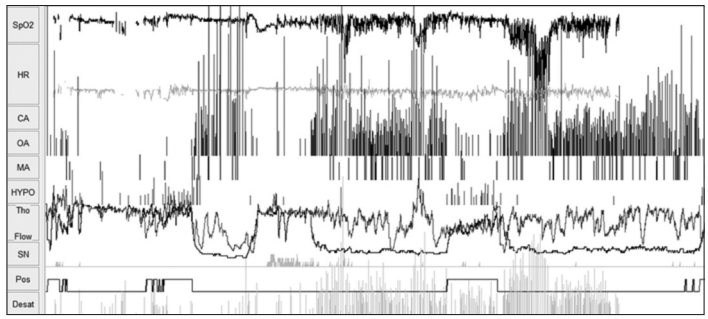

Figure 5. *Polygraphic sleep examination of the patient. The findings confirm severe obstructive sleep apnea syndrome, with phasic worsening pattern*

SpO_2: oxygen saturation, HR: heart rate, CA: central apnoe, OA: obstructive apnoe, HYP: hypopnoe, SN: snore, Pos: position, Desat: desaturation

Table 1. *Differentiation of vascular malformations and hemangiomas [after Willenberg T, Baumgartner I. Vascular birthmarks. Vasa 2008;37(1): 5-17]*

	Vascular malformations	Hemangiomas
Present at birth	Yes	No
Rapid proliferation	No	Yes
Involution	No	Yes
Present in adulthood	Yes	Residual

Compliance and reliability of the CPAP usage

The initiation and daily usage of the appropriate conservative therapy (CPAP/BiPAP) raises many questions, among others, the proper mask fit and the long term effectiveness of the treatment.

The mask fit is one of the most important questions in assuring patient compliance. The vascular malformation or hemangioma can affect the face causing various deformities. Often, effective, proper mask fit is not possible to achieve, if the vascular mass lesion involves the lips, the perioral or perinasal regions due to the risk of ulcerate and bleeding. Based on our clinical experience, this can be avoided with the use of minimal contact CPAP/BiPAP masks. Therefore, we recommend the nostril or nose-tip based masks. The strap of the mask also can ulcerate the vascular mass, therefore some modification of the holding system is suggested in selected cases. If the total closure of the mouth is hindered by the labial vascular mass, the full-face mask can be useful.

Contrary to the hemangiomas, which involute spontaneously by time in most cases, vascular malformations tend to grow slowly but continuously[11]. Propagation of the vascular mass into the oral cavity and pharyngeal region can reduce the effectiveness of the CPAP therapy a great deal. Patient compliance, insufficiency, sign of sleep fragmentation and daytime sleepiness often indicate the need for increased CPAP/BiPAP pressure. To avoid compliance failure, regular follow-up examinations (both sleep and otorhynolaringological) are encouraged.

Propagation of the vascular mass to the pharyngo-laryngeal regions, may serve as a structural background for intermittent closure of the airways through a ventil mechanism, particularly if the lesion involves areas in close proximity to the vocal chords. CPAP/BiPAP therapy may diminish these symptoms with the increased inward flow of air. This possible ventil mechanism emphasizes the importance of a detailed otolaryngological examination using fiberscopes to visualize the affected regions. The exclusion of ventil mechanism by vascular mass at the site of the larynx will improve the safe effectiveness of CPAP/BiPAP therapy.

Effect of fluid shift on vascular malformation

Our patient reported a significant posture dependent size change of the vascular mass that took place in a brief moment (few minutes). Laying down flat on the back immediately increased the patient's shortness of breath which grew worse after 40 minutes. Over the years, the patient admitted experiencing certain body and head positions that helped to avoid the feeling of obstruction. Posture dependent size change of the vascular malformations are subtype dependent, which is, for example, not characteristic for the lymphatic subtype[14], and can affect the pharyngeal diameter.

The "fluid shift theory" is widely recognized and a frequent studied model of position dependent fluid distribution of the body[15]. The prevalence of obstructive sleep apnea syndrome is higher in patients with cardiac failure in which the fluid-retention is more prominent[15].

According to this theory, the plasma volume decreases by 300-400 ml in standing position and accumulates in the interstitial space of the legs and venous pools. In a prone or flat position, redistribution of the fluid can be seen: reabsorption of a fluid from the interstitial space to the vessels. The time span of this process is in the 30-60 minutes range.

The fluid shift is more prominent in patients featuring cardiac failure related fluid accumulation in the legs. The position dependent filling up and the consecutive enlargement of the vascular mass alone can be a significant factor reducing the pharyngeal diameter. In addition, the fluid shift dependent expansion of such vascular masses further decreases the airflow with the consequential worsening of the sleep dependent respiratory failure.

The fiberoscopic examination of our patient proved the position (immediate narrowing) and time (further narrowing in laying position) dependent change of the pharyngeal geometry. The first is the effect of direct immediate filling up of the vessels and positional change of the vascular mass due to gravity, while the second is the result of the fluid shift.

Clearly, CPAP/BiPAP therapy successfully achieves in reducing the effect of redistribution of the fluid into the neck by elevating the intramural pressure in the pharyngeal space.

Recommendation for examination of patient with facial vascular laesion

On the basis of our experience gained while managing our case and reviewing former data from the literature, we propose the following examination protocols in support of sleep apnea syndrome combined with vascular malformation or hemangioma:

To determine the severity of sleep related brea-

thing abnormalities, a polygraphic or polysomnographic examination is necessary.

To elucidate the relationship of vascular mass and pharyngeal obstruction, routine otorhynolaringological examination and fiberoscopic examination must be accomplished in both a sitting and laying position to determine the growing / filling tendency. MR examination (with gadolinium contrast enhancement) of the head and neck can help to determine exact extent of the vascular mass. MR-based angiography or conventional angiography is useful to visualize the main vascular connections of the vascular mass (the feeding arteries and main veins) if surgical interventions are indeed necessary. In case of intracranial propagation, a neurosurgical examination is encouraged. Electroencephalography is recommended in case of epileptic seizure.

Due to the potential risk of pharyngeal vascular mass to obstruct the airways, the polysomnography based CPAP/BiPAP titration must be completed only after the above examinations are implemented.

Regular follow-ups are highly recommended.

Conclusions

Vascular malformation is rare but yet an important structural background for obstructive sleep apnoe syndrome due to the possible upper airway involvement which can cause life threatening events. In addition to the direct structural effect of the vascular malformation, the the position dependent fluid shift and the filling of the vascular mass may constrict breathing during the sleep period. Due to the high risk of bleeding and other side effects during surgical intervention, other therapeutic approaches (like CPAP) must be applied in case of compromised breathing. Our case and data from former examinations suggests, after appropriate polygraphic or polysomnographic and otolaryngological examinations concluded together with an MRI imaging of the head and neck, the use of CPAP/BiPAP equipment is effective, safe and tolerable for the patients. Due to the possible spontaneous growth characteristic of such vascular masses, regular follow-up examinations are recommended by an effective multidisciplinary team.

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MÁGNESESREZONANCIA-KÉPALKOTÁS ALEMTUZUMAB- ÉS TERIFLUNOMIDKEZELÉS SORÁN

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Hungarian | http://dx.doi.org/10.18071/isz.70.0015 | www.elitmed.hu

Összefoglaló közleményünk célja a sclerosis multiplex kezelésére alkalmazott alemtuzumab- és teriflunomidterápiák során nyert mágneses rezonancia (MR) -képalkotás publikált eredményeinek ismertetése. Sclerosis multiplexben az MR-képalkotás érzékenyen detektálja azokat a szubklinikai patofiziológiai és morfológiai folyamatokat, melyek a betegség korai szakában klinikai tünetet még nem okoznak, azonban a betegség hosszú távú prognózisa szempontjából meghatározó fontosságúak. Az MR-képalkotás emiatt a terápiás hatékonyság korai nyomonkövetésében egyre fontosabb helyet kap. Alemtuzumabbal és teriflunomiddal sclerosis multiplex indikációban az elmúlt 15 évben több klinikai gyógyszertanulmány zajlott, melyek a fenti szerek klinikai hatékonyságát bizonyították. Ezekben a tanulmányokban MR-méréseket is végeztek, az eredményeket az elmúlt években a szakirodalomban publikálták. Az elvégzett MR-vizsgálatok a betegség aktivitására és a neurodegeneratív folyamatok gátlására utalnak, mely eredményektől a betegség hosszú távú prognózisa szempontjából kedvező hatás várható.

Kulcsszavak: *MRI, sclerosis multiplex, alemtuzumab, teriflunomid*

MAGNETIC RESONANCE IMAGING IN THE COURSE OF ALEMTUZUMAB AND TERIFLUNOMIDE THERAPY
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Ideggyogy Sz 2017;70(1–2):15–24.

Our work aimed to review the published results of magnetic resonance imaging (MRI) obtained in the course of alemtuzumab and teriflunomide therapy in multiplex sclerosis. In multiplex sclerosis MRI sensitively detects subclinical pathological processes, which do not manifest clinically in the early course of the disease, however have substantial significance from the viewpoint of the long-term disease prognosis. MRI has an increasingly important role in the early monitoring of the therapeutic efficacy. In the last 15 years several clinical trials have been conducted with alemtuzumab and teriflunomide in multiple sclerosis providing evidence about the favourable clinical effect of these drugs. MRI images were acquired in these trials as well, and the results published recently in the scientific literature. These MRI results denote the suppression of the disease activity and the neurodegenerative processes, which may imply a favourable effect on the long-term prognosis of the disease.

Keywords: *MRI, multiple sclerosis, alemtuzumab, teriflunomide*

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Érkezett: 2016. július 6. Elfogadva: 2016. december 9.

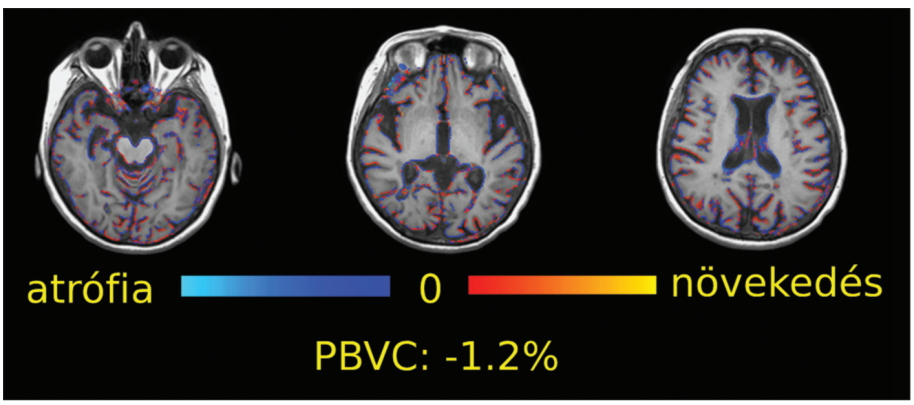
Bevezetés

A sclerosis multiplex (SM) a fiatal nők körében gyakori, a központi idegrendszert érintő krónikus, immunmediált betegség. A kórkép patológiai jellegzetességei a gyulladás, a demyelinisatio, és az axon/neuronpusztulással járó neurodegeneráció. Klinikailag a betegség visszatérő relapszusok és progresszió kombinációjával jelentkezik, és leggyakrabban fiatal, munkaképes betegeknél okoz különböző súlyosságú korlátozottságot mozgásukban, kognitív funkciójukban és életminőségükben.

SM-ben a kezelés fő célja a tartós rokkantság kialakulásának megelőzése. A klinikailag észlelhető tünetek mögött SM-ben a központi idegrendszerben többféle szubklinikai patofiziológiai folyamat zajlik, melyek a betegség hosszú távú prognózisa szempontjából meghatározóak. Úgy tűnik, hogy a gyulladásos folyamatok korai gátlása révén gátolható a hosszú távú rokkantságért felelős komplex patofiziológiai kaszkádfolyamatok beindulása. Számos bizonyíték támasztja alá azt a nézetet, hogy az SM korai szakában indított terápia hatékonyabb és kritikus a hosszú távú neurológiai funkciók megtartásában és a rokkantság kialakulásának megelőzésében[1]. A rokkantság súlyosságát klinikailag pontozóskálák segítségével objektivizáljuk (például Expanded Disability Status Scale, EDSS), melyek azonban a szubklinikai folyamatokról, és ezáltal a betegség hosszú távú kimeneteléről kevés korai információt szolgáltatnak. A mágnesesrezonancia-képalkotás (MRI) érzékenyen detektálja a központi idegrendszerben zajló klinikailag releváns és szubklinikai fokális gyulladás helyét és időbeli változását, valamint a T1-hipointenzív fekete lyukak detektálásával utal a krónikusan zajló neurodegeneratív folyamatokat is. Az MRI ezáltal a klinikai értékelésnél érzékenyebb módszer a betegség prognózisának megítélésében, továbbá a kezelésben használt farmakonok hatékonyságának (és biztonságosságának) nyomonkövetésében[2]. A terápiára nem reagáló betegek korai azonosítása fontos, mert hatékonyabb szerre váltással javítható a hosszú távú prognózis.

A konvencionális MR-mérésekkel meghatározható a T2-hiperintenzív laesiók száma/térfogata, mely utal a betegség aktivitására, és hasznos a betegségakkumuláció hosszú távú megítélésében. A T2-hiperintenzív laesiók össztérfogata/lokalizációja azonban a klinikai tünetekkel gyenge korrelációt mutat, ezt hívjuk klinikoradiológiai paradoxonnak[3]. A betegség progressziójának egy jobb jelzője az utóbbi időben bevezetett agyi szürkeállományi atrófia mérése. Több vizsgálat megmutatta, hogy keresztmetszeti és utánkövetéses vizsgálatokban is jól korrelál az agyi atrófia foka a fizikai rokkantsággal, kognitív funkcióval, és az MR-laesiók mennyiségével[4, 5]. A szürkeállományi arófia már a betegség legkoraibb szakában kimutatható, és előrehaladása gyorsabban, mint egészséges egyénekben. SM-es betegekben az átlagos évi atrófia mértéke 0,5%–1,3%-os, ezzel szemben egészséges egyénekben ez az arány 0,1%–0,4%[6]. A progresszív agyi atrófia hiánya az utóbbi években bekerült a betegségaktivitástól mentesség koncepciójába is (No Evidence of Disease Activity – 4, NEDA-4)[7].

Az agyi atrófia többféleképpen mérhető. A jelenleg használt módszerek egy része az agyat szöveti MR-intenzitások szerint szegmentálja (például SIENAX[8]). Az agy voxeleiből intenzitások szerint készít hisztogramot. Ezen belül meg lehet határozni a szürkeállomány, fehérállomány és a liquornak megfelelő intenzitásgörbéket és végül meghatározható, hogy melyik szöveti típushoz milyen valószínűséggel tartozik az adott voxel. Ezt a módszert elsősorban keresztmetszeti vizsgálatokban alkalmazzák. Az alkalmazások másik része utánkövetéses vizsgálatokban használatos és az egymást követő felvételek egymáshoz regisztrálásán alapszik (például SIENA[8]). Ez a módszer a két egymást követő felvételt egymáshoz idomítja (regisztrálja) és az agy szélmozgásaiból számít térfogatváltozást. Ez a módszer nem alkalmas a szürke vagy a fehérállomány térfogatváltozásának megítélésére, összagyi térfogatváltozást mér **(1. ábra)**.



1. ábra. *A SIENA módszerrel azonosított agyi atrófia egy sclerosis multiplexben szenvedő beteg esetén. A módszer a két időpontban készített MR-felvételek egymáshoz illesztéséből számol agyi atrófiát. Az ábrán a kék és a piros színek az atrófiát és az agytérfogat lokális növekedését jelzik, melyből a program globális agyi parenchimafrakció változását számítja ki*

Az agyi atrófia mérése a rutin klinikai gyakorlatban individuális beteg követésére még nem megbízható módszer, mert az agytérfogatot számos tényező (életmóddal összefüggő faktorok, genetika, kísérő betegségek) befolyásolja. A képelemzéshez használt algoritmusok csak korlátozottan összehasonlíthatók, emiatt a mérésekben jelentős eltérések fordulhatnak elő. Klinikai tanulmányokban azonban az agyi atrófia mérése fontos paraméternek bizonyult az SM kezelésére használt szerek terápiás hatásának monitorizására[9].

Összefoglaló tanulmányunkban ismertetjük azokat a publikált MR-vizsgálati eredményeket, melyeket klinikai gyógyszertanulmányokban relapszáló-remittáló sclerosis multiplexes (RRSM-) betegek kezelésére alkamazott alemtuzumab- és teriflunomidszerek használata során mértek.

ALEMTUZUMABTERÁPIA

Az alemtuzumab az RRSM kezelésére használt humanizált anti-CD52 monoklonális antitest, mely a keringő T- és B-lymphocyták deplécióját okozza. Az ezt követő repopuláció során egyes lymphocyta-alcsoportok száma, aránya, és funkciója megváltozik. Az alemtuzumab Európában mind terápianaiv, mind betegségmódosító terápia mellett áttörő betegséget mutató, aktív RRSM-es betegek kezelésére alkalmazható szer[10].

Módszerek

Az alemtuzumab hatásait vizsgáló adatok egy fázis 2, és két fázis 3 vizsgálatból, valamint ezek kiterjesztett utánkövetéses tanulmányaiból állnak rendelkezésünkre.

Eredmények

CAMMS223 vizsgálat

A fázis 2 randomizált, kontrollált vizsgálat (*CAMMS223* vizsgálat) eredményeit 2008-ban közölték[11]. A CAMMS223-ban az alemtuzumabkezelést heti háromszor 44 μg subcutan (sc.) interferon-β (IFN-β) -1a-terápia alkalmazásával hasonlították össze. A vizsgálatba 334 korai stádiumú, aktív RRSM-es beteget vontak be, akik teljesítették a 2001-es McDonald-kritériumokat, a megelőző két évben több mint két relapszusuk volt, a megelőző négy hónapban havonta végzett MR-vizsgálatok során legalább egy gadolínium (Gd) -halmozó laesiójuk volt, a kiindulási EDSS-pontszámuk három vagy annál kevesebb volt, SM-es tüneteik három éven belül kezdődtek, és korábban az SM-re szteroidon kívül immunterápiát nem kaptak. A rokkantságot értékelő vizsgáló „vak" volt az alkalmazott kezelési módra. Az alemtuzumabot intravénás (iv.) infúzióban alkalmazták a kiindulásnál öt, egymást követő napon át, és 12 hónappal később három, egymást követő napon keresztül. A 24. hónapnál a kezelőorvos döntése alapján 3. kezelésre is lehetőség volt, amennyiben a CD4+ T-sejt-szám $\geq 100 \times 10^6$ sejt/l volt.

A vizsgálat másodlagos végpontjaként MR-méréseket is végeztek. Mérték a T2-súlyozott MR-képeken a laesiók összmennyiségét, valamint kiszámították a T1-súlyozott MR-képek felhasználásával az agytérfogatot. A kiinduláshoz viszonyított 12. hónapnál mért laesio-össztérfogat szignifikánsan alacsonyabb volt az alemtuzumabkezelt csoportban ($p<0,01$), ugyanez volt tapasztalható a 24. hónapnál is ($p<0,005$). A 36. hónapnál mért laesio-össztérfogat mind a két betegcsoportban a kiindulási térfogatnál kisebb volt, és markánsabb csökkenés volt az alemtuzumabbal kezelt csoportban, azonban a különbség nem volt statisztikailag szignifikáns nagyságú. Megjegyzendő, hogy a 36. hónapos mérésnél a betegszám alacsonyabb volt a terápiát abbahagyott betegek számával, mint a megelőző években, valamint további 26 betegnél nem készült vagy nem volt értékelhető az MR-felvétel. A 36. hónapnál számított agyi térfogatmérés mindkét betegcsoportban fogyatkozást jelzett, azonban a csökkenés szignifikánsan lassabb ütemű volt az alemtuzumabbal kezelt betegcsoportban (–0,5% volt a térfogatkülönbségek mediánja az alemtuzumabbal kezelt betegcsoportban, és –1,8% a sc. IFN-β-1a-val kezelt csoportban; $p<0,05$). Az agyiatrófia-méréseknél számításba kell venni a pszeudoatrófia jelenségét, azaz a kezelés kezdetén a gyulladáscsökkentő hatás következtében a gyulladásos ödéma csökken, melynek következtében a teljes agy térfogata is csökken. A pszeudoatrófia zavaró hatását kiküszöbölendő, meghatározták az agyi térfogatkülönbségeket a 12. és 36. hónap között is. Ekkor a sc. IFN-β-1a-val kezelt betegekben –0,2% volt a csökkenés mediánja, míg az alemtuzumabbal kezelt betegekben 0,9%-os agyi térfogat-növekedés volt kimutatható ($p<0,02$)[11].

CARE-MS I és CARE-MS II tanulmányok

Az alemtuzumabbal végzett két fázis 3 vizsgálat, a *CARE-MS* (Comparison of Alemtuzumab and Rebif® Efficacy in Multipe Sclerosis I. és II.) eredményeit 2012-ben publikálták[12, 13]. Mindkét CARE-MS vizsgálat kétéves, randomizált, aktív szerrel kontrollált, fej-fej melletti vizsgálat volt. Bár mindkét vizsgálatba olyan RRSM-es beteget vontak be, akik teljesítették a 2005-ös McDonald-kritériumokat, és betegségük aktív volt (azaz a megelőző két évben ≥2 relapszus és a megelőző évben ≥1 relapszus), a két vizsgálat eltért a célpopuláció kezelési előzményeiben. A CARE-MS I-ben a beválaszott betegek korábban soha nem részesültek betegségmódosító terápiában, a kiindulási EDSS-pontszámuk ≤3,0 volt, és SM-es tüneteik öt éven belül kezdődtek. Ezzel szemben a CARE-MS II-ben a betegek ≥6 hónapja alkalmazott IFNB- vagy glatiramer acetát-kezelés mellett relapszáltak (megelőzően egyéb kezelés alkalmazása, közte a natalizumab szintén engedélyezett volt). Emellett kritérium

volt, hogy a kiindulási EDSS-pontszámuk ≤5,0, és az SM-es tünetek 10 éven belüli indultak. Az alemtuzumbot mindkét vizsgálatban 12 mg/nap dózisban iv. infúzióban alkalmazták öt napon át a kiindulásnál, majd három napon át 12 hónap múlva. A kontrollbetegcsoport mindkét vizsgálatban sc. IFN-β-1a-kezelésben részesült. A rokkantságot és az MRI-t értékelő vizsgálók vakok voltak az alkalmazott kezelési szerre. Évente végeztek standardizált koponya-MR-vizsgálatot, melyek során elemezték a laesiókat, és mérték a normalizált agyi térfogatot. A CARE-MS I vizsgálatba 563 beteget vontak be, akik közül 526-an fejezték be a kétéves vizsgálatot, a CARE-MS II vizsgálatba 840 beteget vontak be, akik közül 715-en maradtak bent végig a két év alatt.

Mindkét fázis 3 vizsgálatban a 24. hónapnál mért T2-hiperintenzív laesiók össztérfogata mind az alemtuzumabbal, mind a sc. IFN-β-1a-val kezelt betegcsoportban a kiindulásinál alacsonyabb volt, de a két betegcsoport között nem volt szignifikáns különbség. Az új és megnagyobbodó T2-hiperintenzív laesiókkal jellemezhető betegek aránya azonban szignifikánsan alacsonyabbnak mutatkozott mindkét CARE-MS vizsgálat alemtuzumabbal kezelt betegcsoportjaiban összehasonlítva a sc. IFN-β-1a-val kezelt betegcsoportokkal (a CARE-MS I-ben $p<0,04$, a CARE-MS II-ben $p<0,0001$). Gd-halmozó laesio megjelenése is szignifikánsan kevesebbszer fordult elő az alemtuzumabbal kezelt betegcsoportokban ($p<0,0001$ mindkét CARE-MS vizsgálatban). Az agytérfogatmérések során mindkét fázis 3-as vizsgálatban azt találták, hogy az alemtuzumabbal kezelt betegcsoportban a sc. IFN-β-1a-val kezelt csoporthoz képest a csökkenés üteme szignifikánsan lassabb volt, a CARE-MS I-ben az agytérfogat fogyása 42%-kal, a CARE MS II-ben 24%-kal volt kevesebb az alemtuzumabbal kezelt betegcsoportban a sc. IFN-β-1a-val kezelt csoporthoz képest (CARE-MS I-ben $p<0,0001$, CARE-MS II-ben $p<0,01$).

CARE-MS I és CARE-MS II tanulmányok kiterjesztett utánkövetéses vizsgálata

A CARE-MS I és CARE-MS II vizsgálatokban részt vett betegeket további kiterjesztett utánkövetéses tanulmányba vonták be, mely vizsgálatok jelenleg is folynak. Mindkét folyó utánkövetéses vizsgálatban végeztek előzetes adatelemzéseket is, melyek eredményeit elsőként 2016 áprilisában, az American Academy of Neurology 68. Éves Konferenciáján ismertették.

A CARE-MS I és CARE-MS II-ben sc. IFN-β-1a-val kezelt betegek a kiterjesztett utánkövetési vizsgálatokban elhagyták a sc. IFN-β-1a-kezelést, és két ciklus alemtuzumabkezelésre váltottak (12 mg alemtuzumab iv. öt, egymást követő napon át a kiterjesztett vizsgálat kezdetén, és 12 hónappal később három, egymást követő napon keresztül). A két kezelési ciklust követően ≥1 évvel a legutolsó kezelés után a betegek kaphatnak újabb ciklus alemtuzumabkezelést (12 mg/nap három, egymást követő napon keresztül), ha ≥1 protokoll szerinti relapszusuk fordul elő, vagy ≥2 új/megnagyobbodó T2-hiperintenzív és/vagy Gd-halmozó agyi vagy gerincvelői laesiójuk jelenik meg. Az agytérfogatot az agyi parenchymafrakció mérésével határozták meg, melyet a protondenzitású/T2-súlyozott képekről származtattak agyi szegmentációs képelemző szoftver használatának segítségével.

A kiterjesztett utánkövetési vizsgálatokban előzetes elemzéseket végeztek azoknak a betegeknek az adataiból, akik legalább egy ciklus alemtuzumabkezelést megkaptak (CARE-MS I-ben 139 beteg, CARE-MS II-ben 143 beteg). A CARE-MS I tanulmányban két éven át sc. IFN-β-1a-kezelésben részesülő, majd a tanulmány kiterjesztett követéses fázisában alemtuzumabra váltó betegek között az eredeti tanulmány 2. kezelési évéhez viszonyítva az utánkövetés 2. évében szignifikánsan magasabb volt azoknak a betegeknek az aránya, akiknél nem jelent meg új/megnagyobbodó T2-hiperintenzív góc, új Gd-halmozó vagy, új nem halmozó T1-hipointenzív laesio ($p<0,05$), és akiknél nem látszott aktivitásra utaló eltérés MR-vizsgálattal ($p<0,001$). A 3. követési évben szignifikáns különbségek ezeket a paramétereket illetően már nem voltak kimutathatóak, de a terápiaváltás után a betegek többsége új laesiók megjelenésétől mentes maradt[14].

Azoknál a betegeknél, akik a CARE-MS I és CARE-MS II tanulmányokban két éven át sc. IFN-β-1a-kezelést kaptak, majd a tanulmány kiterjesztett követéses fázisában alemtuzumabra váltottak, az agytérfogat-csökkenés jelentős lassulását észlelték az elkövetkező három évben. A sc. IFN-β-1a-val kezelt betegek medián éves agyi térfogatcsökkenése a CARE-MS I vizsgálatban a 2. évben –0.50%-os, a CARE-MS II vizsgálatlatban –0,33%-os volt, mely az alemtuzumabra váltás után a CARE-MS I-ben az első évben –0,07%-ra, a 2. évben –0,13%-ra, a 3. évben –0,09%-ra csökkent, míg a CARE-MS II-ben az első évben a agyi parenchymafrakció 0,02%-kal emelkedett, majd a 2. évben –0,05%-kal, a 3. évben –0,14%-kal csökkent. Mind a CARE-MS I, mind a CARE-MS II kiterjesztett vizsgálatában az 5. év végén az agyi atrófia ütemének lassulása kifejezettebb volt az eredeti vizsgálatban is alemtuzumabkezelést kapott betegcsoportban összehasonlítva azokkal, akik a sc.

1. táblázat. *MR-paraméterek változása az alemtuzumabkezelés hatását vizsgáló tanulmányokban*

	T2-laesio-volumen-változás (12 hó)	T2-laesio-volumen-változás (24 hó)	T2-laesio-volumen-változás (36 hó)	Éves agytérfogat-változás (%)
CAMMS I	IFN-β-1a: –12,1%* ALEM 12 mg: –17,7%† ALEM 24 mg: –19,2%†	IFN-β-1a: –9,8%* ALEM 12 mg: –21,2%† ALEM 24 mg: –20,3%†	IFN-β-1a: –13,3%* ALEM 12 mg: –18,2%† ALEM 24 mg: –16,4%†	IFN-β-1a: ~–0,6%** ALEM 12 mg: ~–0,3%N.S ALEM 24 mg: ~–0%†
CARE-MS I		IFN-β-1a: –6.5% ALEM 12 mg: –9,3%N.S.		IFN-β-1a: ~–0,74%*** ALEM 12 mg: ~–0,433%†
CARE-MS II		IFN-β-1a: –1,23% ALEM 12 mg: –1,27%N.S.		IFN-β-1a: ~–0,405%*** ALEM 12 mg: ~–0,308%†

*Medián.
**Közelítő számított érték a közlemény 0–36 hónap között mért értékeiből.
***Közelítő számított érték a közlemény 0–24 hónap között mért értékeiből.
†Szignifikáns különbség a kontrollcsoporthoz képest.
N.S.: Nem szignifikáns.

IFN-β-1a-kezelésről a kiterjeszett utánkövetési szakban váltottak alemtuzumabkezelésre (alemtuzumabbal kezelt csoportban a CARE-MS I-ben a csökkenés az 5. évben –1,352%, a CARE-MS II-ben –0,855%, a sc. IFN-β-1a-ról alemtuzumabra váltó csoportban a csökkenés a CARE-MS I-ben –1,646%, a CARE-MS II-ben –1,044%)[15].

A CARE-MS II-be bevont betegek kiterjesztett utánkövetése során megállapítható volt, hogy az eredeti vizsgálatban talált MR-végpontok a követés során is fennállnak. Az MR-aktivitással nem jellemezhető, és új laesiók megjelenésétől mentes betegek magas aránya a követés három éve alatt továbbra is tartósan fennmaradt[16].

A CARE-MS I és CARE-MS II kiterjesztett utánkövetéses vizsgálataiban megvizsgálták azoknak a betegeknek az adatait, akik az eredeti tanulmányban alemtuzumabkezelést kaptak és a kezelés 2. évében nem mutattak sem klinikai, sem MR-aktivitást, és a továbbiakban nem kaptak sem újabb alemtuzumab-cikluskezelést, sem más betegségmódosító terápiát. A CARE-MS I vizsgálatba bevont betegek 68%-a, a CARE-MS II-be bevont ugyanilyen betegek 59%-a a kiterjesztés 2–5. évig terjedő időszaka alatt sem mutatott semmilyen MR-aktivitást (új/megnagyobbodó T2-hiperintenzív góc, új Gd-halmozó laesio)[17, 18]. Az agytérfogat csökkenésének üteme azok között a betegek között, akik betegségaktivitástól teljesen mentesek voltak [sem klinikai (relapszus, rokkantsági progresszió), sem MR-aktivitást nem mutattak] az utánkövetési időszak alatt is lassúbb volt: a CARE-MS I-ben a 2. évben a csökkenés –0,27% volt, majd az utánkövetés során a 3. évben –0,01%, a 4. évben –0,18%, az 5. évben –0,14%)[17]. a CARE-MS II-ben a 2. évben a csökkenés –0,20% volt, majd az utánkövetés során a 3. évben –0,17%, a 4. évben –0,19,% az 5. évben –0,07%)[18] **(1. táblázat)**.

Alemtuzumab és neuroprotekció

Mind a CAMMS223 vizsgálatban, mind a CARE-MS II kiterjesztett utánkövetési vizsgálatában az agyi térfogatok növekedése volt észlelhető az alemtuzumabkezelés mellett, míg az agyi atrófia tovább haladt előre a sc. IFN-β-1a kezelt csoportban. Emellett a CAMMS223 vizsgálatban az alemtuzumabbal kezelt betegcsoport rokkantsági állapota 0,39 EDSS-pontszámmal csökkent, míg a sc. IFN-β-1a-val kezelt betegcsoportban az EDSS 0,38 ponttal emelkedett. Az agyi atrófia előrehaladásának szignifikáns lassulása volt észlelhető a CARE-MS I, a CARE-MS II, valamint az előbbiek kiterjesztett, követéses vizsgálataiban is. Továbbá a CARE-MS II vizsgálat alemtuzumabbal kezelt betegcsoportjában a rokkantsági állapot szintén javult (a vizsgálat végén az EDSS-pontszám 0,17 ponttal csökkent, míg a sc. IFN-β-1a-val kezelt betegcsoportban 0,24 ponttal emelkedett).

Az alemtuzumabkezelés rokkantsági állapotot javító, és agyi térfogat-növekedést eredményező hatásának pontos mechanizmusa nem ismert. Lehetséges mechanizmusként olyan neutrofinok és oligotrofinok szerepét feltételezik, melyeket az alemtuzumab alkalmazását követően regenerálódott lymphocyták szekretálnak[19]. Erre utalnak azok az *in vitro* vizsgálatok, melyekben kimutatható volt, hogy az alemtuzumabkezelést követően a regenerálódó immunsejtek szignifikánsan több agyi eredetű növekedési faktort (BDNF), ciliaris neutrofikus faktort (CNTF), thrombocytaeredetű növekedési faktort (PDGF), és fibroblastnövekedési-faktort (FGF) termelnek[19]. Az immunsejtek BDNF, CNTF és PDGF szekréciója az *in vitro* kísérletekben specifikusan myelin antigénre, a myelinbázikus proteinre (MBP) adott válaszként következett be, mely arra utal, hogy magának az autoimmun válasznak önmagában neuroprotektív hatása is van.

In vitro kísérletben igazolták továbbá azt is, hogy a BDNF és CNTF, melyeket az alemtuzumabkezelés után regenerálódó T-sejtek termelnek képesek idegsejt-kultúrában elősegíteni a neuronok túlélését és az axon növekedését. Adatok vannak továbbá arról, hogy az alemtuzumabkezelést követően a perifériás immunsejtek még egyelőre további karakterizálásra váró olyan faktorokat termelnek, melyek sejtkultúrában oligodendrocyta prekurzorok proliferációját és érését segítik elő[19].

MRI-eredmények teriflunomidkezelés mellett

A GYÓGYSZER FARMAKODINÁMIÁJA

A teriflunomid (TER), ami a leflunomid aktív metabolitja, hatását elsősorban a pirimidinszintézis gátlásán keresztül fejti ki. Nyugalmi helyzetben, lassú proliferáció esetén a sejtek a pirimidinszükségletüket a meglévő pirimidintartalékok újrafelhasználásával elégítik ki. Gyorsan proliferáló sejtek esetén (mint a lymphocyták) azonban szükség van *de novo* pirimidinszintézisre is. A szintézis a dihidro-orotát dehidrogenáz (DHODH) enzimhez kötött, mely a mitokondrium külső membránján található. A TER a DHODH gátlásával csökkenti az immunsejtek proliferációját és ezáltal elnyomja az aberráns immunválaszt, mely az SM-betegség aktivitásáért felelős[20, 21].

KLINIKAI VIZSGÁLATOK

Fázis II., proof of concept tanulmány

A TER-t először egy 36 hetes randomizált, dupla vak, placebokontrollált, „proof-of-concept", fázis II. vizsgálatban próbálták ki[22]. Ebbe a vizsgálatba 179 relapszáló, járóképes SM-beteget válogattak be, akiknek legalább két relapszus volt a megelőző három évben. A betegeket három kezelési karba randomizálták: placebo (n=61), TER 7 mg (n=61), TER 14 mg (n=57). A betegeknek hathetente készült MR-vizsgálatuk (3 mm-es szeletvastagságú T2/proton-denzitás és pre- és poszt-kontraszt T1-súlyozott felvételek). A tanulmány primer végpontja MR-paraméter volt: *combined unique active lesion* (CUAL), ez a módszer az új laesiók azonosítása során az egy helyen megjelenő új vagy perzisztáló T1-halmozó és a T2-laesiókat egynek számolja. Ezenkívül a további MR-paraméterek a következők voltak: az új T1-halmozó laesiók száma, az új T2-laesiók száma, azon betegek száma, akiknek új CUAL, T2- vagy T1-halmozó laesiója volt. A klinikai kimeneteli változók csak másodlagosak voltak: a relapszust elszenvedő betegek száma, az éves relapszusráta, valamint azon betegek száma, aki relapszusa szteroidterápiát igényelt.

A vizsgálat a 7 mg és a 14 mg-os csoportban is a CUAL számának szignifikáns csökkenését találta és a két kezelt csoport között nem volt érdemi különbség. A CUAL-ok számának csökkenése már a 6. héten is megfigyelhető volt és ez a hatás a vizsgálat 36 hete alatt folyamatosan fennmaradt. Hasonló eredményeket találtak a halmozó laesiók, és az új vagy növekvő T2-laesiók esetében is. Ha azoknak a betegeknek a számát vizsgálták, akiknek új CUAL, T1-halmozó vagy T2-laesiója volt, szintén szignifikáns terápiás hatást találtak mindkét csoportban.

Ebben a relatíve kis elemszámú vizsgálatban a klinikai másodlagos kimeneteli változók tekintetében nem találtak szignifikáns javulást bár pozitív trend mindegyik változó esetében volt.

Egy hétéves utánkövetéses „open-label" vizsgálatban folytatták a fázis II. vizsgálatba bevont betegek megfigyelését[23]. A primer vizsgálat végeztével a placebokaron lévő betegeket a 7 mg és 14 mg-os csoportba sorolták. A kiterjesztéses vizsgálat elején a 7 mg-os csoportban 81, míg a 14 mg-os csoportban 66 beteg volt. A vizsgálat végére 49 és 36 beteg volt a két szárnyban.

Klinikai végpontok tekintetében az éves relapszusráta jelentősen csökkent az alapbetegség-aktivitásához képest. Az MR-markerek tekintetében a pozitív hatás fennmaradt az obszervációs idő alatt.

A TEMSO VIZSGÁLAT

A TEMSO (The *TE*riflunomide *M*ultiple *S*clerosis *O*ral trial) vizsgálat egy 1088 aktív SM beteget beválogató randomizált, multicentrikus vizsgálat volt[24]. A betegeket 18 és 55 év között, 5,5 EDSS-pont alatt válogatták be a három vizsgálati karba (placebo, 7 mg TER, 14 mg TER) és 108 hétig figyelték meg. MR-vizsgálat a klinikai vizsgálat 0., 24., 48., 72. és 108. hetében történt. A vizsgálat elsődleges végpontja az éves relapszusráta volt, másodlagos végpontjaként pedig a 12 hetes igazolt betegségprogressziót és MR-paramétereket vizsgáltak. Az éves relapszusrátát a TER mindkét dózisa 31%-kal csökkentette a placebóhoz képest. A progressziót tekintve a 7 mg dózis által létrehozott kedvező hatás nem volt szignifikáns, de a 14 mg-os dózis szignifikánsan csökkentette az igazolt progressziót észlelő betegek számát (placebo: 27,3%, 7 mg TER: 21,7%, 14 mg TER: 20,2%). A vizsgálat az MR-paraméterek szempontjából is pozitív eredményt hozott mindkét TER-dózisnál. A betegeknek

átlagosan 20 ml-es alap-laesioösszvolumenje volt. A placebocsoportban ez 2,21±7 ml-rel nőtt, míg a 7 mg-os TER-csoportban csak 1,31±6,8 ml, a 14 mg-os TER-csoportban 0,72±7 ml ml volt a változás a vizsgálat ideje alatt ($p<0,03$ és $p<0,001$).

Az MR-paramétereket részletesen egy következő közleményben értékelték[25]. A primer MR-paraméter mellett a T1-halmozó laesiók számában is mindkét gyógyszerdózisnak szignifikáns hatása volt. A MR-felvételenként jelentkező halmozó laesiók száma 1,33 volt a placebocsoportban, a 7 mg-os TER-csoportban 0,57 és 0,261 a 14 mg-os TER-csoportban, ami 57,2%-os és 80,4%-os relatívrizikó-csökkenésnek felelt meg. Hasonlóan pozitív volt a hatás akkor is, ha azon betegek számát nézték, akiknél nem találtak halmozó laesiót. Bár a T1-hipointenzív laesiók térfogata elég alacsony volt a beválogatás idején, a 72. hétig mindkét gyógyszerdózis pozitívan befolyásolta a T1-laesio térfogatváltozását, a 108. héten már csak a nagyobb dózis tudta megőrizni hatását. A CUAL tekintetében is jelentős csökkenést okozott mindkét gyógyszerdózis. A T2-laesiókat, a T1-halmozó laesiókat, a T1-hipointenz laesiókat és az agyi atrófia mértékét magában foglaló Z-értékek is szignifikáns javulást mutattak mindkét gyógyszerdózisnál már a 24. héten is.

Az agyi atrófiát több paraméter szerint is vizsgálták. A „brain parenchymal fraction", azaz az intracranialis volumen aránya a liquortér térfogatához, nem változott szignifikánsan a TER hatására. Hasonló negatív eredményt hozott a szürkeállományi atrófia vizsgálata. A fehérállományi atrófiát azonban mindkét gyógyszerdózis pozitívan befolyásolta.

Fontos, hogy a TEMSO vizsgálatban az agyi atrófiát a University of Texas Health Science Center at Houston MRIAP szoftvercsomagjával végezték. Ez a módszer a különböző szöveteknek megfelelő (liquor, szürke- és fehérállomány) szegmentációját használja a parciális térfogatok meghatározásához. Bár a módszer keresztmetszeti vizsgálatokhoz jól alkalmazható, longitudinális vizsgálatokban egyre többször a regisztráció alapú agytérfogat-változás meghatározást alkalmazzák. Ezt a módszert a University of Oxford, Center for Functional MRI of the Brain csoportja implementálta az FSL programcsomag SIENA alprogramjába. A TEMSO adatait a közelmúltban újraértékelték és az eredményeket 2016 áprilisában, az American Academy of Neurology 68. Éves Konferenciáján ismertették. Az eredeti vizsgálat 808 betegének volt megfelelő MR-felvétele a SIENA analízisre. Az első év végére a TER 14 mg-os dózisa 36,9, a második év végére 30,6%-kal csökkentette az agytérfogat csökkenését[26]. A 7 mg TER esetében hasonló eredményeket találtak, az első évben 34,4%-kal, a második évben pedig 27,6%-kal csökkentette az atrófia rátát. Fontos, hogy mindkét dózis az agytérfogat fogyását körülbelül 0,4%-on stabilizálta, ami *DeStefano* vizsgálata szerint a küszöbérték egészségesek és SM-betegek fogyási rátája között[6]. Bár direkt összehasonlítás nem szerencsés a tanulmányok között, az atrófia mértékében a TER hasonló csökkenést okozott mint a két másik orális készítmény[27–30]. Egy további közleményben alcsoportokat határoztak meg. Azon betegeknek, akiknek a beválogatáskor volt T1-halmozó laesiója, illetve azoknál, akiknek nagy volt a T2-laesio-összvolumenük a bevonáskor, az agyi atrófia rátája is nagyobb volt. Azonban a TER mindkét dózisa hasonlóan kedvező hatású volt minden alcsoportban[31]. Egy következő vizsgálatban a betegeket aszerint csoportosították, hogy kinek volt 12 vagy 24 héten át megmaradó legalább 1 pont EDSS-növekedéssel jellemezhető klinikai progressziója. A progrediáló betegek agyi térfogatvesztése nagyobb volt, de progressziótól függetlenül a TER mindkét dózisa megtartotta a hatását[32].

A TEMSO tanulmány kiterjesztésében 742 beteg vett részt, akik közül 467 maradt TER-kezelésen a magvizsgálatból, a többi beteg pedig a placebocsoportból került ki és váltott vagy 7 vagy 14 mg TER-ra. A klinikai paraméterek közül az éves relapszusráta a placebóról TER-kezelésre váltók esetén jelentősen csökkent és az összes csoportban alacsony maradt a vizsgálat ideje alatt. Ehhez hasonlóan a placebóról váltó betegek között a T1-halmozó laesiók számának jelentős csökkenése volt észlelhető, és a tanulmány ideje alatt ez végig alacsony is maradt.

A TOPIC VIZSGÁLAT

Az „Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC)" vizsgálat 108 hétig tartó, randomizált multicentrikus, placebokontrollált vizsgálat, mely klinikailag izolált szindrómában vizsgálta 618 betegen a TER hatékonyságát két dózisban[33]. Az elsődleges végpont a relapszusig eltelt idő, így a definitív SM konverzióideje volt. A másodlagos végpont az új relapszusig tartó idő vagy az MR-en megjelenő T2- vagy T1-halmozó laesio (bármelyik is legyen előbb). A 14 mg-os TER-dózis 42,6%-kal, a 7 mg-os dózis pedig 37,2%-kal csökkentette a konverziót. Az MR-paramétereket illetően, bár a laesiói volumen növekedés nagyon kicsi volt (átlagosan 0,044 ml) a placebocsoportban a 14 mg-os TER-csoportban szignifikánsan kisebb volt, mint a place-

2. táblázat. *MR-paraméterek változása az teriflunomidkezelés hatását vizsgáló tanulmányokban*

	T2-laesio-volumen-változás (18. hét)	T2-laesio-volumen-változás (36. hét)	T2-laesio-volumen-változás (108. hét)	Éves agytérfogat-változás
Fázis II.	Placebo: 1,1%* TER 7 mg: –0,1%*, N.S. TER 14 mg: –3,8%*, N.S.	Placebo: 5,2%* TER 7 mg: 2,9%*, N.S. TER 14 mg: –4,1%*, ‡		
TEMSO			Placebo: 2,21 ml* TER 7 mg: 1,31 ml*, ‡ TER 14 mg: 0,72 ml*, ‡	Placebo: –0,004 ml*, N.S. TER 7 mg: –0,003 ml*, N.S. TER 14 mg: –0,003 ml*, N.S. TER 7 mg: –34,4%**, ***, ‡ TER 14 mg: –36,9%**, ***, ‡
TOPIC			Placebo: 0,044* TER 7 mg: 0,023 ml*, N.S. TER 14 mg: –0,028 ml*, ‡	Placebo: ∼–0,003 ml†, N.S. TER 7 mg: ∼–0,002 ml†, N.S. TER 14 mg: ∼–0,003 ml†, N.S.

*Változás a kezdeti értékhez képest.
**Változás a placebocsoporthoz képest egy év alatt.
***A TEMSO tanulmány újraértékelése SIENA módszerrel.
†Közelítő számított érték a közlemény 0–108. hét között mért négyzetgyök transzformált értékeiből.
‡Szignifikáns különbség a kontrollcsoporthoz képest.
N.S.: Nem szignifikáns.

bocsoportban. A felvételenkénti halmozó T1-laesiók száma szintén a 14 mg TER-csoportban volt kisebb. Az agytérfogat vagy a laesio-összvolumen tekintetében nem találtak szignifikáns különbséget a kezelt és a placebocsoport között **(2. táblázat)**.

Megbeszélés

Az elmúlt években végzett klinikai tanulmányok igazolták, hogy RRSM-ben az alemtuzumabkezelés szignifikánsan lassítja az agyi atrófia ütemét, továbbá a kezelés mellett az agytérfogat növekedése is előfordulhat. Alemtuzumabkezelés mellett az MR-aktivitással (új és megnagyobbodó T2-hiperintenzív laesiók, Gd-halmozó laesiók, új T1-hipointenzív laesiók megjelenése) jellemezhető betegek aránya kisebb volt. Az utánkövetési vizsgálatok során igazolható volt továbbá, hogy az alemtuzumabkezelés MR-paraméterekre kifejtett hatása tartós, az utánkövetés 3. évében továbbra is fennállt.

A klinikai vizsgálatok[22, 24, 33–35] a TER hatékonyságát is igazolták relapszus-remisszió kórformájú sclerosis multiplexben és klinikailag izolált szindrómában. A vizsgálatok közül a TEMSO és a TOPIC vizsgálatból áll rendelkezésre MR-adat, mely mindkét tanulmány esetében támogatta a gyógyszer hatékonyságát, ha a különféle laesiók megjelenését tekintjük. A közelmúltban az AAN 2016-os konferenciáján bemutatott eredmények szerint a gyógyszer nem csak a laesiók kialakulására van pozitív hatással, de az agyi atrófia kialakulását is csökkenteni tudja más orális készítményekkel hasonló mértékben[36].

Összességében kiemelendő, hogy mind az alemtuzumab, mind a teriflunomid pozitív hatást mutatott SM-ben a mért MR-paraméterekre. A laesiók számának és térfogatának mérése már régen a klinikai gyógyszervizsgálatok standard kimeneteli változója. Az utóbbi években az agyi atrófia mérése is kiemelkedő jelentőségűvé vált. Mivel a különböző gyógyszervizsgálatokban mért MR-paraméterek, és az atrófiaszámítási módszerek sokszor eltérőek, a tanulmányok eredményei nehezen összehasonlíthatók. A legtöbb gyógyszernek azonban pozitív hatását mutatták ki az agyi atrófiára.

Az SM kezelésére kifejlesztett gyógyszerek hatékonyságának vizsgálatát a laesioszám-, -térfogat- és agyiatrófia-mérések mellett a jövőben várhatóan egyéb MR-biomarkerek is segíteni fogják[37]. Az újabb mérési módszerek közé tartozik a szürke- és fehérállományi atrófia, továbbá a corticalis, subcorticalis, és gerincvelői atrófia külön-külön történő értékelése, valamint a kvantitatív MR-alapú biomarkerek (magnetisation transfer ratio, diffusion tensor imaging, spektroszkópia, relaxációsidő-mérés) meghatározása. Az utóbbiakkal kapcsolatosan az utóbbi időben több fontos közlemény jelent meg, várhatóan a módszerek validitásának tisztázását követően ezek is bekerülhetnek a klinikai vizsgálatok tárházába. Természetesen a végső cél az, hogy az alapkutatásban és a klinikai vizsgálatokban kipróbált képalkotó biomarkerek a klinikai gyakorlatba is bekerüljenek.

KÖSZÖNETNYILVÁNÍTÁS
A kézirat a Sanofi-Aventis Magyarország Kereskedelmi és Szolgáltató Zrt. felkérésére készült. Dr. Kincses a Nemzeti Agykutatási Programból kapott támogatást sclerosis multiplex irányú kutatásaihoz (KTIA_13_NAP-A-II/20).

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THE TIMING OF WEANING ALTERS THE VULNERABILITY TO STRESS-INDUCED GASTRIC EROSION IN ADULT RATS

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0025 | www.elitmed.hu

Background – Weaning is an important period of life and its timing may influence the resilence for later stress. One of the most important stress-related disorder is gastric ulceration.
Purpose and methods – Therefore we aimed to investigate the sensitivity of gastric mucosa to cold (at 16°C) water immersion stress (WIS for 3h) in adult (75-day-old) female and male rats after weaning them at different timepoints (at 17, 21, 30, 36 or 42 postnatal days). The connection with stress was studied by comparing control groups to those underwent WIS at the time of weaning and measuring corticosterone levels at the time of collecting the stomach samples.
Results – The timing of weaning has strong impact on all studied parameters. Stress-induced erosion development was the smallest in rats weaned at 36-day independently from preconditioning with WIS at weaning, or sex, despite a clear sex-effect on blood corticosterone levels and body weight. WIS at weaning influenced only the body weight in adult rats weaned at 30-day, being higher in stressed than in control groups. There was no clear overall correlation between erosion area and blood corticosterone measures.
Conclusions – Taken together our results confirm that the timing of weaning has long-lasting impact on the resiliance of gastric mucosa to ulcerogenic stressful events. In rats the postnatal day 30–36 seems to be optimal for weaning in both sexes as both earlier and later weaning increased vulnerability. Females seems to be more vulnerable to the effect of weaning than males.

Keywords: *gastric mucosal lesion, postnatal development, water immersion stress, corticosterone*

AZ ELVÁLASZTÁS IDŐZÍTÉSE BEFOLYÁSOLJA A STRESSZ INDUKÁLTA GYOMORFEKÉLY-KÉPZŐDÉST FELNŐTT PATKÁNYBAN

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Ideggyogy Sz 2017;70(1–2):25–32.

Háttér – Az anyától való elválasztás fontos szakasza az életnek és az időzítése alapvetően meghatározhatja a későbbi stresszekkel szembeni ellenálló képességet. Az egyik legfontosabb stresszfüggő megbetegedés a stresszfekély.
Célkitűzés és módszertan – Ezért megvizsgáltuk a gyomornyálkahártya érzékenységét hideg (16 °C) vízbe mártásos stresszel (VMS, 3 óra) szemben felnőtt (75 napos) nőstény és hím patkányokon, akik különböző időpontokban (a 17., 21., 30., 36. vagy 42. postnatalis napon) voltak elválasztva. A stresszel való kapcsolatot az elválasztáskor VMSzen átment csoport kontrollokkal való összehasonlításával tanulmányoztuk és vérmintákat gyűjtöttünk kortikoszteronmeghatározásra a gyomorminták gyűjtésének időpontjában.
Eredmények – Az elválasztás ideje erőteljesen befolyásolta az összes vizsgált paramétert. A VMS indukálta gyomorfekély-képződés a legkisebb a 36 napos korban elválasztott állatokban volt, függetlenül az elválasztáskori VMS-prekondicionálástól, vagy a nemtől, annak ellenére, hogy a nem erősen hatott a kortikoszteronszintekre és a testsúlyra. Az elválasztáskori VMS csak a 30 napos korban elválasztott állatok testsúlyát befolyásolta, ami nagyobb volt a stresszelt csoportban. A fekély mérete nem mutatott általános korrelációt a kortikoszteronszinttel.
Következtetések – Összefoglalva, eredményeink alátámasztják, hogy az elválasztás időzítése hosszú távú hatást gyakorol a gyomornyálkahártya ellenálló képességére a fekélyképződésre vezető stresszelő hatásokkal szemben. A postnatalis 30–36. nap tűnik a patkányok elválasztására legoptimálisabbnak mindkét nemben, mivel mind a korábbi, mind a későbbi elválasztás növeli az érzékenységet. A nőstények érzékenyebbnek tűnnek a hímeknél az elválasztás hatására.

Kulcsszavak: *gyomornyálkahártya-laesio, postnatalis fejlődés, vízbe mártásos stressz, kortikoszteron*

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Érkezett: 2016. november 19. Elfogadva: 2016. november 26.

Early life events have been associated with profound consequences on later development[1], among others it is known to influence the permeability of the intestinal tract[2]. The environmental alterations, which permanently affect the adult phenotype and lifetime vulnerability to diseases, are stressors and are monitored presumably by the the hypothalamic-pituitary-adrenocortical axis (HPA)[3].

The endhormones of the HPA axis are glucocorticoids, in rodents presumably corticosterone. Our previous results demonstrated a gastroprotective action of stress-induced glucocorticoid elevations[4–6] as well as time- and dose-dependent effects of exogenous glucocorticoids on the gastric mucosa[6–8]. Moreover, previous stressors can increase the adaptive defense's capabilities and in this way may play important role in maintaining the physical health[9]. The „natural" elevation of glucocorticoids during preconditioning stress is an important component of gastroprotection, because inhibition the glucocorticoid synthesis by metyrapone shortly before the onset of preconditioning stressor eliminated its protective influence against gastric injury induced severe stressor[10]. Our further studies confirmed the participation of glucocorticoid in preconditioning effect in an ischemia-reperfusion-induced gastric injury model as well[11]. Additionally to the results obtained in adults rats, we found that in pups maximal vulnerability of gastric mucosa to ulcerogenic stimulus may coincide with the period of nonstable stress reaction of the HPA axis[12].

Weaning is actually a maternal separation, characterized by maternal reduction of resources, therefore is both psychologically and energetically stressful to the offspring[13]. This weaning conflict between the less parental investments from the mother side and requirement more parental care from the side of the offspring stimulates the HPA axis of the pups but not the mothers[14, 15]. The reduced maternal care in this late phase of lactation also has been associated with alterations in the behavioral and physiological responses to stress in adult progeny[16, 17]. However, the age of the pups stongly determines the level HPA axis activation[18]. In animal facilities weaning is an arteficial process determined mainly by breeding considerations. Namely, the length of pregnancy in rats is around 22 days[19], therefore the pups are separated from their mothers around day 21 postnatally (PND), before a new litter could be delivered. In their natural environment the dietary transition period of rats commences around PND16 and the spontaneous weaning continues until PND30, when the pups cease milk intake completely[19–21]. Around PND21 there is stress-hyperresponsive period with enhanced basal and stimulated steroidogenesis[22]. Thus, it does not seem to be an optimal timepoint for weaning.

Our goal was to determine a timepoint for weaning, when the resilience to gastric ulceration would be maximal in adulthood. To further clarify if stress at weaning might be responsible for the late effects in half of the animals we used an additional strong stressor at the time of weaning as well. As a pathological condition-inducing treatment ulcerogenic water-immersion stress (WIS) was applied in adults and the development of erosion was studied in the stomach together with the evaluation of corticosterone levels. Males and females are otherwise sensitive to different challenges[23] already during the perinatal period[24], therefore sex-differences were also evaluated.

Methods

ANIMALS

Female Wistar rats were matted with males (both 10-12 week old, Pavlov Institute of Physiology, Russian Academy of Sciences, Saint-Petersburg, Russia) for 24h and after giving birth the 20 dams were kept alone in one cage with the offspring. The sex and size of the litter was not controlled. Rats were kept in controlled environment (23±1°C, 50–70% humidity, 12 h light starting at 07:00 h) and given commercial rat chow and tap water *ad libitum* if not otherwise stated. Animals were naive to experimentation. Experiments were carried out in accordance with European Communities Council Directive (2010/63/EU) and the local animal care committee at the Pavlov Institute of Physiology RAS.

MANIPULATIONS AT THE TIME OF WEANING

The offsping were separated from mothers (4-6 litter for each timepoint) at different timepoints (PND17, 21, 30, 36 and 42) and randomly assigned to control and water immersion stress (WIS) groups forming 4 groups (female-control; female-WIS; male-control and male-WIS) at each weaning day. **(Table 1.)** PND17 was taken as an early timepoint of weaning (often refered as early weaning[25]). PND21 is the more common time of weaning in the animal facilities. According to a Science paper PND30 seems to be more optimal for weaning take into consideration the long term neurological and psychological consequence[26]. We were curios if

prolongation of weaning will further increase the positive consequences, therefore later weaning timepoints (PND36 and PND42) were also studied[27, 28].

Cold (16°C) WIS was carried out at immobilizing the animals in tubes fitted to their size for 3 h taken immediatelly from the mothers. After stress the animals were put in a new breeding cage 4-5animals/sex/group. Control animals were separated from the mother at the same time, and was kept 4-5/sex/cage until a further, ulcerogenic WIS in adulthood.

MEASUREMENTS IN ADULTHOOD

In all adult (75-day-old) animals a WIS stress was carried out. The body weight was measured, grid floors were placed in the home cages to prevent coprophagy and animals were deprived of food but not water for 24 h before initiation of the restraint procedure at 16°C immobilizing them in tubes fitted to their size. At the end of 3h WIS the rats were decapitated, trunk blood was collected in tubes and stomach was taken and filled with 10ml saline for at least 1h.

The gastric injury were examined opening the stomach at the greater curvature cleaned and spread. The stomach was examined with a binocular dissection microscope. The area of each lesion was measured in square millimeters and the cumulative area of all lesions in a rat served as the measure of erosion damage. Although the lesions were acute hemorrhagic gastric erosions, they are commonly referred to as "stress ulcers"[29].

Corticosterone level of plasma was measured by microfluorometry[30] using fluorescence spectrophotometer (Hitachi, Ltd. Tokyo, Japan). Intra- and interassay variation of measurements was 5.1% and 7.4%, respectively.

STATISTICAL ANALYSIS

Data were analyzed by analysis of variance (ANOVA) using the ANOVA/MANOVA module of the STATISTICA 12.0 software package (Tulsa, OK, USA). The factors for the three-way ANOVA were time of weaning, WIS at weaning and sex. ANOVA assumptions were evaluated by the Levene's test. Multiple pairwise comparisons were made by the Fischer LSD method. Lineal correlations were calculated by the Pearson method. Data are expressed as mean±standard error of the mean (SEM) and the level of significance was set at $p<0.05$.

Table 1. *Number of animals in each group*

	Time of weaning				
Groups	17-day	21-day	30-day	36-day	42-day
Female-control	10	10	8	7	10
Female-WIS	12	11	8	6	8
Male-control	10	10	6	10	10
Male-WIS	6	10	8	6	9

None of the animals died between weaning and examination in adulthood

Results

We found that the area of *gastric lesion* to WIS in adulthood was clearly dependent on the time of weaning [$F(4,155)=4.74$; $p<0.01$; **Figure 1**]. More precisely, when the animals were weaned at PND36, they were more resistant to stressful ulcerogenic stimulus in both sexes (lowest ulcer area). In females weaning at PND30 had similar effect, while in male weaning at PND21 resulted in similarly small ulcer area. Weaning at PND42 lead to an enhancement of erosion area compared to the wening at PND36, which was significant ($p=0.04$) in males, but showed only a tendency ($p=0.059$) in females.

The WIS at weaning as well as the sex had no profound effect and did not influence the effect of weaning (no main effects and interactions). However, we have to add that a separate analysis in males lead to only a tendency of weaning [$F(4,75)=2.47$; $p=0.052$; **Figure 1B**] suggesting a more profound effect of the timing of weaning in females [$F(4,80)=2.67$; $p=0.038$; **Figure 1A**].

The accompanied *corticosterone* levels were also influenced by the time of weaning [$F(4,152)=10.4$, $p<0.01$; **Figure 2**]. It means that when the time of weaning was PND30 or 36 the adult WIS stressor-induced corticosterone elevation was smaller compared to the weaning PND17. However, when the weaning was at PND42, it resulted in a significantly higher WIS-induced corticosterone rise compared to PND36-weaned adult rats.

We have to add however, that the effect of weaning was highly dependent on the sex [time of weaning x sex interaction: $F(4,152)=3.0$, $p<0.05$]. Not only the females had higher corticosterone levels [sex: $F(1,152)=293.3$, $p<0.01$], but the effect of weaning was far more significant in this sex [$F(4,78)=7.75$, $p<0.01$; **Figure 2A**] with a significant difference between weaning at PND17 and PND30-36 ($p<0.05$), as well as weaning at PND42 and PND30-36 ($p<0.01$). In males the effect of

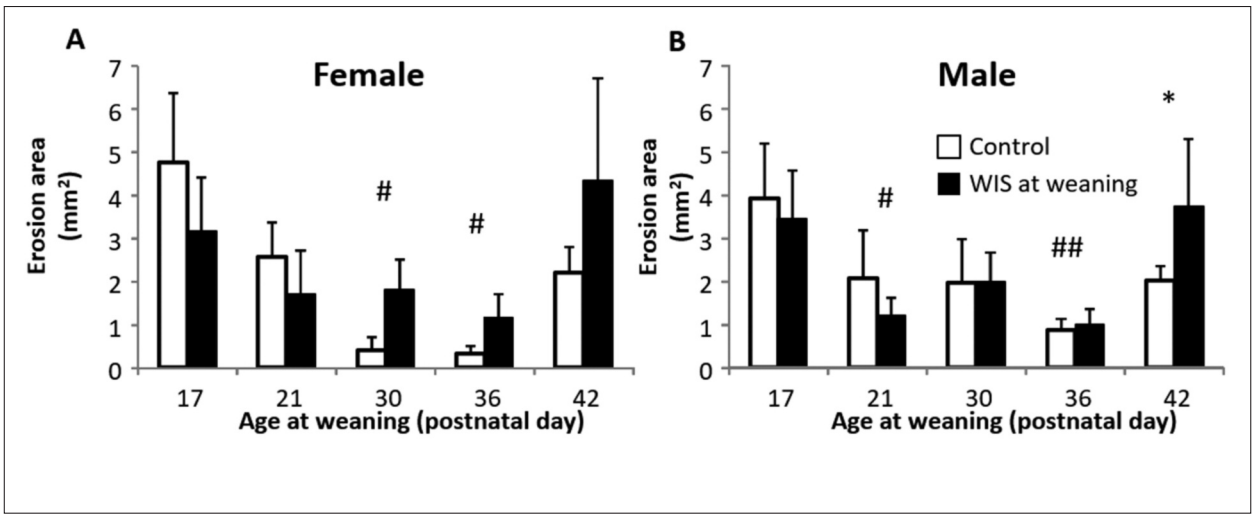

Figure 1. *Erosion area at the end of 3h water immersion stress (WIS) at 16 °C in adult animals weaned at different timepoint with and without WIS at the time of weaning.* **A.** *females* **B.** *males; #p<0.05, ##p<0.01 main effect of the time of weaning compared to day 17; *p<0.05 main effect of time of weaning compared to day 36*

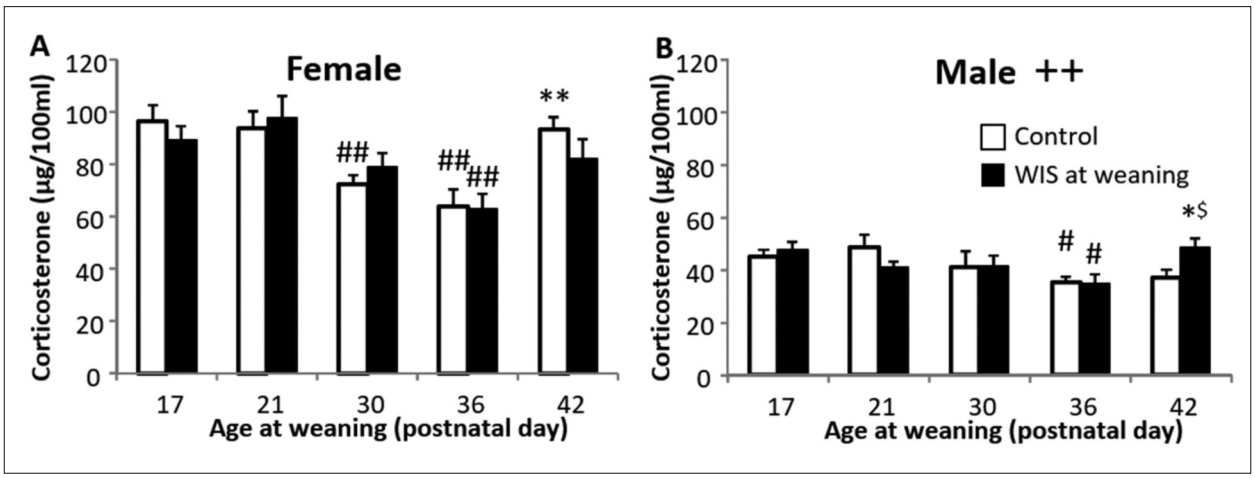

Figure 2. *Corticosterone levels at the end of 3h water immersion stress (WIS) at 16°C in adult animals weaned at different timepoint with and without WIS at the time of weaning.* **A.** *females* **B.** *males; #p<0.05, ##p<0.01 vs weaned at day 17 of the same sex with same stress at weaning; *p<0.05, **p<0.01 vs weaned at day 36 of the same sex with same stress at weaning; $ p<0.05 vs control, not WIS at weaning of the corresponding group; ++p<0.01 main effect of sex*

weaning was smaller [F(4,74)=2.98, p=0.02; **Figure 2B**] and there was a difference between the effect of weaning at PND17 and 36 (p<0.05) and day PND42 and 36 (p<0.05).

The WIS at weaning had no profound influence on blood corticosterone levels at the end of a stressful stimulation in adulthood. The only significant difference was detectable in males weaned at PND42 having higher corticosterone levels in the WIS group (p<0.05).

Similarly to the afore mentioned parameters the *body weight* was also influenced by the timing of weaning [F(4,155)=5.16, p<0.01; **Figure 3**]. It is again meant that the weight of adult animals weaned at PND30 was significantly higher than that of the animals weaned at PND17 (p=0.01), and weaning at PND42 resulted in a significant diminution compared to PND21 (p=0.02) and PND30 (p<0.01).

However, we have to mention that the effect of weaning was significantly influenced by the sex (time of weaning x sex interaction: F(4,155)=3.38, p=0.01). Females were smaller [sex: F(1,155)= 155.6, p<0.01], and the weaning at PND30 resulted

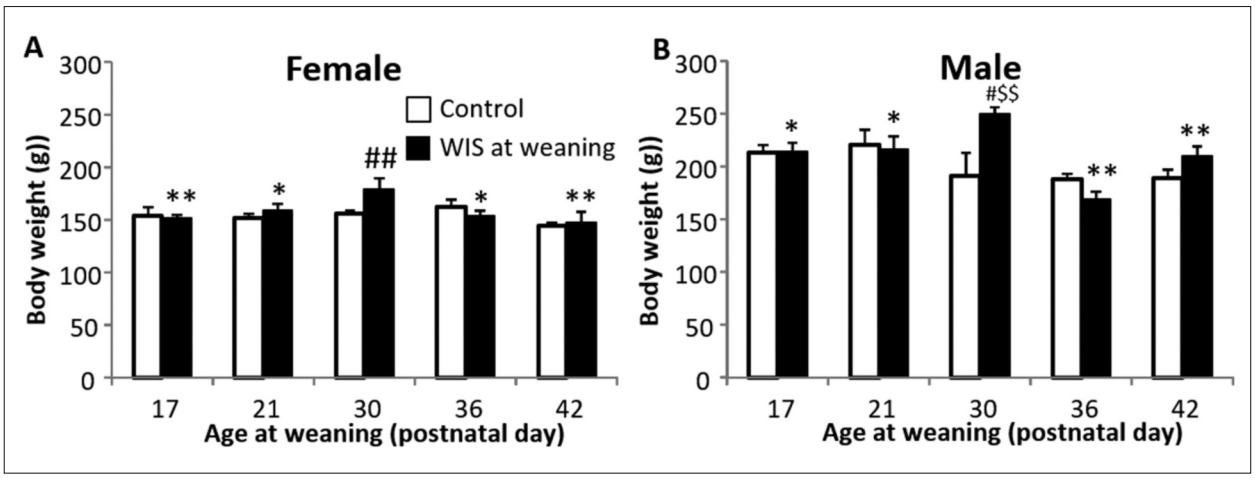

Figure 3. *Body weight of adult animals (75-day-old) weaned at different timepoint with and without WIS at the time of weaning*. **A.** *females* **B.** *males; #p<0.05, ##p<0.01 vs weaned at day 17 of the same sex with WIS at weaning; *p<0.05, **p<0.01 vs weaned at day 30 of the same sex with WIS at weaning; $$ p<0.01 vs control, not WIS at weaning of the corresponding group*

in a significant elevation in their body weight compared to both PND17 and 42 of weaning (p<0.01; **Figure 3A**). In contrast in males the effect of weaning was more profound [F(4,75)=4.9, p<0.01; **Figure 3B**] compared to the effect of weaning in females [F(4,80)=2.84, p=0.03] and the WIS at weaning had a significant influence on it [sex x WIS at weaning interaction: F(4,75)=3.36, p=0.01]. In males weaned at PND30 the effect of WIS at weaning was significant (p<0.01). We have to add, however, that in both sexes the adult animals weaned at age 30 with WIS had significantly higher body weight than corresponding animals weaned at any other day (p<0.05).

There was a significant positive linear *correlation* between ulcer area and corticosterone levels in case at weaning unstressed female animals (r=0.43, p<0.01) and male rat weaned at PND21 (r=0.65, p<0.01) and a negative correlation in male rats weaned at PND17 (r=–0.58, p=0.01). The ulcer area was not correlated with body weight, while there was significant negative correlation between corticosterone level and body weight (r=–0.48, p<0.01), which was mainly due to the effect of sex as the correlation disappeared when we examined the two sex separately.

Discussion

Our results clearly demonstrate that the timing of weaning has profound consequences on adult vulnerability to the development of stress-induced gastric erosion, which was not influenced profoundly by additional WIS-stress at weaning as well as by the sex. PND30-36 seems to be the best timepoint of weaning as not only earlier, but also later weaning enhanced the erosion formation in adulthood. Beside the clear sex differences in body weight as well as on plasma total corticosterone content the effect of weaning was also significant on these parameters. Although the HPA axis seems to be an indispensible component of stress reaction, thereby an effect of its main endhormone, corticosterone on the gastric mucosa was supposed, but there was no clear overall correlation between erosion area and blood corticosterone measures. However, the erosion area significantly correlated with the corticosterone at weaning non-stressed females. Together with the stronger effect of weaning in females than males this suggests an overall increased vulnerability of female pups to the effect of weaning.

Maternal feeding and strocking seem to be important components for programming the offsping's HPA axis, with a more prominent role of the nutrition than maternal care on adrenal steroidogenesis[15]. In this sense the early weaning (PND15-18)-induced learning impairment[26] was restored by high fat diet[31]. Not only the quantity and quality of the digested food are changing, but also the gastrointestinal tract undergoes major developmental changes postnatally[32]. The glandular stomach shows stepwise growth relative to body weight, with a significant increase at PND18-20. The forestomach exhibits a decrease in growth relative to body weight during the same period. The basal acid secretion, one of the most important ulcerogenic

factor, as well as its reactivity to wide range of secretagogues starts to functioning between PND15-18[33], but does not change substantially during the later postnatal development[34]. Pepsinogen content starts to increase at PND15, and constantly rises till adulthood[20, 35]. The level of cycloxygenase (COX) mRNA 1, an important component of the mucosal protective mechanisms, was shown to be also altered during ontogenesis, being the highest in 4 week old (PND 28) rats compared to 1, 2 or 8 week old pups[36]. This elevation may contribute also to the long-lasting positive effect of the weaning at PND30-36.

Previous results showed, that precocious weaning (PND15) increased the size of villi, depth and number of crypts in the duodenum and jejunum, while the number of villi decreased[37]. However, pups nursed up to 32 days showed no alterations in the previously mentioned parameters. It was also shown that the time of separation of young animals from mothers is essential for the formation of small intestinal digestive enzymes[27]. Comparing the effect of the timing of weaning several intestinal[27] and pancreatic[25] enzymes showed alterations with prematurely induced activity in early weaned group, while with delayed increase during prolonged nursing. The pattern of development of gastric mucosa seems to be similar to small intestine with a rapid proliferation starting from PND 15-18[38] accompanied by enhancement of the secretagogue content[20]. However, the sensitivity of gastric mucosa to trophic factors, like gastrin, develops between PND20-28[38], supporting further our notion about the PND30 as optimal timing of weaning, when the gastric mucosa is already fully functional.

Corticosterone may induce premature changes in the newborn stomach[39], which than will influence the adult vulnerability/resilience. In mice the resting corticosterone levels as well as the *in vitro* stimulated glucocorticoid rise was the highest around PND21 compared both PND14 and 28[22]. In rats the basal level of glucocorticoids was higher in PND20 compared to PND5 and 10[18] or adulthood[40], but no information was available about the period between PND 21 and adulthood. However, the stressor-induced changes may vary and the life-long consequences may be independent from the actual levels at weaning. Nevertheless, in our hand additional stressor at weaning did not influence the gastric ulceration, as well as corticosterone elevation to WIS in adulthood, thus, it seems that acute alteration of the HPA axis does not seem to substantially contribute to the effect of the timing of weaning. However, we have to add, that certain stress-related gastric lesions are 'brain-driven' events[41] and we cannot close out the role of changes in the central limb of the HPA axis.

Previous studies comparing the body weight gain in PND15-, 21- and 30-weaned rats up to PND150 did not found alteration between the groups[16]. Our results confirmed this assumption. However, a strong stressor, applied at PND30, resulted in an increase in body weight in both sexes. In the face of other positive changes at PND30 weaning we consider this body weight increase a positive phenomenon, further supporting the notion, that stressor may also help the adaptation.

Previous studies on sex-different sensitivity showed that female pups were more vulnerable showing at weaning more robust increase in intestinal permeability enhancement to early postnatal stressors[42]. In adulthood, maternally separated females reacted to footshock-induced conditioned fear with higher corticosterone rises than males[43]. Although the above mentioned results support our finding about the superior vulnerability of females than males, but other data indicate the opposite. E.g. maternal separation led to reduced freezing in conditioned fear paradigm, and this reduction representing less anxiety was more pronounced in females[44]. Moreover, prenatal stress induced anxiety and depression-like behaviour only in adult male but not in female offspring[23]. Thus, perinatal stressors may aggravate but also diminish later stressor sensitivity in a sex-dependent manner.

All in all we established, that in contrast to the general practice, weaning at PND30-36 would be optimal for rats leading to maximal mucosal resistance. Additional stress at weaning does not make too much difference. Our present results did not confirm a strong correlation between stress at weaning as well as the ulcerogenic-stressor-induced glucocorticoid elevation and the sensitivity of the adult animals, however this question requires further investigation. Beside glucocorticoids other possible pathogenetic-defensive factors (e.g. COX) have to be taken into consideration. Females seemed to be more vulnerable than males.

ACKNOWLEDGEMENTS

This study was supported by the Russian Science Foundation (RSF) (N 14-15-00790). Filaretova L. was responsible for general experimental design, performing experiments in adult rats and analysis of the results, Vataeva L. performed the first step experimental study (weaning part), Zelena D. was responsible for statistical analysis and the article writing.

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THE EVALUATION OF THE RELATIONSHIP BETWEEN RISK FACTORS AND PROGNOSIS IN INTRACEREBRAL HEMORRHAGE PATIENTS

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0033 | www.elitmed.hu

Objective – Patients were assessed in terms of risk factors, hematoma size and localization, the effects of spontaneous intracerebral hemorrhage (ICH) on mortality and morbidity, and post-stroke depression.
Materials and methods – The present study evaluated the demographic data, risk factors, and neurological examinations of 216 ICH patients. The diagnosis, volume, localization, and ventricular extension of the hematomas were determined using computed tomography scans. The mortality rate through the first 30 days was evaluated using ICH score and ICH grading scale. The Modified Rankin Scale (mRS) was used to determine the dependency status and functional recovery of each patient, and the Hamilton Depression Rating Scale was administered to assess the psychosocial status of each patient.
Results – The mean age of the patients was 65.3±14.5 years. The most common locations of the ICH lesions were as follows: lobar (28.3%), thalamus (26.4%), basal ganglia (24.0%), cerebellum (13.9%), and brainstem (7.4%). The average hematoma volume was 15.8±23.8 cm^3; a ventricular extension of the hemorrhage developed in 34.4% of the patients, a midline shift in 28.7%, and perihematomal edema, as the most frequently occurring complication, in 27.8%. Over the 6-month follow-up period, 57.9% of patients showed a poor prognosis (mRS: ≥3), while 42.1% showed a good prognosis (mRS: <3). The mortality rate over the first 30 days was significantly higher in patients with a low Glasgow Coma Scale (GCS) score at admission, a large hematoma volume, and ventricular extension of the hemorrhage (p=0.0001). In the poor prognosis group, the presence of moderate depression (39.13%) was significantly higher than in the good prognosis group (p=0.0001).

A KOCKÁZATI TÉNYEZŐK ÉS A PROGNÓZIS KÖZÖTTI KAPCSOLAT ELEMZÉSE INTRACEREBRALIS VÉRZÉST KÖVETŐEN

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Ideggyogy Sz 2017;70(1–2):33–41.

Célkitűzés – A betegeket az alábbiak szerint értékeltük: kockázati tényezők, a haematoma mérete és lokalizációja, a spontán intracerebralis haematoma (ICH) hatása a mortalitásra, a morbiditásra és a post-stroke depresszióra.
Betegek és módszerek – A vizsgálat 216, ICH-t szenvedett beteg demográfiai adatait, kockázati tényezőit és neurológiai vizsgálati eredményeit elemezte. A haematoma diagnózisát, méretét, lokalizációját és kamrai kiterjedését CT-vizsgálattal határoztuk meg. Az első 30-on belüli mortalitási arányt az ICH-pontszám és az ICH súlyossági skála alapján értékeltük. A módosított Rankin-skálát (mRS) alkalmaztuk minden betegnél a függőségi állapot és a funkcionális javulás meghatározásához, a pszichoszociális állapot megítéléséhez pedig a Hamilton-féle Depresszió Skálát.
Eredmények – A betegek átlagos életkora 65,3±14,5 év volt. Az ICH leggyakrabban az alábbi lokalizációkban volt jelen: lobaris (28,3%), thalamicus (26,4%), basalis ganglionbeli (24,0%), kisagyi (13,9%), agytörzsi (7,4%). A haematomák átlagos volumene 15,8±23,8 cm^3 volt, a haematoma a betegek 34,4%-ánál terjedt ki a kamrára. Középvonali struktúrák eltolódása a betegek 28,7%-ánál, haematoma körüli oedema pedig, mint a leggyakrabban előforduló szövődmény, 27,8%-uknál. A hat hónapos követési időszak alatt a betegek 57,9%-a esetében bizonyult kedvezőtlennek a prognózis (mRS≥3), kedvező prognózist (mRS<3) pedig 42,1%-nál észleltünk. Az első 30 napra vonatkozó mortalitási arány szignifikánsan magasabb volt a felvételkor kis GCS (Glasgow Coma Scale) -pontszámú betegek esetében, továbbá nagy haematomavolumen és kamrai kiterjedés esetén (p=0,0001). A kedvezőtlen prognózisú csoportban a közepes erősségű depresszió szignifikánsan gyakrabban fordult elő (39,13%), mint a kedvező prognózisúak csoportjában (p=0,0001).

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Érkezett: 2015. július 8. Elfogadva: 2015. november 24.

Conclusion – Determination and evaluation of the factors that could influence the prognosis and mortality of patients with ICH is crucial for the achievement of more effective patient management and improved quality of life.

Keywords: *intracerebral hemorrhage, risk factors, prognosis, mortality, post-stroke depression*

Következtetés – Intracerebralis haematoma esetén a prognózist és a mortalitást befolyásolni képes faktorok meghatározása és értékelése döntő fontosságú a hatékonyabb betegellátás és a jobb életminőség eléréséhez.

Kulcsszavak: *intracerebralis vérzés, kockázati tényezők, prognózis, mortalitás, post-stroke depresszió*

After heart disease and cancer, stroke is the third leading cause of death in developed countries, the second leading cause of death worldwide, and a source of long-term disability. More specifically, the mortality and morbidity rates are approximately 10-15% higher in patients with an intracerebral hemorrhage (ICH) than in those with an ischemic stroke or subarachnoid hemorrhage[1]. The incidence of ICH is reported to be 15-19/100,000 among the general population and 200/100,000 among the elderly population[2]. The main risk factors of ICH are advanced age, male sex, hypertension (HT), alcohol consumption, African or Asian heritage, low levels of low-density lipoprotein (LDL)-cholesterol and triglycerides (TG), diabetes mellitus (DM), and smoking[3]. The 30-day mortality rate of ICH patients is approximately 40-50%, while approximately 20% regain functional competence within 6 months[4, 5]. In the present study, patients with spontaneous ICH were evaluated in terms of risk factors, hematoma size and localization, the effects of ICH on mortality and morbidity rates, and post-stroke depression.

Methods

All patients included in the present study were diagnosed with spontaneous ICH in the Department of Neurology at Dr. Sadi Konuk Bakırköy Education and Research Hospital between January 2010 and February 2014. All procedures in this study were approved by the Republic of Turkey Ministry of Health and the Ethics Committee of Dr. Sadi Konuk Bakırköy Education and Research Hospital (date: 05/05/2014 and decision #: 2014/07/29).

Patients diagnosed with ICH after a review of their medical history and undergoing neurological and neuroradiological examinations were eligible for inclusion in the present study. Patients with subarachnoid hemorrhage, epidural or subdural hematom, and bleeding from an arteriovenous malformation were excluded, because they were followed in neurosurgery clinics. A diagnosis of hemorrhagic stroke such as a vasculitis, a trauma, a coagulopathy or a tumor were excluded.

Information regarding the age, gender, history of HT, history of DM, presence of chronic renal failure (CRF), smoking, alcohol consumption, antiplatelet and/or oral anticoagulant (OAC) use, medical history, and neurological examinations were obtained from the files of each patient. Additionally, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and blood glucose levels were recorded at the time of admission. Because this was a retrospective study, some patient files did not include data regarding alcohol consumption or hyperlipidemia, and thus, only recorded values were evaluated. These data may have been lost due to the fact that when ICH patients worsen during the early stages of their disorder, they may be transferred to other clinics. On the other hand, if they are transferred to the intensive care unit within the same hospital, the data are usually saved.

The National Institutes of Health (NIH) scoring system for neurological status was used to determine the state of each patient upon admission. Cranial computed tomography (CT) scans were used to obtain radiological images, from which the localization, volume, and the presence or lack of ventricular expansion were recorded. Control CT scans were taken at the first week (±1 day) of the stroke if possible. The localizations of the hemorrhages were categorized into five groups: basal ganglia, thalamus, lobar, brainstem, and cerebellum. To calculate the volume of the hematomas, a majority of the mass (A) and the length (B) of the lesions were assessed using the cranial CT sections in which height could be determined (C); these values were multiplied and then divided by 2 [(A×B×C)/2]. If bleeding was present, the volume was classified as either small (<10 cm³), medium (10–30 cm³), large (30–60 cm³), or very large (>60 cm³). To determine the initial 30-day mortality rate of the patients, the ICH score and the ICH grading

scale (ICH-GS) were used[6, 7]. To evaluate the prognosis of each patient after 6 months, they were contacted by telephone and asked to come to the hospital for reassessment in an outpatient setting. If the patient had died or could not come to the hospital, their information was obtained over the phone. The dependency status and functional recovery of each patient were evaluated using the Modified Rankin Scale (mRS), for which a score of <3 is considered to be a good prognosis and a score of ≥3 a poor prognosis. The Hamilton Depression Rating Scale was administered to patients to evaluate the influence of ICH on the psychosocial status of each patient control 6-month later[8].

DATA ANALYSIS

The 2007 Number Cruncher Statistical System (NCSS) software (Dr. Jerry L. Hintze Kaysville; Utah, USA) was used for all statistical analyses, and all data are represented as means± standard deviations. Independent t-tests were used to compare the two groups. Correct for the multiple comparisons with the two subsets, a Bonferroni correction. Chi-square and Fisher's exact tests were used to compare qualitative data, and receiver operating characteristic (ROC) curves were used to assess sensitivity and predictive variables. A p value <0.05 was considered to indicate statistical significance.

Results

A total of 216 patients diagnosed with spontaneous ICH were recruited from our clinics and enrolled in the present study. Of the patients, 34.3% were female (n=74), 65.7% were male (n=142), the mean age was 65.3±14.5 years, 80.6% (n=166) had HT, 18.5% (n=40) had DM, 15.3% (n=50) had hyperlipidemia, and 8.3% (n=18) had CRF. The SBP values ranged from 90 to 285 mmHg with a mean of 190.8±36.4 mmHg, and the DBP values ranged from 46 to 187 mmHg with a mean of 105.3±22.2 mmHg. At admission, the blood glucose levels of the patients ranged from 3.6 to 28 mmol/l with a mean of 8.5±3.8 mmol/l. Smoking or alcohol consumption history of 123 patients were available, and 24.4% (n=30) of them were smokers but 8.1% (n=10) had a history of alcohol consumption. Clear medical history was available for 195 and 21.5% (n=42) were using antiplatelet and 9.7% (n=19) were using OAC drugs. Of the patients using OAC drugs, the international normalized ratio (INR) values ranged from 1.2 to 6.4 with a mean of 3.70±1.79. Among the patients under OAC treatment, the rate of the patients with the INR value ≥3 was 63.2%.

The lipid profiles of the 140 patients with available data were analyzed; the LDL values ranged from 1.08 to 5.8 mmol/L with a mean of 3.2±0.9 mmol/L, the total cholesterol levels ranged from 2.8 to 8.5 mmol/L with a mean of 4.9±1.08 mmol/L, and the TG levels ranged from 0.4 to 9.4 mmol/L with a mean of 1.3±0.9 mmol/L. The LDL values were normal (≤3.4 mmol/L) in 67.1% (n=94) of the patients and high (>3.4 mmol/L) in 32.9% (n=46) of the patients.

In terms of seasonal variations, 37.7% (n=81) of the patients were admitted in the winter, 26.5% (n=57) in the spring, 21.9% (n=47) in the fall, and 13.9% (n=30) in the summer. It is important to note that more than 60% of the patients were admitted in the winter and spring. The length of hospital stay ranged from 1 to 64 days with a mean of 11.28± 10.00 days. When the locations of the hematomas were examined, 79.2% (n=171) were supratentorial, 20.8% (n=45) were infratentorial, 28.3% (n=61) were lobar hematomas, 26.4% (n=57) were thalamic hematomas, 24.0% (n=52) were basal ganglia hematomas, 13.9% (n=30) were cerebellum hematomas, and 7.4% (n=16) were brainstem hematomas. The volumes of the hematomas ranged from 0.15 to 180 cm^3 with a mean of 15.8±23.8 cm^3. When classified by volume, 58.8% (n=127) of the hematomas were small (<10 cm^3), 23.6% (n=51) were medium (10–29.9 cm^3), 12.0% (n=26) were large (30–59.9 cm^3), and 5.6% (n=12) were very large (≥60 cm^3).

The complications associated with ICH included ventricular extension of the hemorrhage in 34.4% (n=74) of patients, a midline shift in 28.7% (n=62), perihematomal edema in 27.8% (n=60), an expansion of the hematoma in 15.3% (n=33), hydrocephalus in 13.0% (n=28), seizures in 10.7% (n=23), and deep vein thrombosis (DVT) in 1.4% (n=12) of the patients.

The NIH neurological scores ranged from 1 to 30 with a mean of 10.3±7.4. The mRS scores ranged from 0 to 6, with a mean of 3.9±0.9 at admission and a mean of 3.3±2.4 at the final assessment. At the 6-month follow-up, 57.9% (n=125) of all patients had a poor prognosis (mRS: ≥3) and 42.1% (n=91) a good prognosis. Of the 125 patients with a poor prognosis, 64.8% (n=81) were male, 35.2% (n=44) were female, and the mean age was 65.70±15.4 years. Of the 91 patients with a good prognosis, 67.0% (n=61) were male, 33.0% (n=30) were female, and the mean age was 59.97±12.7 years. There was no statistically significant gender difference, but the mean age of the poor prognosis

Table 1. *The relationship between ICH risk factors and patient prognosis*

	Good prognosis n=91	Poor prognosis n=125	p
Blood glucose at admission (mmol/L)	8.1±3.5	8.9±4.1	0.139
SBP at admission (mmHg)	190±37.3	191.6±35.9	0.770
DBP at admission (mmHg)	108.5±23.5	102.7±21.0	0.085
LDL levels (mmol/L)	3.2±1.0	3.1±0.8	0.576
Cholesterol levels (mmol/L)	5.0±1.2	4.7±0.9	0.121
TG levels (mmol/L)	1.5±1.1	2.0±0.6	0.092

Table 2. *The distribution of complications according to patient prognosis*

Complications	Good prognosis n=91		Poor prognosis n=125		p
	n	%	n	%	
Ventricular extension of the hemorrhage	16	17.6	58	46.4	*0.0001*
Hematoma expansion	3	3.3	30	24.0	*0.0001*
Midline shift	8	8.8	54	43.2	*0.0001*
Perihematomal edema	15	16.5	45	36.0	*0.002*
Hydrocephalus	1	1.1	27	21.8	*0.0001*
Deep vein thrombosis	1	1.1	2	1.6	0.751
Seizures	8	8.8	15	12.0	0.450

group was significantly higher than that of the good prognosis group (p=0.003). In particular, patients over 75 years of age were more likely to have a poor prognosis (p=0.001).

There were no significant differences between the prognosis groups regarding the presence of chronic diseases such as HT, DM, hyperlipidemia, or CRF. Likewise, there were no significant differences between the prognosis groups at admission in terms of SBP, DBP, or levels of blood glucose, mean LDL, total cholesterol, and TG (**Table 1**). There were also no significant differences between the good and poor prognosis groups regarding the use of antiplatelet medications and/or OAC drugs, INR level, or seasonal admission. Although the average length of stay was longer in the poor prognosis group (12.4±12.5 days) than the good prognosis group (9.7±4.7 days), this difference was not statistically significant. Finally, there were no significant differences between the prognosis groups in terms of the localization of bleeding.

The development of a ventricular extension of the hemorrhage (p=0.0001), hematoma expansion (p=0.0001), a midline shift (p=0.0001), perihematomal edema (p=0.002), and hydrocephalus (p=0.0001) was significantly higher in the poor prognosis group (**Table 2**). The average NIH score was 5.6±3.5 in the good prognosis group and 13.8±7.6 in the poor prognosis group at the initial evaluation (p=0.0001).

When the mortality rates of all patients were examined, 19.4% (n=42) of the patients died in the first month and 16.8% (n=36) after the first month. Of those that died in the first 30 days, 69.0% (n=29) were male, 31.0% (n=13) were female, and the mean age was 59.1±16.7 years. The mean age of the patients who died was significantly higher than the mean age of those who survived (p=0.036). Of the patients who died in the first month, the mean blood glucose level was 10.1±4.3 mmol/L, the mean SBP was 202.1±25.4 mm Hg, and the mean DBP was 108.9±19.1 mm Hg; furthermore, 78.6% (n=33) of the hematomas were supratentorial and 21.4% (n=9) infratentorial. There were no significant differences in gender distribution or the localization of the hematomas between the patients who survived versus died in the first month. Of the patients who died within the first 30 days, the GCS scores of during the first admission were 12–15 in 4.8% (n=2), 5–12 in 64.3% (n=27), and 3–4 in 30.9% (n=14), and the mean hematoma volume was 37.1±35.1 cm^3. Moreover, approximately half of these patients 52,4% (n=22) had a large hematoma volume, 47,6% (n=20) had a small or medium volume is lost, and 71.4% (n=30) exhibited ventricular extension of the hemorrhage. and 71.4% (n=30) exhibited ventricular extension of the hemorrhage. The mortality rate during the first 30 days was significantly higher in patients with a low GCS score (3–4) at admission (p=0.0001), with a large

Table 3. *Mortality rate distribution during the first 30 days*

Patient demographics		First 30 days				p
		Living patients (n=174)		Deceased patients (n=42)		
		n	%	n	%	
Gender	Female	61	35.1	13	31.0	0.615
	Male	113	64.9	29	69.0	
Locations	Supratentorial	138	79.3	33	78.6	0.916
	Infratentorial	36	20.7	9	21.4	
GCS score	13–15	124	71.3	2	4.8	*0.0001*
	5–12	49	28.2	27	64.3	
	3–4	1	0.6	13	30.9	
Hematoma volume (cm^3)	0-9,9	121	69.5	6	14.3	*0.0001*
	10–29.9	37	21.3	14	33.3	
	30–59.9	11	6.3	15	35.7	
	≥60	5	2.9	7	16.7	
Ventricular extension of hemorrhage	No	130	74.7	12	28.6	*0.0001*
	Yes	44	25.3	30	71.4	

Table 4. *The relationships between ICH and ICH-GS scores with mortality and mRS scores using ROC curve values*

	Area under the ROC curve	Standard deviation	p	95% confidence interval	
ICH score-mortality	0.915	0.0222	0.0001	0.869	0.948
ICH-GS-mortality	0.863	0.0281	0.0001	0.810	0.906
ICH score-mRS admission	0.787	0.0509	0.0001	0.726	0.839
ICH-GS-mRS admission	0.745	0.0661	0.0002	0.681	0.802
ICH score-final mRS	0.810	0.0272	0.0001	0.751	0.860
ICH-GS-final mRS	0.806	0.0281	0.0001	0.747	0.856

hematoma volume (p=0.0001), and with a ventricular extension of the hemorrhage (p=0.0001; **Table 3**).

The ICH scores of all patients ranged from 0 to 4 with a mean of 1.4±1.1. During the first 30 days, all patients with an ICH score of 0 (25.5%; n=55) survived, while those with ICH scores of 1 (33.3%; n=72), 2 (21.7%, n=47), 3 (15.8%, n=34), and 4 (3.7%, n=8) had mortality rates of 4.1%, 17.0%, 67.6%, and 100%, respectively. None of the patients had ICH scores of 5 or 6. The ICH-GS scores ranged from 5 to 12 with a mean of 7.6±1.5, and all patients with ICH-GS scores of 5 or 6 survived the first 30 days. None of the patients had an ICH-GS score of 13. The relationships of the ICH and ICH-GS scores with mortality rate, mRS score at admission, and mRS score at the final assessment were determined using ROC curves. A high level of significance was observed in the mortality curve, but the curves for admission and final mRS scores showed only slight levels of significance (**Table 4**).

The predictive value of the 30-day mortality rate for the ICH score was significantly higher than that of the ICH-GS score (p=0.002), but there were no significant differences in the mRS score at admission or at the final examination.

The Hamilton Depression Rating Scale was used to evaluate the ongoing influence of ICH on the psychosocial status of each patient, and scores on this measure were employed as a control. This scale was administered to only 29.1% (n=63) of the 216 patients, because 36.1% (n=78) of the patients died and 34.7% (n=75) were uncooperative. The scores of the patients ranged from 0 to 25; 54.0% (n=34) had scores of 0–7, which indicate no depression, 25.4% (n=16) had scores of 8–15, which indicate mild depression, and 20.6% (n=13) had scores of 16–25, which indicate moderate depression. Of the female patients, 23.5% (n=4) had mild depres-

Table 5. *Relationships between Hamilton Depression Rating Scale scores and patient prognosis*

Hamilton Depression Rating Scale score	Good prognosis n=40		Poor prognosis n=23		p
	n	%	n	%	
0–7	29	72.5	5	21.8	0.0001
8–15	7	17.5	9	39.1	
16–25	4	10.0	9	9.1	

sion and 47.0% (n=8) moderate depression. Of the male patients, 26.0% (n=12) had mild depression and 10.8% (n=5) moderate depression. The presence of moderate depression was significantly higher in the poor prognosis group (39.13%, n=9) than in the good prognosis group (10.0%, n=4; p= 0.0001; **Table 5**).

Discussion

In the present study, the mean age of the patients was 65.3±14.5 years, and 71.8% (n=155) were over 55 years of age. The risk of ICH increases with advancing age which may be explained by the the increased prevalence of hypertension in older individuals[3, 9]. Additionally, several studies have identified male sex and age >55 years as risk factors for spontaneous ICH[3, 10]. In agreement with these findings, 34.3% of the patients in the present study were female (n=74), and 65.7% were male (n=142). HT is also a major risk factor of ICH and is present in 72–81% of patients with ICH; in the present study, 80.6% (n=174) of patients had HT[3, 11]). DM was present in 18.5% (n=40) of the patients in the present study, but there was no significant relationship observed between DM and ICH. *Woodward* et al. reported that DM is associated with an increased risk of ICH, but other studies did not find DM to be a risk factor[3, 12, 13].

In recent studies, cholesterol levels were found to reduce the overall incidence of stroke despite a small increase in the incidence of ICH. Furthermore, previous studies have shown that LDL cholesterol, total cholesterol, and TG levels are inversely related to the risks of ICH, mortality, and hematoma growth. It has been demonstrated that low cholesterol and TG levels weaken the endothelium and lead to arterial fragility, hemorrhages, and small hemorrhages, which in turn are associated with slow healing[14–16]. In the present study, the mean LDL level was 3.2±0.9 mmol/L, the mean total cholesterol level was 4.9±1.08 mmol/L, and the mean TG level was 1.3±0.9 mmol/L; these values did not affect hyperlipidemia. Additionally, 67.1% of the patients in the present study had LDL values ≤3.4 mmol/L and 32.9% (n=71) LDL levels >3.4 mmol/L.

Previous studies have reported that 90% of hematomas are supratentorial and 10% infratentorial, and the most common type of hematoma is a basal ganglia hematoma[17]. Of all patients in the present study, 79.2% (n=171) had supratentorial hematomas, and the most common type of ICH was a lobar hematoma. This discrepancy in terms of location may be explained by the fact that patients with large basal ganglia hematomas are more likely to be referred to the intensive care unit due to a poor general state of health.

ICH lesions generally occur more often in the winter, which may be explained by the increase in blood pressure that results from exposure to the cold. Patel et al. reported a trend towards an increased incidence of ICH during the winter and spring seasons, but this did not achieve statistical significance nor was there an impact on the mortality of the 253 ICH patients in that study[18]. In the present study, 37.7% (n=81) of the patients were admitted in winter and 26.5% (n=57) in spring.

The present study also assessed mortality rates within the first 30 days after admission for spontaneous ICH. The factors that influenced the prognoses of the patients were evaluated, and the patients who had survived 6 months were compared with those who had died during the first 30 days. Furthermore, the mRS scores were used to determine which patients had a good versus poor prognosis. Although the present study did not find a significant difference between genders in terms of prognosis, previous studies have identified differences among female patients in terms of prognosis[19–21]. In the present study, the mean age of the poor prognosis group was significantly higher than that of the good prognosis group; in particular, patients over 75 years of age were more likely to have a poor prognosis. The mean age of the patients who died during the first 30 days was significantly higher than that of those who survived to 6 months. Thus, it appears that advanced age is a factor that contributes to a poor prognosis; this has been demonstrated by several previous studies[2, 22].

Hyperglycemia develops after the occurrence of ICH in approximately 60% of patients. The development of hyperglycemia increases the risks of mortality and poor outcome in both non-diabetic and diabetic patients with ICH, as well as exacerbates brain edema and perihematomal cell death after ICH[23, 24]. In a study of 100 ICH patients, the mean blood glucose level during the first 14 days was 205 mg/dL in those who died and 131 mg/dL in those who survived[25]. Those authors reported that a plasma glucose level > 150 mg/dL is an independent risk factor of early death in ICH patients. In that study, the mean blood glucose levels of the patients who died within the first 30 days were higher than those who did not; however, no significant differences were observed in the blood glucose levels between the prognosis groups in the present study.

Hematoma expansion, perihematomal edema, and ventricular extension of a hemorrhage are common and serious complications of ICH that influence the prognosis of a patient as well as increase mortality rate[26–28]. In the present study, hematoma expansion, perihematomal edema, midline shift, ventricular extension of a hemorrhage, and hydrocephalus were factors that predicted a poor prognosis and risk of an early death. In particular, the presence of a very large lesion (≥ 60 cm^3 volume) was associated with a high rate of mortality during the first 30 days. *Tuhrim* et al. suggested that if the volume of a hematoma exceeds 30 cm^3, the risk of mortality increases[29].

Various scales are available to identify ICH patients likely to have a poor outcome. The most commonly used scale, the ICH score, is a simple model developed by *Hemphill* et al.[6]. Factors independently associated with the 30-day mortality rate include GCS score, age ≥80 years, infratentorial origin of an ICH, ICH volume, and presence of an intraventricular hemorrhage[6]. The ICH score has been validated in several Asian countries including Taiwan and Malaysia[30, 31]. *Yousuf* et al. demonstrated that a low GCS score, bleeding in the posterior fossa, a hematoma volume >60 ml, and intraventricular hemorrhages are significant independent predictors of mortality in ICH patients; these factors are consistent with the parameters of the ICH score[32]. In the present study, a higher ICH score was associated with an increased mortality rate, as patients with an ICH score of 4 had a mortality rate of 100%, and the prediction rate of the ICH score for 30-day mortality was significantly higher.

The ICH-GS, developed by *Ruiz-Sandoval* et al. uses the same parameters as the ICH score but with different assigned points and cutoff values[7]. Relative to the ICH score, the ICH-GS has a higher sensitivity for predicting in-hospital and 30-day mortality rates, and it performed equally well when predicting good functional outcomes at the 30-day follow-up visit. According to the ICH-GS, the factors associated with mortality are age > 65 years, a GCS score at hospital admission <8, a ICH volume > 70 ml, the presence of an intraventricular hemorrhage, and infratentorial hematomas[7]. The different scoring systems and cutoff values substantially improve the prognostic power of the predictors[7]. However, in the present study, the ICH score was a significantly better predictor of the 30-day mortality compared with the ICH-GS score (p=0.002).

In the present study, the relationships of the ICH and ICH-GS scores with mortality were highly significant, but there was only a slight significance with the mRS score at admission and 6 months. Additionally, there was no significant difference between the mRS scores at admission and at 6 months. *Wang* et al. compared mRS scores between these two time points to determine their prognostic value and found that both the ICH score and the ICH-GS were inaccurate when predicting favorable short-term and long-term outcomes. However, when predicting 6- and 12-month outcomes, the ICH-GS score was significantly better than the ICH score[33].

The prevalence of post-stroke depression is approximately 25–79%. *Paolucci* et al. observed post-stroke depression in 36% of survivors, and suggested that a mRS score of 3 (poor prognosis) and female sex facilitate the development of this disorder[34]. In a Brazilian study from 2009, 28.8% of post-stroke patients (age range: 19–79 years) had experienced a major depressive episode[35]. In the present study, mild-to-moderate depression was observed in approximately half (46%) of the patients evaluated for a mood disorder. Moreover, similar to previous studies, females and patients in the poor prognosis group had a greater incidence of depression[34].

Several limitations of this study have to be considered. Because this was a retrospective study, some patient files did not include data regarding smoking, alcohol consumption or hyperlipidemia, and thus, only recorded values were evaluated. Hamilton Depression Rating Scale was not applied in a certain time period, it was applied at any time that 6-six month later. Subarachnoid hemorrhage patients were not included the study since they are followed up in neurosurgery clinics and we could not have their data.

In conclusion, a greater knowledge of the risk factors and preventative measures associated with the prognoses of ICH patients will allow for more

effective patient management and reductions in their mortality and morbidity rates. Additionally, the present findings demonstrate that the psychosocial status of an ICH patient is important when determining quality of life, status management, and rehabilitation.

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SYMPTOM PROFILES AND PARENTAL BONDING IN HOMICIDAL VERSUS NON-VIOLENT MALE SCHIZOPHRENIA PATIENTS

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0043 | www.elitmed.hu

Objective – To compare the intensity and the profile of psychotic symptoms and the characteristics of parental bonding of male schizophrenia patients with a history of homicide and those without a history of violent behaviour.
Clinical question – We hypothesized more intense psychotic symptoms, especially positive symptoms as signs of a more severe psychopathology in the background of homicidal behaviour. We also hypothesized a more negatively perceived pattern (less Care more Overprotection) of parental bonding in the case of homicidal schizophrenia patients than in non-violent patients and non-violent healthy controls.
Method and subjects – Symptom severity and symptom profiles were assessed with the Positive and Negative Syndrome Scale in a group of male schizophrenia patients (n=22) with the history of committed or attempted homicide, and another group (n=19) of male schizophrenia patients without a history of violent behaviour. Care- and Overprotection were assessed using the Parental Bonding Instrument (PBI) in a third group of non-violent healthy controls (n=20), too.
Results – Positive, negative and general psychopathology symptoms in the homicidal schizophrenia group were significantly ($p<0.005$) more severe than in the non-violent schizophrenia group. Non-violent schizophrenia patients scored lower on Care and higher on Overprotection than violent patients and healthy controls. Homicidal schizophrenia patients showed a pattern similar to the one in the healthy control group.

A TÜNETI PROFIL ÉS A SZÜLŐI BÁNÁSMÓD AZ EMBERÖLÉST ELKÖVETETT ÉS A NEM ERŐSZAKOS SZKIZOFRÉN BETEGEK CSOPORTJAINÁL
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Ideggyogy Sz 2017;70(1–2):43–52.

Célkitűzés – Összehasonlítani a pszichotikus tünetek intenzitását és profilját, valamint a szülői bánásmód jellegzetességeit az emberölést elkövetett és a nem erőszakos szkizofrén betegek csoportjainál.
Kérdésfeltevés – Hipotézisünk az volt, hogy az emberölés hátterében intenzívebb pszichotikus tünetek, elsősorban intenzívebb pozitív tünetek állnak, amelyek súlyosabb pszichopatológia jelzései. További feltevésünk az volt, hogy az emberölést elkövetett betegek a szülői bánásmód kedvezőtlenebb mintázatát mutatják, mint a nem erőszakos betegek, illetve nem erőszakos, egészséges kontrollszemélyek.
Módszer és vizsgálati személyek – A tünetek erősségét és a tüneti profilt a Pozitív és Negatív Tünetskála (Positive and Negative Syndrome Scale, PANSS) segítségével mértük olyan, szkizofréniával diagnosztizált férfi betegeknél (n=22), akik emberölést, vagy annak kísérletét követték el, illetve szkizofrén férfi betegek illesztett mintáján (n=19), akiknek előzményeiben nem szerepelt erőszakos viselkedés. A törődést, illetve a túlvédést a Szülői Bánásmód Kérdőív (Parental Bonding Instrument, PBI) magyar változatával (H-PBI) vizsgáltuk a két betegcsoport tagjainál, valamint nem erőszakos, egészséges kontrollszemélyeknél (n=20).
Eredmények – Mind a pozitív, mind a negatív, mind az általános pszichopatológia-pontszámok magasabbak voltak az emberölést elkövetett, illetve azt megkísérelt szkizofrén betegek csoportjában, mint a nem erőszakos betegeknél. A nem erőszakos szkizofrén betegek alacsonyabb törődés- és magasabb túlvédéspontszámmal a szülői bánásmód ked-

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Érkezett: 2016. szeptember 6. Elfogadva: 2016. november 22.

Conclusions – It seems imperative to register intense positive psychotic symptoms as predictive markers for later violent behaviour. In the subgroup of male homicidal schizophrenia patients negatively experienced parental bonding does not appear to be major contributing factor to later homicidal behaviour.

Keywords: *schizophrenia, homicide, parental bonding, symptom severity*

vezőtlenebbnek tekinthető mintázatát mutatták, mint az emberölést elkövetett csoport tagjai és a nem erőszakos egészséges kontrollszemélyek. Az utóbbi két csoport tagjai hasonló szülői bánásmódról számoltak be.
Következtetések – Az intenzív pszichotikus tüneteket fontos a későbbi erőszakos viselkedés lehetséges előre jelző markereiként regisztrálnunk. Az emberölést elkövetett szkizofrén férfi betegek nem számolnak be negatív szülői bánásmódról, így ebben a csoportban ez nem feltétlenül a súlyosan erőszakos viselkedést elősegítő tényező.

Kulcsszavak: *szkizofrénia, emberölés, szülői bánásmód, a tünetek súlyossága*

Introduction

SCHIZOPHRENIA PATIENTS WITH A HISTORY OF HOMICIDE: CLINICAL CHARACTERISTICS

Previous studies have explored a number of clinical characteristics of schizophrenia patients with a history of homicide, including symptom profile, biological markers and a number of comorbid factors. The characteristics of attachment and parental bonding, on the other hand, have not been explored in the subsample of homicidal schizophrenia patients. The objective of our study was to investigate the characteristics of parental bonding and secondly, to assess symptom severity and symptom profile in this special subgroup. Our results contribute to the understanding of the underlying factors of homicidal behaviour in psychotic patients.

Previous studies[1, 2] have found paranoid and other positive psychotic symptoms to be more frequent and more severe in homicidal schizophrenia patients compared to non-violent ones. Also, hostility as measured by the Positive and Negative Syndrome Scale (PANSS) has been found to be significantly correlated with severely violent behaviour[3].

There are a number of possible associations between the presence of psychotic symptoms and committing a severely violent crime like homicide. The association is frequently not causal and the correlation between the diagnosis of a psychotic disorder and the rate of violent crime varies within a wide range. In a recent study, *Skeem* et al.[4] found that psychotic symptoms immediately preceded only some 12% of the incidents among violent offenders with a mental illness. Also, only some 20% of mentally ill offenders had some psychosis-preceded violence, while 80% had exclusively non-psychotic preceded violence.

In a review following a predictive approach[5], we argued for the need to address possible predictive factors of later violent behaviour in psychotic patients, including heightened impulsivity and deficits in executive functions.

PARENTAL BONDING CHARACTERISTICS OF SCHIZOPHRENIA PATIENTS

Parental bonding describes the attitudes and behaviours in the emotional relationship between the parent and the child. One aspect of this relationship is the bonding experienced by the child. Negatively experienced parental bonding has been shown to be a contributing factor in the etiology of several psychiatric disorders. The role of parental bonding in the etiology of psychotic disorders, on the other hand, has long been neglected in favour of the dominant biogenetic paradigm.

Comparing the self-report parental bonding profiles of patients diagnosed with schizophrenia, borderline personality disorder (BPD) and non-clinical control subjects, no significant differences were found between the two clinical groups, with a low Care-high Overprotection pattern in both[6]. *Gomes* et al.[7] compared the parental bonding characteristics of patients with schizophrenia and bipolar disorder (BD) as well as healthy controls. Schizophrenia patients scored higher than BD-patients on maternal and paternal Care. On maternal care, interestingly, schizophrenia patients also scored higher than healthy controls. BD-patients had lower Care-scores in both maternal and paternal domains than schizophrenia patients and healthy controls. BD-patients had significantly higher Overprotection-scores in both maternal and paternal domains than schizophrenia patients and healthy subjects. No difference was found between the Overprotection-scores of schizophrenia patients and healthy con-

trols[7]. *Willinger* et al.[8] explored maternal bonding in schizophrenic and schizo-affective patients as well as their same-sex, healthy siblings. Premorbid personality traits were assessed by the mothers of the patients on both their schizophrenic/schizo-affective children and their healthy siblings. Patients described their mothers as less caring and more overprotective than their healthy siblings did. Mothers described their schizophrenic/schizoaffective children as having less social resonance, less permeability (social accessibility), less social competence and more frequently being in a depressed and anxious mood than their healthy siblings. The authors found significant correlations between maternal bonding scores and premorbid personality traits assessed by the mothers of the patients.

In summary, studies exploring parental bonding in the case of schizophrenia patients have yielded conflicting results. It remains questionable if a distinctive pattern of bonding (characterized, as some studies suggest, by lower Care and higher Overprotection) can be determined in this patient group.

Studies investigating characteristics of the early parent-child relationship in samples of non-psychotic violent offenders suggest a more frequent and more severe traumatisation, especially frequent physical abuse, in early childhood than in the case of non-violent (and non-psychotic) subjects[9].

OBJECTIVES OF OUR STUDY

In our study, we assessed the intensity of psychotic symptoms as well as the components of Care and Overprotection in parental bonding in a sample of male schizophrenia patients with the history of committed or attempted homicide and in a sample of matched male schizophrenia patients with no history of violent behaviour. Care and Overprotection were also assessed in a third group of matched male control subjects with no history of psychiatric disorders or violent behaviour.

We hypothesized that homicidal behaviour in the sample of schizophrenia patients is an indication of more severe psychopathology. We therefore expected more intense positive psychotic symptoms in homicidal schizophrenia patients than in non-violent patients. Our second hypothesis was that more severe psychopathology in homicidal patients is correlated with lower perceived parental Care and higher Overprotection as compared to non-violent schizophrenia patients and non-violent healthy controls. This pattern indicates a more negatively perceived parental bonding in the subsample of homicidal schizophrenia patients.

Method

SUBJECTS

Altogether 41 male schizophrenia patients and 20 matched male control subjects with no history of violent behaviour or psychiatric treatment or diagnosis participated in our study. We only included male subjects since the sample of homicidal schizophrenia patients available for the study consisted in over 90% of men. We only included subjects with the diagnosis of schizophrenia established in previous clinical records by a registered psychiatrist. We had an independent clinician trained in the use of the Positive and Negative Symptom Scale (PANSS) conduct a clinical interview to confirm the diagnosis. Schizophrenia patients were subdivided into two groups. The first group (SCH-HOM, n=22) consisted of male individuals diagnosed with schizophrenia with a history of committed or attempted homicide. They were committed to the Institute of Forensic Psychiatry (Igazságügyi Megfigyelő és Elmegyógyító Intézet, IMEI) in Budapest where they received involuntary psychiatric treatment. Mean age in this group was 37.6 years (SD=8.27). 14 subjects (63.6%) had elementary education (elementary education consists of eight years of elementary school in Hungary), six (27.3%) had secondary education and two subjects (9%) had a university degree. six (27.2%) homicidal patients murdered or attempted to murder a family member.

The second group (SCH-nonHOM, n=19) consisted of male subjects diagnosed with schizophrenia with no history of violent behaviour treated in the Department for Psychiatry and Psychotherapy at the University of Pécs. Mean age in this group was 39.4 years (SD=7.80). 11 subjects (55%) had elementary education, seven (35%) had secondary education, while two subjects (10%) had a university degree.

Table 1 describes the mean age, the duration of illness, the duration of hospitalization of the members of the two schizophrenia patient groups as well as the number of psychotic episodes reported prior to their current hospitalisation. In 'Duration of illness', we indicated the time period between the first recorded diagnosis of current psychiatric illness and the conduction of the interview. In 'Duration of hospitalization', we indicated the time period between the start of current psychiatric treatment and the conduction of the interview. As seen in **Table 1**, non-violent schizophrenia patients had a significantly longer history of illness and hospitalization than homicidal patients. We found no significant differences on the other variables.

Table 1. *Mean age, duration of illness and duration of hospitalization in the homicidal and the non-violent schizophrenia group*

	SCH-HOM mean (SD)	SCH-nonHOM mean (SD)
Age	37.60 (4.62)	39.40 (3.88)
Duration of illness (month)	36.51 (7.67)	42.42 (6.51)*
Duration of hospitalization (month)	3.1 (2.73)	4.3 (3.45)*
Number of psychotic episodes prior to hospitalization mean)	1.3 (3.34)	1.1 (2.46)

*$p<0.05$

Table 2. *Clinical characteristics of the homicidal and the non-violent schizophrenia group*

	SCH-HOM mean (SD)	SCH-nonHOM mean (SD)
Age at the onset of schizophrenia (years)	22.5 (3.84)	24.7 (4.02)
History of comorbid substance abuse (%)	45.45 (3.61)	40.00 (2.59)
Family history of diagnosed psychiatric disorder (%)	59.09 (4.67)	55.00 (2.85)
History of childhood abuse (%)	11.63 (6.88)	10.00 (5.27)

Further relevant clinical characteristics of our subjects included age at the onset of the illness, a family history of psychiatric disorder as well as a history of childhood abuse as reported retrospectively by the subjects themselves. These clinical data are based on interviews conducted for our study during their current hospitalisation. **Table 2** shows that there were no significant differences between the members of the two schizophrenia groups regarding any of these clinical variables.

The third group (NORM, n=20) consisted of healthy, non-violent male control individuals matched to the first two groups by age (mean 37.8 years, SD=4.9) and education (11, 55% had elementary education, 6, 30% had secondary education and 3, 15% had a university degree). In a questionnaire assessing socio-demographic data, subjects were asked about a history of psychiatric illness, treatment in a psychiatric institution as well as criminal records or problems in connection to violent behaviour in their past. We excluded subjects with a history of psychiatric illness, psychiatric treatment or violent behaviour. Control subjects were recruited through advertisements published at the University of Pécs with a short description of the study. The study was carried out in accordance with the latest version of the Declaration of Helsinki and was evaluated following institutional ethical guidelines adopted by the University of Pécs and approved by the local ethical committee. All subjects gave informed consent.

The relatively small number of subjects is due to the limited number of available patients (we excluded patients in a severe acute psychotic state due to their inability to complete the test battery). Also, it was difficult to match the members of the two schizophrenia groups on a number of variables (sex, age, education, diagnosis, duration of illness, duration of hospitalization).

Antipsychotic medication

Antipsychotic medication received prior to and at the time of the study may significantly impact on symptom severity and symptom profile. Matching the antipsychotic medication received by the members of the two schizophrenia groups was not possible due to different guidelines and treatment protocols applied for homicidal versus non-violent schizophrenia patients in their respective institutes. In **Table 3**, we described the antipsychotic medication received by subjects at the time the interview was conducted. "Monotherapy typical" means one type typical antipsychotic medication administered, "monotherapy atypical" means one type atypical antipsychotic medication administered and "polytherapy" means a combination of different typical and atypical antipsychotic medication administered simultaneously. As shown in **Table 3**, typical antipsychotic medication in monotherapy was the dominant treatment for the members of the SCH-HOM group, with about one third receiving polytherapy. Patients in the SCH-nonHOM group were much more likely to receive atypical antipsychotics in monotherapy, with roughly one third involved in

Table 3. *Antipsychotic medication received by the homicidal and the non-violent schizophrenia group during their current treatment*

	SCH-HOM n=22	SCH-nonHOM n=19	Total n=41
Monotherapy typical	15 (68.18%)	3 (15.78%)*	18 (43.90%)
Monotherapy atypical	0 (0%)	11 (57.89%)*	11 (26.83%)
Polytherapy	7 (31.81%)	6 (31.58%)	13 (34.15%)

*$p<0.05$

polytherapy and some 15% in typical antipsychotics in monotherapy.

INSTRUMENTS

We used the Positive and Negative Syndrome Scale (PANSS, 10) to measure the intensity of positive, negative and general psychopathology symptoms of schizophrenia. Unfortunately, raters of the PANSS were not blind to the history of homicide since the evaluation for homicidal patients could only be carried out at the forensic psychiatry unit of the IMEI.

For the assessment of parental bonding, we used the Hungarian version (Szülői Bánásmód Kérdőív, H-PBI[11] of the Parental Bonding Instrument (PBI)[12] in the three groups. The PBI is a self-administered questionnaire that assesses maternal and paternal behaviours and attitudes as experienced by the child in the first 16 years of life. It consists of two scales: Care vs Rejection and Overprotection vs Encouragement of Autonomy/Independence. On the positive end of the Care-Rejection axis we can find a parental attitude and behaviour that is warm, loving, empathic and resonant to the needs of the child, while the attitude and behaviour at the other end can be described as cold, omissive and indifferent. On the dimension of Overprotection vs Encouragement of Autonomy/Independence, the overprotective end stands for an intrusive, infantilizing and controlling parental behaviour. The other end represents a respectful and accepting attitude, encouraging the growth and the autonomy of the child. The H-PBI has been shown to be a reliable (test-retest Pearson coefficients between 0.88 and 0.93 on the three scales for both parents) and valid tool to assess subjects' perception of parental bonding in a Hungarian sample of some 179 subjects[11].

Due to the treatment protocol applied in the IMEI, it was not possible to administer the PBI immediately after the act of homicide but only after antipsychotic medication had been started. This means, our results on the PBI reflect a state when the psychotic symptoms of subjects had been, at least to a certain degree, controlled by antipsychotic medication.

Parental ratings of bonding and their connection to self-ratings of our subjects would have been of great relevance. Unfortunately, we were able to contact only 11 parents (26.80%), nine of whom (21.90%) gave their consent to participating in the study. Of these nine, only two (4.76%) parents completed the entire battery of questionnaires. Based on these facts, we decided to leave out this source of information.

STATISTICAL ANALYSES

We used Kruskal-Wallis analysis of variance between the three groups and the Tukey HSD-test for the post hoc comparisons of two groups where differences were significant. Statistical analyses were carried out using STATISTICA Version 10.0.

Results

INTENSITY OF PSYCHOTIC SYMPTOMS AND SYMPTOM PROFILES

Figure 1 shows the significant differences on all three subscales of the PANSS between the homicidal and the non-violent patient groups, including the Positive Scale (p=0.000143, mean SCH-HOM=32.44, SD=6.33, mean SCH-nonHOM= 23.04, SD=7.36), the Negative Scale (p=0.000435 mean SCH-HOM=32.87, SD=4.51, mean SCH-nonHOM=25.75, SD=6.89), and the General Psychopathology Scale (p=0.002575, mean SCH-HOM=66.37, SD=9.11, mean SCH-nonHOM= 55.07 SD=13.39). Confirming our hypothesis, members of the homicidal group scored significantly higher on all three subscales than members of the non-violent schizophrenia group. As seen in **Figure 2**, we found the largest difference between the scores of the two groups on the items Delusions (p=0.000132), Suspiciousness/persecution (p=

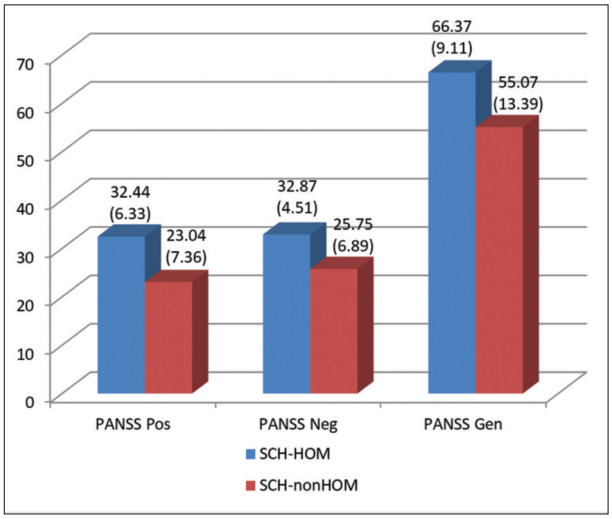

Figure 1. *Symptom profiles, symptom severity in the homicidal and the non-violent schizophrenia group – PANSS Scales*

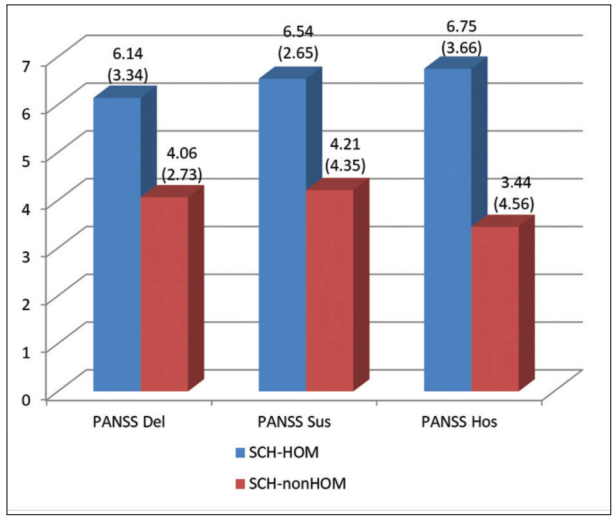

Figure 2. *Symptom profiles, symptom severity in the homicidal and the non-violent schizophrenia group – PANSS Items*

Table 4. *Symptom profiles, symptom severity in the homicidal and the non-violent schizophrenia group*

	SCH-HOM n=22 mean (SD)	SCH-nonHOM n=19 mean (SD)	F	dF	p
PANSS Positive Scale	32.44 (6.33)	*23.04 (7.36)*	*17.68*	*40*	*0.00014*
PANSS Negative Scale	32.87 (4.51)	*25.75 (6.89)*	*14.71*	*40*	*0.00044*
PANSS General Psychopathology Scale	66.37 (9.11)	*55.07 (13.39)*	*10.34*	*40*	*0.00257*
PANSS Delusions	6.14 (3.34)	*4.06 (2.73)*	*9.67*	*40*	*0.00013*
PANSS Susp/persec	6.54 (2.65)	*4.21 (4.35)*	*11.65*	*40*	*0.00097*
PANSS Hostility	6.75 (3.66)	*3.44 (4.56)*	*10.67*	*40*	*0.00071*

0.00097) and Hostility (p=0.00071). (See detailed results in **Table 4**).

PARENTAL BONDING

We administered separate questionnaires for the mothers and for the fathers of our subjects.

In the case of paternal bonding, we found no significant differences on any scale or item between the members of the three groups.

Figure 3 shows all significant differences in maternal bonding between the members of the three groups on the scales Care (p=0.001077) and Overprotection (p=0.030936, as well as on items 1 (*Spoke to me in a warm and friendly voice*, p= 0.0041), 4 (*Seemed emotionally cold to me*, p= 0.0009), 5 (*Appeared to understand my problems and worries*, p=0.0034), 6 (*Was affectionate to me*, p=0.0063), 8 (*Did not want me to grow up*, p=0.016), 9 (*Tried to control everything I did*,

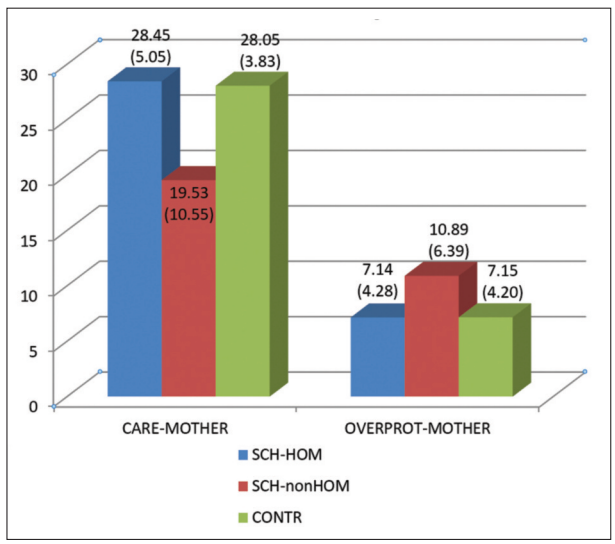

Figure 3. *Care- and Overprotection scores in the homicidal vs non-violent schizophrenia vs healthy control group*

Table 5. *Care- and Overprotection scores in the homicidal vs non-violent schizophrenia vs normal control group*

	SCH-HOM (n=22) mean (SD)	Sch-nonHOM (n=19) mean (SD)	NORM (n=20) mean (SD)	F	dF	p
Care_Mother	28.45 (5.05)	19.53 (10.55)	28.05 (3.83)	14.71	59	0.001077
Overprot_Mother	7.14 (4.28)	10.89 (6.39)	7.15 (4.20)	5.01	59	0.030936

Table 6. *Effect sizes between the two schizophrenia groups for symptom severity and between the three groups for paternal and maternal Care- and Overprotection-scores*

	d Cohen	Glass, d	Confid interval (95%)
PANSS Pos Scale	–0.291	–0.272	–0.899–0.317
PANSS Neg Scale	–0.343	–0.290	–0.959–0.266
PANSS Gen Psychopath Scale	–0.175	–0.149	–0.781–0.431
Care_Paternal	–0.224	–0.217	–0.831–0.383
Overprot_Paternal	–0.388	–0.382	–0.998–0.223
Care_Maternal	–0.242	–0.190	–0.89–0.365
Overprot_Maternal	–0.368	–0.313	–0.978–0.242

p=0.0042), 11 (*Enjoyed talking things over with me*, p=0.00083), 12 (*Frequently smiled at me*, p=0.0015), 14 (*Did not seem to understand what I needed or wanted*, p=0.0013), 16 (*Made me feel I wasn't wanted*, p=0.00013), 17 (*Could make me feel better when I was upset*, p=0.042), 18 (*Did not talk with me very much*, p=0.0046), 19 (*Tried to make me feel dependent on her/him*, p=0.00095), 20 (*Felt I could not look after myself unless she/he was around*, p=0.021), 24 (*Did not praise me*, p=0.00012). On all of the above mentioned items, members of the non-violent schizophrenia group gave significantly lower Care- (items 1, 2, 4, 5, 6, 11, 12, 14, 16, 17, 18 and 24) and significantly higher Overprotection-scores (items 8, 9, 19 and 20) than members of the other two groups. There were no significant differences between the scores of homicidal schizophrenia patients and normal controls on any of the above listed items. The subgroup of homicidal patients who murdered or attempted to murder a family member (n=6), scored significantly higher on Care (p=0.00098) and lower on Overprotection than the total homicidal group (p=0.00125) and higher on Care (p=0.00091) and lower on Overprotection (p=0.0011) than the non-violent schizophrenia group and the control group.

Non-violent schizophrenia patients (the SCH-nonHOM group) scored significantly lower on the maternal Care scale (mean=19.53, SD=10.55) than homicidal schizophrenia patients (mean=28.45, SD=5.05), and normal controls (mean=28.05, SD=3.83). There was no significant difference between the scores of homicidal schizophrenia patients and normal controls. Similarly, on the scale of maternal Overprotection, non-violent schizophrenia patients scored significantly higher (mean=10.89, SD=6.39), than homicidal schizophrenia patients (mean=7.14, SD=4.28) and normal controls (mean=7.15, SD=4.20). We found no significant differences between the scores of homicidal schizophrenia patients and normal controls. (See detailed results in **Table 5**).

We indicated effect sizes between the two schizophrenia groups for symptom severity and between the three groups for paternal and maternal Care and Overprotection scales in **Table 6**.

Discussion and conclusions

SEVERITY OF PSYCHOTIC SYMPTOMS AND SYMPTOM PROFILE

Confirming our hypothesis, we found significantly higher scores on the scales of positive and negative psychotic symptoms as well as general psychopathology in the members of the homicidal schizophrenia group compared to non-violent schizophrenia patients.

Our results are in line with previous findings in schizophrenia research. Among psychotic symptoms, delusions, hostility and suspicious-persecutory ideation were the symptoms in which the differ-

ence between homicidal and non-violent patients were largest in our study. It is reasonable to expect that these symptoms are most closely associated with the commission or attempt of homicide in the sample of schizophrenia patients. It is, on the other hand, important to note that homicidal schizophrenia patients were available to our study only after having committed a violent crime. We were not able to assess symptom profile and symptom severity before the commission of homicide. Due to the design of our study, we can establish no causal relationship between the presence of more severe symptoms and committing homicide.

There was a significant difference in the ratio of patients receiving typical, atypical antipsychotic medication and polytherapy (khi^2=19.1697, p= 0.000069). It is reasonable to expect that the differences in the medication of the two schizophrenia patient groups had a significant impact on the intensity of psychotic symptoms in the members of the two groups. Unfortunately, this difference could not be avoided for practical reasons. The treatment of the members of the two schizophrenia patient groups followed two separate guidelines and different treatment protocols in their respective institutes. Homicidal schizophrenia patients were in most cases treated with typical antipsychotics or polytherapy in the forensic psychiatry unit while non-violent schizophrenia patients had a less uniform medication protocol at their home institute. This difference must be mentioned as a limitation to our results.

PARENTAL BONDING

We found no significant differences on any scale or item of paternal bonding between the three groups. Differences in perceived paternal bonding – in case there were any – did not seem to be significantly related to homicidal behaviour in subjects with schizophrenia in our sample. This result seems counter-intuitive, since both low maternal care and low paternal overprotection has been shown to be correlated with higher psychopathy scores in adult life[13], which, in turn, is associated with violent behaviour. Negatively perceived paternal bonding (especially extremely low overprotection and supervision) correlates with violent behaviour in non-psychotic samples. In the case of schizophrenia patients, contrary to our expectations, we found indication for a reverse association.

The low Care – high Overprotection pattern in the non-violent schizophrenia patients indicates a more negatively experienced maternal bonding in this subgroup. Members of the homicidal schizophrenia group reported higher Care- and lower Overprotection, a more positively perceived pattern of maternal bonding than non-violent schizophrenia patients. This is also similar to the one we found in healthy control subjects. To our knowledge, there has been no previous study to explore the differences between parental bonding in homicidal versus non-violent schizophrenia patients versus healthy controls. These findings are, thus, new in literature.

The finding that homicidal schizophrenia patients retrospectively report more care and less overprotection from their mothers than non-homicidal patients is counter-intuitive, too and requires an explanation. A possible interpretation is that negatively experienced maternal bonding, contrary to our hypothesis, is in fact not associated with committing a violent crime in the sample of schizophrenia patients. Our results imply that the association may be, despite our intuition, reverse. This suggestion needs to be evidenced in later studies. Homicidal schizophrenia patients who murdered (or attempted to murder) a family member, reported (with highest Care- and lowest Overprotection-scores) the most positive maternal bonding among the three groups. This seemingly paradoxical result raises questions. A retrospective report of highly positive maternal bonding may also be interpreted as an attempt of – perhaps not even conscious – emotional compensation or even reparation after the homicidal act. We were not able to follow up on indices of this interpretation. Also, due the extremely small size of this subgroup, this interpretation remains speculative and needs to be evidenced in studies involving a larger sample. We must also consider the limitations of our use of the PBI. First, recall bias significantly impacts on memories of parental bonding when assessed retrospectively after years or even decades. We were not able to assess the actual mother-child bond but rather a subjective recollection thereof and that is the source of a number of possible distortions. Second, we administered the PBI only after psychotic symptoms had been, at least to a degree, controlled by antipsychotic medication. The recollections of child-mother relationship in our study are not assessments made in an acute psychotic state. Antipsychotic medication impacts on emotional availability and memory function. This may influence the way patients remember the relationship to their mothers. Due to the design of our study, we assessed parental bonding retrospectively and after our patients had committed homicide. As in the case of symptom intensity, our results do not provide evidence for any causal relationship between

experienced parental bonding and the commission of homicide.

Our findings concerning the intensity of psychotic symptoms indicate that schizophrenia patients with more intense positive, negative and general psychopathological symptoms may be at a heightened risk of committing or attempting homicide. It is therefore important to register severe psychotic symptoms as potential predictors of violent behaviour. Promoting a predictive-preventive approach in psychiatry, in an earlier paper[14] we argued for the identification and targeting of early markers of later violent behaviour in schizophrenia.

In previous studies, negatively experienced parental bonding was found to be characteristic for non-psychotic homicide offenders. Our findings concerning maternal bonding suggest that this pattern does not necessarily apply to homicide offenders with schizophrenia and even raise the possibility of a reverse association. Other studies suggest that biological, possibly neuro-developmental factors may play a more important role in homicidal behaviour in schizophrenia than parental bonding. In a previous study[15] we found a higher number of minor physical anomalies (MPAs) in a homicidal subgroup of schizophrenia patients compared to a matched sample of non-violent schizophrenia patients and a group of healthy control subjects. This result suggests the possibility of a more seriously aberrant brain development in the case of schizophrenia patients with a history of committed or attempted homicide than non-violent schizophrenia patients.

The intriguing question, namely which factors contribute to the commission of homicide in schizophrenia patients, however, remains open.

LIMITATIONS

First, due to the relatively small size of our sample, our results should be considered suggestions that require further support from studies on larger samples. Also, female subjects were excluded from both patient groups due to their very small number in the homicidal group which means that our results are relevant for male schizophrenia patients only. Second, as already mentioned in the Discussion section, we only had access to schizophrenia patients who had already committed homicide. Hence, we were not able to assess the intensity of psychotic symptoms, symptom profile or components of parental bonding of patients before the commission of the crime. Also, our results do not provide evidence for any causal relationship between the intensity of symptoms, the characteristics of parental bonding and the act of homicide. Third, we assessed parental bonding only from the perspective of the child and have not included parental ratings. Fourth, differences in antipsychotic medication, a variable on which we were not able to match the members of the two patient groups might have impacted on the intensity of psychotic symptoms. Fifth, we assessed parental bonding with only one tool, the Hungarian version of the Parental Bonding Instrument. A study including several diagnostic tools for the assessment of parental bonding might have yielded more complex results.

ACKNOWLEDGEMENTS

Tamás Tényi was supported by the National Brain Resrach Program Grant No. NAP KTIA NAP-A-II/12.

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EATING BEHAVIORS AMONG THE PARTICIPANTS OF AN INPATIENT WEIGHT LOSS TREATMENT

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0055 | www.elitmed.hu

Background and purpose – Eating behaviors play a crucial role in the development and maintenance of excess weight. The aim of the study was to explore the predictors and changes in eating behaviors among overweight and obese patients.
Methods – The sample of the 6-month prospective survey consisted of patients who participated in the inpatient weight loss treatment program in the Lipidological Department of the Szent Imre Hospital (baseline: N=339, 19% men; follow-up: N=175, 16% men). The mean age was 50.2 years (SD=13.47), the mean BMI was 38.6 (SD=7.58) at baseline. Measures: self-reported anthropometric data, Three-Factor Eating Questionnaire Revised 21-Items, CES-D Depression Scale.
Results – According to the results of Multiple Indicators and Multiple Causes analysis, older age predicted greater cognitive restraint (β=0.12, p=0.047). Women were more prone to emotional eating than men (β=0.21, p<0.001). Higher levels of education predicted greater uncontrolled eating (β=0.16, p=0.007) and emotional eating (β=0.12, p=0.039). Depression showed a positive relationship with emotional eating (β=0.19, p=0.001), and mediated the relationship between gender and emotional eating (β=0.04, p=0.009), and BMI and emotional eating (β=0.03, p=0.015). Those whose weight loss was at least 5% showed a greater improvement in the eating behaviors than those whose weight loss was below 5% (cognitive restraint: $t_{(168)}$=–4.765, p<0.001, uncontrolled eating: $t_{(168)}$=–2.442, p=0.016, and emotional eating: Z=–2.011, p=0.044).
Conclusions – Results reveal certain determinants of eating behaviors that enhance or obstruct successful long term weight loss and highlight the role of eating behavior changes in weight loss. These mark intervention points for the optimization of results achievable by weight loss treatments.

Keywords: *obesity, eating behaviors, inpatient weight loss treatment, structural equation modeling, reliable change index*

AZ EVÉSI MAGATARTÁS SÚLYCSÖKKENTŐ KEZELÉS ALATT ÁLLÓ PÁCIENSEK KÖRÉBEN

Czeglédi E, PhD

Ideggyogy Sz 2017;70(1–2):55–62.

Háttér és célkitűzés – Az evési magatartások kulcsszerepet játszanak a súlyfelesleg kialakulásában és fennmaradásában. A vizsgálat célja az evési magatartások prediktorainak és változásának felmérése volt túlsúlyos és elhízott pácienseknél.
Módszerek – A prospektív, féléves vizsgálat résztvevői a Szent Imre Kórház Lipidológiai Profilján zajló intézeti súlycsökkentő kezelés páciensei (kiindulás: n=339; 19% férfi; utánkövetés: n=175, 16% férfi). A kezdeti átlagéletkor 50,2 év (SD=13,47), BMI-átlag 38,6 (SD=7,58). Mérőeszközök: önbeszámolóval nyert antropometriai adatok, 21 tételes Háromfaktoros Evési Kérdőív, CES-D Depresszió Skála.
Eredmények – A többszörös indikátor és többszörös ok elemzés eredményei szerint az idősebbek jobban korlátozzák a táplálékbevitelüket (β=0,12; p=0,047). A nők hajlamosabbak az érzelmi evésre, mint a férfiak (β=0,21; p<0,001). A magasabb iskolai végzettség előrejelzi a kontrollálatlan és az érzelmi evésre való nagyobb hajlamot (β=0,16; p=0,007; β=0,12; p=0,039). A depresszió pozitív irányú kapcsolatot mutat az érzelmi evéssel (β=0,19; p=0,001), illetve mediálja a nem és az érzelmi evés (β=0,04; p=0,009), valamint a BMI és az érzelmi evés (β=0,03; p=0,015) kapcsolatát. A legalább 5%-os súlycsökkenést elérők körében mindhárom evési magatartás nagyobb mértékben javul, mint az ennél kevesebbet fogyóknál (kognitív korlátozás: $t_{(168)}$=–4,765; p<0,001, kontrollálatlan evés: $t_{(168)}$=–2,442; p=0,016, érzelmi evés: Z=–2,011; p=0,044).
Következtetések – Eredményeink rávilágítanak a hosszú távú, sikeres testsúlykontrollt elősegítő és akadályozó evési magatartások egyes determinánsaira, illetve az evési magatartások változásának a fogyásban játszott szerepére. Mindez intervenciós pontokat jelöl ki a súlycsökkentő kezelések által elérhető eredmények optimalizálásához.

Kulcsszavak: *elhízás, evési magatartások, kórházi súlycsökkentő kezelés, strukturális egyenletek modellje, megbízható változás index*

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Érkezett: 2015. augusztus. 17. Elfogadva: 2015. október 22.

Obesity is a highly prevalent, complex disorder with multi-factorial etiology and severe health consequences, often putting heavy loads both on the individual and society. Eating behaviors play a crucial role in the development and maintenance of excess weight. Although many aspects of food intake regulation have a hereditary component, eating behaviors and habits are largely influenced by cultural, social, environmental and psychological factors. Eating can be a source of pleasure or an affect regulation strategy. Emotional eating is a coping strategy for dealing with negative emotions and experiences (e.g., stress, boredom, anxiety). The obese people demonstrate more emotion induced eating than those who are not obese; and this form of coping with the unfavourable mood plays a causal role in the etiology of obesity[1].

Women are more prone to emotional eating than men[2]. Emotional eating shows association with emotional and relationship problems, consumption of high energy dense snack food and it correlates with higher BMI[3, 4]. Emotional eating may help the individual overcome negative emotions in the short term, however it does not contribute to the solution of the problem. Moreover, it can cause weight gain that may lead to obesity and various co-morbid diseases. Results of longitudinal studies consistently suggest that emotional eating has deleterious consequences on the long-term weight status[5].

The main aim of weight loss treatment is to reduce the engery intake of patients that can be realized by increasing the conscious restriction of food intake and decreasing the disinhibited eating. Studies consistently demonstrated that there is a significant improvement in these eating behaviors as a result of professional weight loss treatment[6–8]. The greatest change is manifested in cognitive restraint. However, compared to cognitive restraint and uncontrolled eating, emotional eating resists change to a greater extent[7]. Results of the prospective studies show that the eating behaviors measured at baseline do not have predictive value as far as the degree of weight loss is concerned. The changes occurred in eating behaviors during the weight loss program usually show association with the degree of weight loss[6, 7].

In order to treat and prevent obesity there is an urgent need to clarify the predictors of adaptive and maladaptive eating behaviors. The main purpose of this study was to investigate predictors of eating behaviors among the participants of an inpatient weight loss treatment. The theoretical model is presented in **Figure 1**. We also aim to assess the changes in eating behaviors. We hypothesized that, within six months after the inpatient weight loss treatment, cognitive restraint increases while uncontrolled eating and emotional eating decreases. We expected to find the greatest change in cognitive restraint. Our goal was to assess the predictive value of changes in eating behavior concerning successful weight loss. Since according to professional consensus modest weight losses of 5% to 10% are successful, it was considered as successful weight loss when an individual lost at least 5% of their initial body weight.

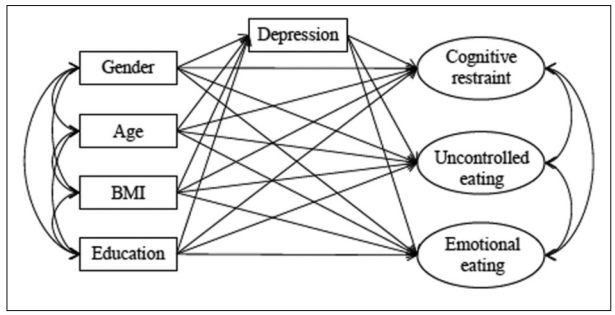

Figure 1. *The theoretical model*

Methods

PARTICIPANTS AND PROCEDURE

We conducted a prospective, questionnaire-based survey. The time interval was six months which contained two data collection waves. The sample consisted of patients who participated in the inpatient weight loss treatment in the Lipidological Department of the Szent Imre Hospital in Budapest (N=339, 19% men). The mean age was 50.2 years (SD=13.47, range 18–85). Almost half of the participants (47.0%) lived in the capital. Educational level was elementary in 15%, secondary school in 42% and university or college degree in 43% of the respondents. The mean BMI was 38.6 (SD=7.58, range 25.1–79.3). Eighty-nine percent of the participants were obese (BMI ≥30.0). One hundred and seventy-five participants took part in the follow-up (16% men). The study was carried out with the permission of the Research Ethics Committee of the Faculty of Education and Psychology at Eötvös Loránd University.

MEASURES

Sociodemographic and anthropometric data on age, education, place of residence, height (cm) and weight (kg) were gathered.

Table 1. *Means, standard deviations and pairwise correlations between the variables at baseline*

Variables	Cronbach's α [95% CI] (item number)	Mean (SD) [range]	2. BMI	3. Cognitive restraint	4. Uncontrolled eating	5. Emotional eating	6. Depression
1. Age	– (1)	50.21 (13.47) [18–85]	–0.19***	0.09	–0.07	*–0.05*	0.00
2. BMI	– (1)	38.59 (7.58) [25.1–79.3]		–0.05	0.12*	*0.09*	0.12*
3. Cognitive restraint	0.79 [0.75–0.82] (6)	2.53 (0.59) [1.0–3.8]			–0.40***	*–0.12**	–0.01
4. Uncontrolled eating	0.85 [0.82–0.87] (9)	2.41 (0.60) [1.0–4.0]				*0.55****	0.08
5. Emotional eating	0.93 [0.92–0.94] (6)	2.39 (0.89) [1.0–4.0]					*0.24****
6. Depression	0.88 [0.86–0.90] (20)	18.02 (9.63) [0–48]					

Note. N=319–338. *p<0.05, ***p<0.001. Values in italics are Spearman's rank correlation coefficients.

Three-Factor Eating Questionnaire Revised 21-Items (TFEQ-R21)[9] measured three aspects of eating behavior. The *Uncontrolled eating scale* assessed the respondent's tendency to lose control over eating when hungry or exposed to external food stimuli. The *Cognitive restraint scale* assessed the extent to which the respondent attempted to control food intake to regulate body weight and shape. The *Emotional eating scale* measured propensity to overeat in negative mood states, for example when the individual experiences loneliness, anxiety or depressed mood. Higher scores indicated a greater tendency to uncontrolled eating, cognitive restraint or emotional eating.

Center for Epidemiologic Studies Depression Scale (CES-D)[10] is a 20-item scale assessed the frequency of depressive symptoms, used primarily in the general population. Respondents rated how often they were characterized by the certain cognitive, affective, conative and interpersonal symptoms of depression during the last week. Higher scores on the CES-D indicated increased level of depression. In this study, Cronbach's α coefficients were acceptable for all measures and are reported in **Table 1**.

STATISTICAL ANALYSES

Cronbach's α coefficient was used to estimate the internal consistency of scales. Means, standard deviations and pairwise correlations between the variables were calculated. Predictors of eating behaviors were assessed with Structural Equation Modeling. In the applied Multiple Indicators and Multiple Causes (MIMIC) analysis eating behaviors were treated as latent variables. In order to explore the changes in eating behaviors, paired-samples T-test was used. Effect size was estimated with Cohen's *d*. By applying the formula of *Jacobson* and *Truax*[11] and calculating the reliable change index (RCI), we determined the rate of those individuals who demonstrated statistically reliable changes in eating behaviors. We obtained the variable representing the given eating behavior change. In the case of uncontrolled eating and emotional eating, we subtracted the second measure from the first measure; while in the case of cognitive restraint we subtracted the first measure from the second measure. Thus the higher score indicated more favourable change in eating behavior. We examined the associations of changes in eating

behaviors with correlation analysis. The relationship between successful weight loss and changes in eating behaviors was tested with independent-samples T-test and multiple binary logistic regression analysis. Analyses were conducted using SPSS 21.0 and MPLUS 7.11 statistical packages.

Results

DESCRIPTIVES

Descriptive statistics and pairwise correlations between the variables measured at baseline are presented in **Table 1**.

PREDICTORS OF EATING BEHAVIORS

Results of the MIMIC model indicated that older age predicted greater cognitive restraint. Emotional eating was significantly higher among women in comparison to men. Higher levels of education predicted increased uncontrolled eating and emotional eating. Women and those with lower levels of education were characterized with a significantly higher level of depression than men, and individuals with higher levels of education. BMI associated positively with depression. Of the three eating behaviors, depression only showed a significant positive relationship with emotional eating. At the same time, depression partially mediated the relationship between gender and emotional eating (β=0.04, p=0.009), and between BMI and emotional eating (β=0.03, p=0.015). Cognitive restraint showed a strong negative relationship with uncontrolled eating and a weak negative relationship with emotional eating. Uncontrolled eating is strongly associated with emotional eating. The fit indices showed an acceptable model fit ($\chi^2_{(276)}$=623.3, p<0.001, CFI=0.967, TLI=0.961, RMSEA=0.061 [0.055–0.067]). The model accounted for 2.4% of variance in cognitive restraint, 4.7% of variance in uncontrolled eating and 10.1% of variance in emotional eating. The results are shown in **Figure 2**. For clarity, standardized factor loadings of the latent variables are not included.

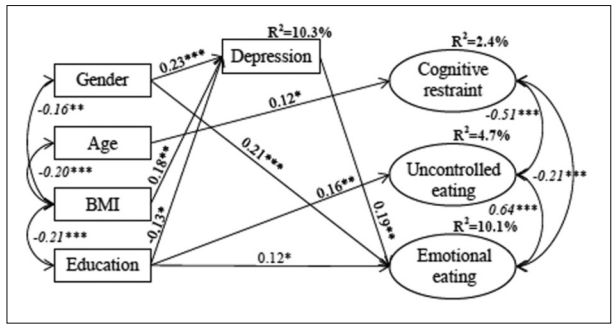

Figure 2. *The final model, that contains only significant (p<0.05) standardized path coefficients*

Note. N=339. Arrows: regression weights, double arrows with italicized text: covariances. *p<0.05, **p<0.01, ***p<0.001. Gender is coded: 0: male, 1: female. Education is coded: 0: up to secondary school, 1: higher education. R^2: explained variance.

THE RESULTS OF THE FOLLOW-UP

Table 2 shows in detail the means of body weight, BMI and eating behaviors in the subsample of individuals (N=175, 28 men és 147 women) who participated in both waves, six months apart. According to the results of the paired-samples T-tests, favourable and significant changes occurred in all three eating behaviors. The effect size indexes indicate a large increase in cognitive restraint and small decrease in uncontrolled eating and emotional eating. Body weight and body mass index also showed a significant and statistically large decrease.

The mean of cognitive restraint increased by 0.34 points (SD=0.54). The mean of uncontrolled eating decreased by 0.14 points (SD=0.52), while the mean of emotional eating by 0.18 points (SD=0.58). According to the results of the RCI calculation[11], in the case of cognitive restraint, 0.6% of the respondents showed statistically reliable

Table 2. *The means of variables in the subsample of the follow-up participants in the two data collection times, and the comparison of means*

Variables	Baseline mean (SD)	Follow-up mean (SD)	$t_{(df)}$	Cohen's *d*
Body weight (kg)	105.11 (21.14)	100.58 (21.07)	$t_{(174)}$=8.426***	0.90
BMI	38.42 (7.35)	36.56 (7.21)	$t_{(174)}$=9.534***	1.02
Cognitive restraint	2.54 (0.57)	2.88 (0.45)	$t_{(169)}$=–8.231***	–0.91
Uncontrolled eating	2.46 (0.58)	2.31 (0.55)	$t_{(169)}$=3.622***	0.39
Emotional eating	2.46 (0.87)	2.29 (0.91)	$t_{(171)}$=3.974***	0.43

Note: N=170–175. *** p<0.001.

decline, 90.0% showed no change and 9.4% showed statistically reliable improvement. In the case of uncontrolled eating, the rates are as follows: statistically reliable decline 1.8%, stagnation 93.5%, statistically reliable improvement 4.7%. In regard to emotional eating, we found that it statistically reliably increased in 1.2% of the respondents, while there was no change in 91.3%. However, 7.6% showed statistically reliable improvement. The increase in cognitive restraint significantly correlated with the decrease in uncontrolled eating (r=0.24, p=0.001) and emotional eating (r_s=0.23, p=0.002). However, the associations are weak. The decrease in uncontrolled eating showed a moderate relationship with the decrease in emotional eating (r_s=0.41, p<0.001).

The follow-up participants lost on average 4.3% (SD=6.30%, range: –12.4%–25.3%) of the baseline weight six months after the inpatient weight loss treatment. Forty percent of the respondents (N=70) achieved clinically significant (≥5%) successful weight loss (female: 42.2%, male: 28.6%, $\chi^2_{(1)}$= 1.814, p=0.178). Among individuals successful at weight loss all three eating behaviors improved significantly more than among those patients who achieved less than 5% of body weight loss (cognitive restraint: $t_{(107)}$=–4.765, p<0.001, Cohen's d= 0.81, uncontrolled eating: $t_{(168)}$=–2.442, p=0.016, Cohen's d=0.38, and emotional eating: Z=–2.011, p=0.044, Cohen's d=0,26). **Figure 3** shows the mean of changes in eating behaviors.

According to the results of the binary logistic regression analysis **(Table 3)**, after adjusting for gender, age, levels of education, and BMI, depression measured at baseline, only the increase in cognitive restraint predicted significantly higher odds for successful weight loss. The variance explained by the model is 28.3%.

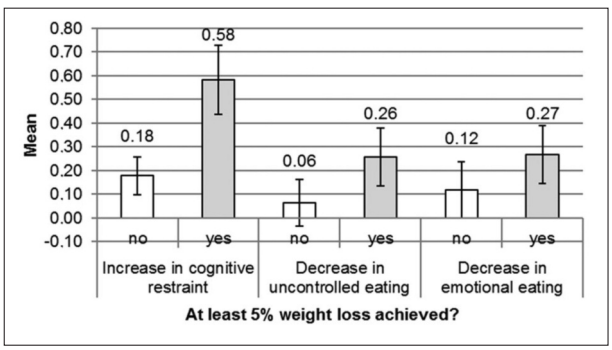

Figure 3. *The mean of changes in eating behaviors in the group of individuals who achieved at least 5% weight loss and those who achieved less*

Note: We indicate the 95% confidence interval of means.

Table 3. *The predictors of successful (≥5%) weight loss*

Variables	OR	OR 95% CI
Increase in cognitive restraint	5.75***	2.58–12.79
Decrease in uncontrolled eating	1.54	0.70–3.41
Decrease in emotional eating	0.97	0.49–1.89
Gender (ref.: male)	2.77+	0.90–8.54
Age	0.97+	0.95–1.00
Education (ref.: up to secondary school)	1.19	0.56–2.52
BMI at baseline	1.02	0.97–1.07
Depression at baseline	1.03	0.99–1.07

Note: N=163. +p<0.10, ***p<0.001.

Discussion

The participants of the present prospective survey were overweight and obese patients undergoing one-week intensive inpatient weight loss treatment in the Lipidological Department of the Szent Imre Hospital in Budapest. This was a distinct treatment since the one-week multi-component program (very low calory diet, physical exercise, medical examination, viewing educational films, educational workshops led by a dietitian) was not followed by other interventions. During the inpatient treatment, the patients acquired knowledge and skills necessary for weight management.

Since primarily lifestyle (overeating and physical inactivity) can be held responsible for excess weight in the modern obesogenic environment, there was an urgent need to clarify the predictors of adaptive and maladaptive eating behaviors. In line with previous results[2], it was found that women were more prone to emotional eating than men were. It might have been due to exposure to more intensive and more enduring stress in combination with women's greater propensity to manage stress using emotion-focused coping strategies[12]. Individuals with higher levels of education had a higher tendency for both uncontrolled eating and emotional eating than those with secondary or lower levels of education. Since higher socioeconomic status usually associate with higher health awareness, the present finding was unexpected and requires further exploration. Older people aimed to deliberately restrain their food intake to a greater extent than young people. In another study, significant positive correlation was found between age and cognitive restraint, and negative correlation between age and uncontrolled eating[2]. These findings encouraged the consideration of age effects in studies of eating behavior and when designing weight loss treatments.

Scores above 15 points on the CES-D Depres-

sion Scale indicate significant degree of depression[10]. In the present study, the mean of CES-D was 18 points, suggesting that the participants of the weight loss treatment were characterised by an increased level of depression. Our results showed that depression is higher among women, individuals with lower education, and people with greater excess weight. According to a meta-analysis of the longitudinal studies, excess body weight measured at baseline was a risk factor for depression. In case of overweight (BMI 25–29.9), the relationship was more moderate than in the case of obesity (BMI≥30), which reflects a dose-response gradient[13].

Depression is a risk for both mental and physical health. The aim to reduce depression is important since our survey also confirmed its relationship with emotional eating. In a Finnish population based study, depression and emotional eating showed a positive relationship, and both correlated with higher BMI. Regardless of depression and cognitive restraint, emotional eating correlated with higher consumption of sweets in both sexes. At the same time, emotional eating mediated the relationship between depression and consumption of sweets. Higher level of depression also correlated with lower consumption of fruit and vegetables, suggesting that depression affects the choice of unhealthy food in various ways[4]. Furthermore, according to our results depression plays a partial mediating role in the relationship between gender and emotional eating, and BMI and emotional eating, respectively. These suggest that striving to moderate the relationship between depression and emotional eating may be of great clinical importance. In order to do this, it would be necessary to explore the explanatory factors in the relationship between depression and emotional eating. For example, it was found that alexithymia and impulsivity partially mediated the relationship between depression and emotional eating[3].

We hypothesized that cognitive restraint increases within six months after the inpatient weight loss treatment, while uncontrolled eating and emotional eating decreases. We expected to find the greatest change in cognitive restraint. Our results supported the hypotheses. We found statistically large change in cognitive restraint and small changes in uncontrolled and emotional eating. In another study, by the end of a commercial weight loss program, both men and women showed favourable changes in eating behaviors. The greatest improvement was observed in cognitive restraint. In the case of disinhibited eating (inability to resist emotional and social eating cues when not hungry) and hunger (susceptibility to subjective feelings of hunger), more modest but significant decrease could be observed. The decrease in disinhibition and hunger correlated significantly with the extent of weight loss[7]. In a controlled clinical trial conducted among women by applying a six-month dietary treatment and cognitive therapy, a huge improvement was found in cognitive restraint. Disinhibition and hunger showed a large decrease. Both the increase in restraint and decrease in disinhibition correlated with greater weight loss[6]. Significant favourable changes were noticed in restraint, disinhibition and hunger in a sample of obese individuals six months after their bariatric surgery. However, at the two-year follow-up some regression was manifested towards the values at baseline in all three eating behaviors[8]. All these point out that in order to have a long term successful weight management, it would be necessary to apply interventions (e.g., booster sessions) for the stabilization of changes achieved in eating behaviors and eventually enhance further favourable changes. It should be noted that in the studies above, the Eating Inventory (EI) was used to measure eating behaviors. The Cognitive restraint scale of the TFEQ-R21, in its content, corresponded to the EI Restraint scale. However, the items of the Disinhibition and Hunger scales formed a global factor within the Uncontrolled eating scale. The Emotional eating factor was a subsequently identified dimension of the EI[9]. Therefore, our results were in line with the previous results, although the changes in eating behaviors cannot be compared directly.

We aimed to estimate the clinical significance of the changes in eating behaviors. By calculating reliable change index RCI[11], we determined the rate of participants who showed statistically reliable improvement, respectively deterioration. According to our results, cognitive restraint increased in statistically reliable degree in 9% of respondents. Considering the nature of the inpatient weight loss program and patients received minimal psychological support, this rate is remarkable and encouraging. Restraint may be a sensitive marker of adherence associated with the changes in behaviors necessary for weight loss. Repeatedly measuring restraint may be helpful in the case of patients whose weight loss pace decreases despite their reported compliance with treatment. The analysis of responses to certain items is most informative for both professionals and clients in order to understand which aspects of behaviors have changed (e.g., portion control)[6]. Reliable decrease in uncontrolled eating was observed in 5% of respondents. Since studies confirmed that decrease in disinhibit-

ed eating correlates with greater degree of weight loss[6, 7], it would be worth laying emphasis on this in inpatient weight loss programs besides focusing on cognitive restraint. With regard to emotional eating 8% of respondents demonstrated statistically reliable decrease. Since emotional eating may induce weight gain in the long run[5], yet this eating behavior is the most resistant to change[3], this finding is remarkable. It would be worth integrating the issue of emotional eating in the educational work in the Lipidological Department. It may be useful to lay emphasis on assessing emotional eating during the treatment, and to replace this emotion-focused coping strategy with a more adaptive behavior, such as relaxation.

We considered a minimum 5% decrease in body weight to be successful weight loss. The changes in eating behavior proved to be significantly more favourable among those who successfully lost weight than among those who achieved less than 5% body weight loss. According to the results of a longitudinal survey, increase in restraint correlates with decrease in fat intake, while the decrease in external eating (demostrating characteristics similar to those of uncontrolled eating behavior) lead to reduction in both energy and fat intake[14]. We can hypothesize that changes in restraint and uncontrolled eating correlated with favourable changes in relation to food choice and energy intake.

We examined the potential predictors of successful weight loss as well. According to the results, those individuals achieved successful weight loss who managed to increase to a greater degree their cognitive restraint related to food intake during the survey. Female sex and lower age predicted higher odds of successful weight loss at a tendency level. In a prospective study, after adjusting for sex, age, and BMI measured at baseline, increase in restraint and decrease in disinhibition predict the successful (≥5%) weight loss among individuals who participated in a weight loss treatment in various health care centers. The psychological variables did not have predictive value as far as successful weight loss is concerned[15]. This finding is in line with the results of the present study related to depression. Since the prediction of successful weight loss has significant practical implications, further research would be necessary in order to explore the predictors of successful weight management.

The chief merit of the present study was the prospective study design that made it possible to draw causal conclusions. However, as far as the predictors of eating behaviors were concerned, we could only determine cross-sectional predictions; moreover, the possibility of circular causality repeatedly emerged, e.g., in case of the relationship between depression and obesity[13]. Further advantage of the study is that the data collection was carried out in a well-defined large sample derived from a clinical population.

Several limitations of the present study should be mentioned. We do not have any data about those people who refused participation in the study, thus we are not aware of the nature of the potential selection bias. There were no objective measure of anthropometric data, thus, the BMI scores should be interpreted carefully. We could detect the changes only in short-term and we could test only the short-term predictive value of weight loss predictors. Generalization of our results is limited to non-invasive, professional inpatient weight loss treatment program for obese people. The model explains only a small fraction of the variance in eating behaviors, indicating that further examination is required for the comprehensive understanding of predictive factors of eating behaviors.

Despite the limitations, results pinpoint certain determinants of eating behaviors that enhance or hinder long-term successful body weight control, and the role eating behavior changes play in weight loss. All this designates intervention points for optimizing the results achievable by treatments. Further randomized controlled trials are necessary in order to explore the degree of changes in obesogenic and adaptive eating behaviors in inpatient weight loss programs, to determine the factors that predict the clinically significant changes in these behaviors, to identify the participants among whom these changes have clinical significance with regard to their weight loss, and to establish the nature and degree of changes in diet composition and energy intake induced by changes in eating behaviors.

ACKNOWLEDGEMENTS

The financial background of the research was provided by ELTE PK 2008 strategic resource tender. The author thanks Natalie Cooper for her help in proof reading the article.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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PATIENT WITH A SPONTANEOUSLY EVOLVING CAROTID CAVERNOUS FISTULA IN THE EMERGENCY DEPARTMENT

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PRINT | English | http://dx.doi.org/10.18071/isz.70.0063 | www.elitmed.hu

Background – Approximately 2% of patients admitted to the emergency department present with headache, which is often associated with vomiting, ocular pain, and earache. In rare cases, the presence of an abnormal communication between a cavernous sinus and the carotid arterial system that creates a carotid cavernous fistula is the main cause of these symptoms.
Case presentation – A 32-year-old woman presented at the emergency department with unilateral headache associated with earache on the same side, and pulsating tinnitus. On examination, we observed unusual appearance of our patient (small stature, unusually visible skin, lobeless ears). In the first 5 hours of our observation no neurological symptoms had been present, but after a severe vomiting, exophthalmos, subconjunctival suffusion and moderate ptosis developed. First, regarding the initial general symptoms, otorhinolaryngologist assessed the patient, and did not find any abnormality. Further, we ordered computed tomography and consulted a neurologist. Despite of the negative results we continued the observation because her symptoms did not improve. After appearance of neurological symptoms, carotid cavernous fistula was suspected. Magnetic resonance imaging and ophthalmologist consultation verified the diagnosis. For therapy, she was transferred to interventional neuroradiology. Because of the unusual appearance and carotic cavernous fistula, we ordered genetic examination. This indicated the presence of Ehlers-Danlos syndrome type IV in the background. The first major manifestation of the syndrome was observed at our department.
Conclusions – Carotid cavernous fistula is an uncommon diagnosis in the emergency department; however, the early recognition of symptoms and early treatment can prevent further consequences of this potentially severe condition.

Keywords: *carotid-cavernous sinus fistula, Ehlers-Danlos syndrome, emergency medicine*

SPONTÁN KIALAKULÓ CAROTIDEOCAVERNOSUS FISTULA A SÜRGŐSSÉGI OSZTÁLYON

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Ideggyogy Sz 2017;70(1–2):63–67.

Bevezetés – Irodalmi adatok alapján a sürgősségi osztályokon jelentkező betegek körülbelül 2%-a panaszkodik kizárólag fejfájásra. A fejfájáshoz gyakran társul féloldali zsibbadás, fülfájás és szemfájdalom. Igen ritka esetben ezeket a tüneteket a sinus cavernosust a carotisrendszerrel patológiásan összekötő úgynevezett carotideocavernosus fistula okozhatja.
Esetbemutatás – Sürgősségi osztályunkon jelentkezett egy 32 éves nőbeteg, aki féloldali fejfájást panaszolt, ehhez azonos oldali fülfájdalma és pulzáló fülzúgás társult. Vizsgálatkor felfigyeltünk a beteg szokatlan megjelenésére, beleértve alacsony termetét, átlátszó bőrét és a fülcimpa hiányát. Megfigyelésünk első öt órájában a beteg panaszai nem változtak, viszont egy súlyos hányást követően exophthalmus, subconjunctivalis suffusio és ptosis alakult ki. A kezdeti tünetek általános mivoltából adódóan fül-orr-gégészeti konzíliumot kértünk, amely során nem találtak eltérést. A továbbiakban neurológiai és komputertomográfiás vizsgálat történt, szintén negatív eredménnyel. Mivel a fejfájás az alkalmazott kezelésre nem csökkent, folytattuk a megfigyelést. A neurológiai tünetek megjelenésével carotideocavernosus fistula lehetősége merült fel, amelyet a mágneses rezonanciás vizsgálat és a szemészeti konzílium is megerősített. A beteget intervenciós neuroradiológiai intézetbe szállítottuk további ellátás céljából. A beteg szokatlan külleme és a carotideocavernosus fistula kialakulása miatt genetikai vizsgálatot végeztünk, amely IV. típusú Ehlers–Danlos-szindrómát igazolt.
Következtetés – A carotideocavernosus fistula nagyon ritka lelet a sürgősségi osztályon. A tünetek korai felismerése és kezelése viszont elengedhetetlen a lehetséges súlyos következmények kialakulásának megakadályozása érdekében.

Kulcsszavak: *carotideocavernosus fistula, Ehlers–Danlos-szindróma, sürgősségi betegellátás*

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Érkezett: 2016. szeptember 26. Elfogadva: 2017. január 3.

Headache, dizziness, back pain, weakness, and seizures are among the most common symptoms of patients admitted to the emergency department. Approximately 2% of patients present to the emergency department with headache; of these, 90% have a benign aetiology[1]. In rare cases, an abnormal communication between a cavernous sinus and the carotid arterial system may create a carotid cavernous fistula (CCF) and cause these symptoms[2]. Hence, after the exclusion of the most common causes in these patients, CCF should be considered, particularly in cases where the headache is unilateral and associated with tinnitus, earache, and orbital pain. If not treated with methods such as trans-arterial balloon or coil embolisation, in CCF cases total blindness may develop[3].

Case presentation

A 32-year-old Caucasian woman presented to the emergency department with a 1-day history of acute onset of left-sided headache, and vomiting. On admission, she said that her migraine-like one-sided headache started at noon on the previous day. Her symptoms worsened during the afternoon, and tinnitus appeared. Tinnitus was on the same side, pulsating and painful. Vomiting also developed in the evening. The patient took 1500 mg metimazol orally during the afternoon for relieving the pain; however, the symptoms persisted. On the morning of admission she vomited and experienced tremors and chills without fever. There was no history of any obvious injuries or previous neurological condition, and no evidence of headache or migraine was recorded in the patient's previous medical notes. Apart from hypertension, patellofemoral syndrome, anterior cruciate ligament repair, previous ovarian cyst, and well-controlled hypothyroidism, the patient appeared fit and well. However, the patient's appearance differed from the average woman's with her small stature, translucent skin, and unusually visible veins **(Figure 1)**.

On examination, vital signs were normal. The patient experienced pain in the left temporal region on palpation. With regard to laboratory values, the white blood cell count was slightly elevated at 14 G/l. Based on the patient's condition, the potential for an inflammatory reaction of the paranasal sinuses or the middle ear was considered. Hence otorhinolaryngology examination was performed, which did not indicate any evidence of inflammation or any other abnormality. Intravenous tramadol, metimazol, mannisol was administered without any improvement. Due to the severe and treatment-resistant headache, plain computed tomography (CT) was performed and neurologist assessed the patient. CT showed no evidence of intracranial bleeding, ischaemia, or other abnormalities, neurologist did not observe any signs of meningeal irritation, neck stiffness, vertigo, weakness, and numbness **(Figure 2)**. Her pupils were equal and reflexes were normal. At noon after eating dinner, severe vomiting occurred. Following this, the first neurological symptoms appeared: double vision, conjunctival suffusion, and chemosis. Pulsating tinnitus was accompanied by unbearable pain. Regar-

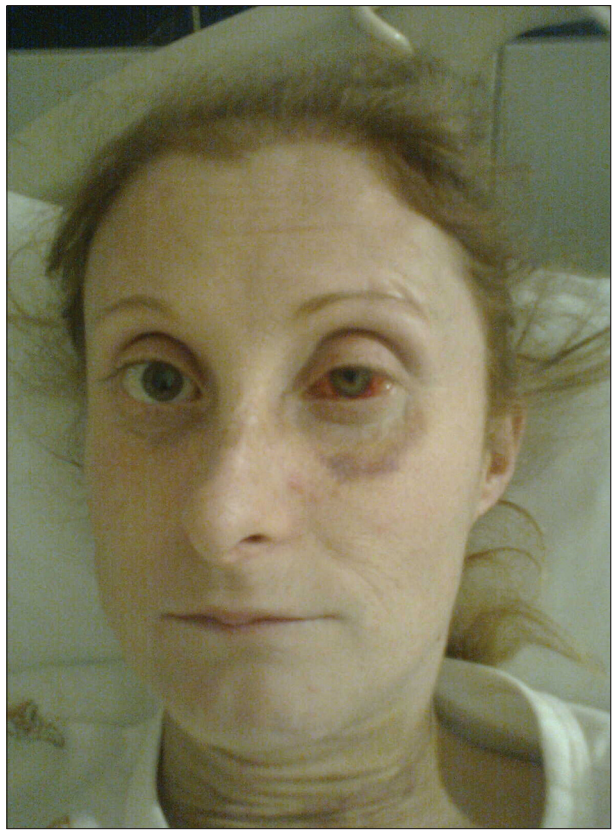

Figure 1. *Exophthalmos on the left side, moderate ptosis, and subconjunctival suffusion*

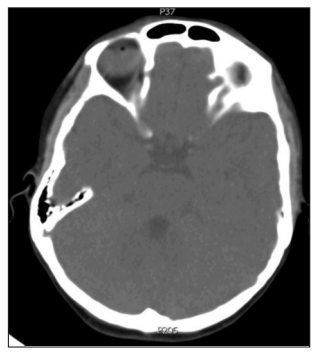

Figure 2. *Negative computed tomography findings of cavernous sinus*

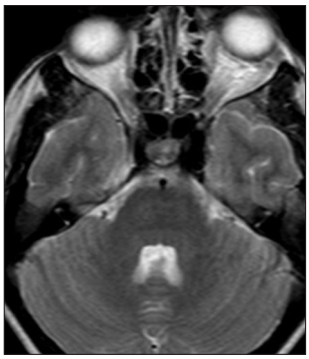

Figure 3. *T1-weighted skull magnetic resonance imaging. The left cavernous sinus is dilated due to CCF*

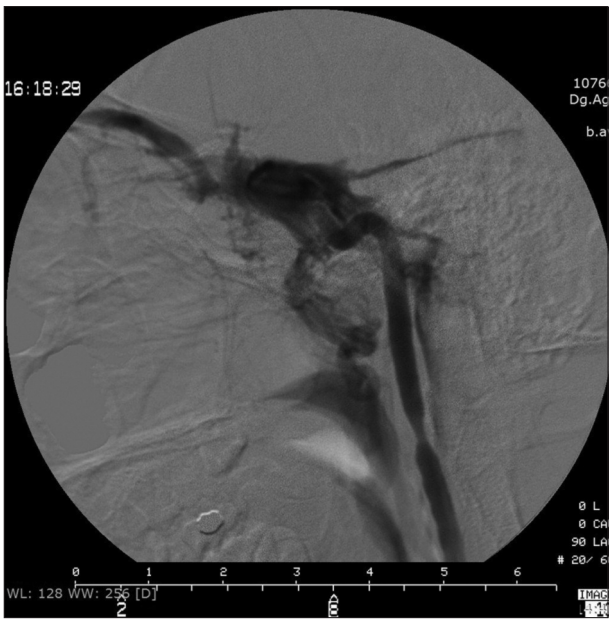

Figure 4. *Cerebral angiography confirms the diagnosis of carotid cavernous fistula*

ding the complexity of her symptoms, cranial magnetic resonance angiography (MRA) combined with venous angiography was performed. The examinations showed normal intra- and extracerebral liquor spaces with normal signal intensity in the brain tissue. The cavernous sinus and the superior ophthalmic vein on the left side were enlarged **(Figure 3)**.

The patient was then assessed by ophthalmologist who indicated left-sided exophthalmos (Hertel 91 14/17), slight ptosis, subconjunctival suffusion, conjunctival chemosis, and eye bulb pulsation. Eye movements were painful when the patient was asked to look upwards, and double vision was noted due to nerve palsy of the 3rd and 6th cranial nerves. The patient's visual acuity was 20/20. During the slit lamp examination, wider blood vessels were found on the left side as compared to that on the

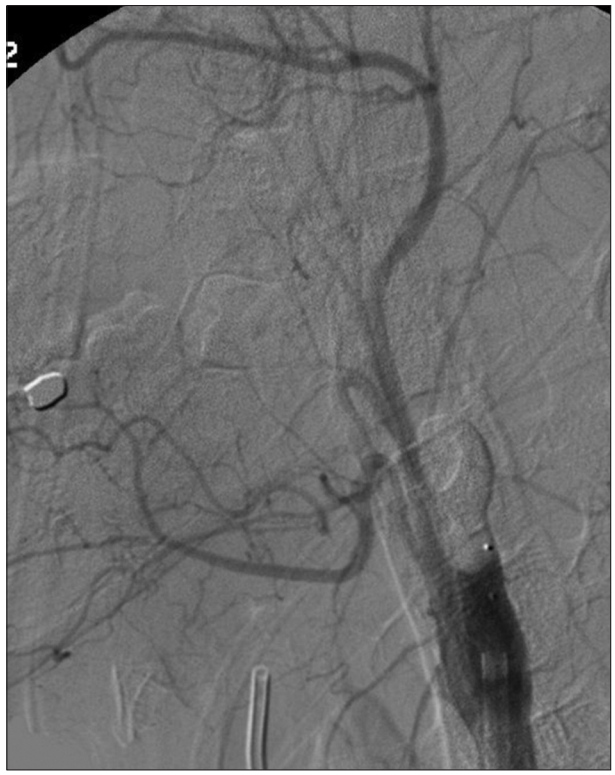

Figure 5. *Digital subtraction angiography. Left common carotid artery injection is performed after the occlusion of the left internal carotid artery (ICA). The shadow of a balloon can be seen in the proximal region of the ICA. Only the external carotid artery is filled. No fistula is observed*

right side; however, there was no evidence of intraocular bleeding or papillary stasis. The clinical signs, diagnostic examinations, and assessments at several specialties suggested the presence of CCF; hence, a neurosurgical referral was sought.

On the following day, the patient was transferred to the Department of Neurointerventions, National Institute of Neurosciences, where digital subtraction angiography was performed via the transfemoral route under local anaesthesia. This examination confirmed the diagnosis of CCF **(Figure 4)**. Selective occlusion of the fistula was not feasible due to the presence of significant damage of the intra-cavernous part of the left internal carotid artery. Therefore, the internal carotid artery was occluded temporarily and the collateral function of Willis's circle was tested by contralateral internal carotid artery injection. The function was deemed to be adequate, and the left internal carotid artery and fistula were then successfully closed with a detachable balloon **(Figure 5)**.

After an uneventful observation period, the patient was discharged to home. During her follow-

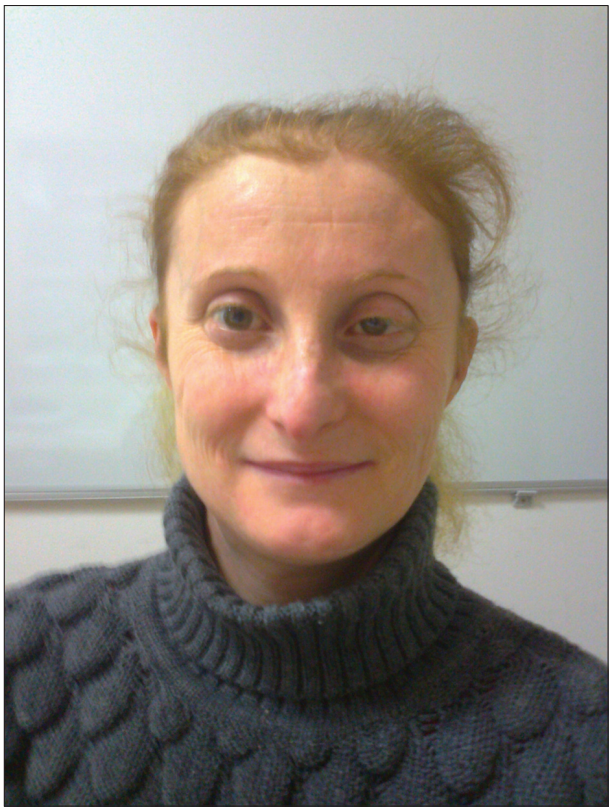

Figure 6. *At 6 weeks after the intervention, the 3rd cranial nerve palsy was resolved and the 6th cranial nerve palsy had improved*

up appointment after 6 weeks, she was found to be free from the previous signs and symptoms. Even the 3rd cranial nerve palsy was relieved and the 6th cranial nerve palsy had somewhat improved **(Figure 6)**.

Based on the clinical findings, the patient was suspected as having Ehlers-Danlos syndrome. Genetic analysis was performed for mutations in the COL1A1, COL1A2, COL3A1, COL5A2, FKBP14, PLOD1, and TNXB genes; the analysis found heterozygous mutations in the COL3A1 gene. These findings prove the presence of Ehlers-Danlos syndrome type IV.

Conclusions

Unilateral headache, earache, tinnitus accompanied by temporal pain and vomiting are commonly encountered in the emergency department. The primary underlying causes of most of these symptoms include migraine[4], cluster headache[5], venous sinus thrombosis[6] intracranial tumours[7], rupture of an intracranial aneurysm[8], dissection of the internal carotid artery (ICA)[9], and CCF[2]. Some of these causes may lead to fatal consequences, therefore prompt diagnosis is necessary.

CCF is an abnormal communication between the carotid arterial system and the cavernous sinus. A direct CCF develops in cases where there is a direct connection between the intracavernous part of the ICA and the cavernous sinus. The most frequent cause of direct CCF is head injury, when the fracture of the skull base results in a tear in the intracavernous portion of the artery. Dural CCF is characterised by a communication between 1 meningeal branches of the ICA, or external carotid artery, or both[2]. This condition develops spontaneously in most cases without any previous trauma. The spontaneous formation of direct CCF is very rare; it can result from the rupture of an intracavernous ICA aneurysm, and may be associated with fibromuscular dysplasia[10], Ehlers-Danlos syndrome[11] or other connective tissue disorders, arteriosclerotic changes of the arterial wall, and pregnancy. Ehlers-Danlos syndrome has several typical features including easy and significant bruising, lobeless ears, fine hair, unusually visible veins, thin nose and lips, prominent eyes, acrogeria. These features accompanied by unilateral headache should raise the possibility of CCF.

The characteristic clinical signs of CCF include exophthalmos, chemosis, ptosis, eye movement disorders, and ophthalmoplegia[2]. Chemosis and exophthalmos are caused by elevated venous pressure; in particular, oculomotor and abducens nerve palsy develops due to the compression caused by high pressure in the intracavernous sinus. Venous stasis and compression both lead to vision disorders. The bruit detected in the eye through auscultation is caused by pulsatile arterial blood flow within the superior ophthalmic vein. In rare cases, if the cavernous sinus drains into the sphenoparietal sinus and towards the cortical veins in a retrograde manner, another dangerous complication – subarachnoid haemorrhage – may develop[12].

The diagnosis of CCF is based on medical history, physical and neuroradiological examination. The presence of exophthalmos, chemosis, red eye, and pulsatile bruit on physical examination may be indicative of CCF. Contrast-enhanced CT scan and native magnetic resonance imaging can help to detect a dilated cavernous sinus and the superior ophthalmic vein, which increase the risk of CCF; furthermore, MRA can be used to confirm the diagnosis.

CT and MRI are now more frequently used in the emergency department, which makes it easier to determine the underlying cause (whether vascular or malignancy) of headaches. Between 1998 and

2008, the proportion of patients presenting to the emergency department with atraumatic headache who underwent such imaging procedures increased from 12.5% to 31.0%, whereas the prevalence of significant intracranial pathology among those who visited decreased from 10.1% to 3.5%[13].

The only suitable treatment for CCF is endovascular occlusion with detachable balloon or coil embolisation. Pulsatile bruits and other eye symptoms are known to immediately disappear after this intervention[14]. However, certain eye movement disorders may persist for a long time and may become permanent. The deteriorated vision may also improve, but recovery is not possible after the progression to total blindness. Ehlers-Danlos syndrome may also be found in severe cases of spontaneous direct CCF. It is a connective tissue disorder that is caused by the abnormality of type III collagen; this is also called the vascular type of Ehlers-Danlos syndrome. It manifests as rupture, dissection, or aneurysm formation that affects large or medium-sized arteries[15].

In the present case, we could follow the progression of spontaneous CCF from the first symptom (headache) until the development of a pulsating eye. Considering the first symptoms, more common diseases were encountered. In our case, patient's appearance, localized symptoms, and therapy-resistant headache made us to continue the examinations despite the first negative results. As new symptoms appeared around the eye, additional imaging techniques were performed and further referrals were made to diagnose CCF. In case of unilateral headache diagnosis of CCF is easily missed, if no other symptoms present. ED physician should watch the patient's appearance especially if that differs from the average. Attention should be paid to those patients who's having small stature, unusually visible skin and lobeless ears among patients who admitted to the ED with unilateral headache and vomiting. Physician may easily be misled by the common symptoms, and the subsequent delay in process of making the diagnosis can lead to serious consequences.

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THROMBOLYSIS AGYI INFARKTUST OKOZÓ AORTADISSECTIO ESETÉN

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Hungarian | http://dx.doi.org/10.18071/isz.70.0069 | www.elitmed.hu

Az agyi infarktus hátterében ritkán akut aortadissectio is állhat. A dissectio hirtelen fellépő, nagy mellkasi fájdalommal járhat, de a betegek 5–15%-ában a fájdalom nem jelentkezik, s ezen betegek felénél a kialakuló neurológiai tünetek elfedhetik az alapbetegséget. A statisztikai adatok alapján hazánkban évi 15–20 hasonló eset fordulhat elő. Munkánkban egy ilyen esetet szeretnénk ismertetni, mely tudomásunk szerint az első ilyen jellegű, magyar nyelvű esetismertetés.
Az 59 éves férfi beteg felvételére jobbra irányuló bulbusdeviáció, bal oldali hemiplegia, bal centrális facialis paresis, dysarthria miatt került sor. Fizikális és eszközös vizsgálata során akut ischaemiás jobb féltekei stroke-ot véleményeztünk, aortadissectióra utaló eltérést nem találtunk. A protokoll szerint kontraindikáció nem állt fenn, így szisztémás, intravénás thrombolysis történt. A beteg gócjelei megszűntek, kontroll-koponya-CT-n sem szövődmény, sem friss hypodensitas nem ábrázolódott. Thrombolysis után 36 órával a beteg nyugtalanná és hypoxiássá vált, neurológiai státuszában eltérés nem volt, de rákérdezve háti fájdalmat jelzett. Ekkor aortadissectio gyanúja miatt sürgős mellkas-CT történt, mely Stanford A típusú dissectiót igazolt. Akut aortaív-rekonstrukciót követően a beteg szívét nem sikerült újraindítani, de vérzéses szövődményt nem találtak.
Esetünk felhívja a figyelmet arra, hogy akut stroke hátterében aortadissectio is állhat. A néhány irodalmi esetismertetés és betegünk kórtörténetének retrospektív elemzése alapján felvethető, bár utólag nem igazolható, hogy az aortadissectio a stroke jelentkezésekor panaszt vagy tünetet nem okozó formában már fennállt, és az ennek talaján kialakult thromboembolia okozta a neurológiai tüneteket, melyeket a thrombolysis megszüntetett. Amennyiben a dissectio a thrombolysis előtt igazolódott volna, első lépésben thrombolysis nélkül az aortaív rekonstrukciójára került volna sor.

Kulcsszavak: *stroke, aortadissectio, thrombolysis*

THROMBOLYSIS IN CASE OF ISCHEMIC STROKE CAUSED BY AORTIC DISSECTION

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Ideggyogy Sz 2017;70(1–2):69–72.

Seldom, an acute aortic dissection can be the etiology of an acute ischemic stroke. The aortic dissection typically presents with severe chest pain, but in pain-free dissection, which ranges between 5-15% of the case, the neurological symptoms can obscure the sypmtos of the dissection. By the statistical data, there are 15-20 similar cases in Hungary in a year. In this study we present the case history of an acute ischemic stroke caused by aortic dissection, which is the first hungarian publication in this topic.
A 59-year-old man was addmitted with right-gaze-deviation, acute left-sided weakness, left central facial palsy and dysarthric speech. An acute right side ischemic stroke was diagnosed by physical examination without syptoms of acute aortic dissection. Because, according to the protocol it was not contraindicated, a systemic intravenous thrombolysis was performed. The neurological sypmtoms disappeared and there were no complication or hypodensity on the brain computed tomography (CT). 36 hours after the thrombolysis, the patient become restlessness and hypoxic with back pain, without neurological abnormality. A chest CT was performed because of the suspition of the aortic dissection, and a Stanford-A type dissection was verified. After the acute aortic arch reconstruction the patient died, but there was no bleeding complication at the dissection site caused by the thrombolysis.
This case report draws attention to the fact that aortic dissection can cause acute ischemic stroke. Although it is difficult to prove it retrospectively, we think the aortic dissection, without causing any symptoms or complain, had already been present before the stroke. In our opinion both the history of our patient and literature reviews confirms that in acute stroke the thrombolysis had no complication effect on the aortic dissection but ceased the neurological symptoms. If the dissection had been diagnosed before the thrombolysis, the aortic arch reconstruction would have been the first step of the treatment, without thrombolysis.

Keywords: *stroke, aortic dissection, thrombolysis*

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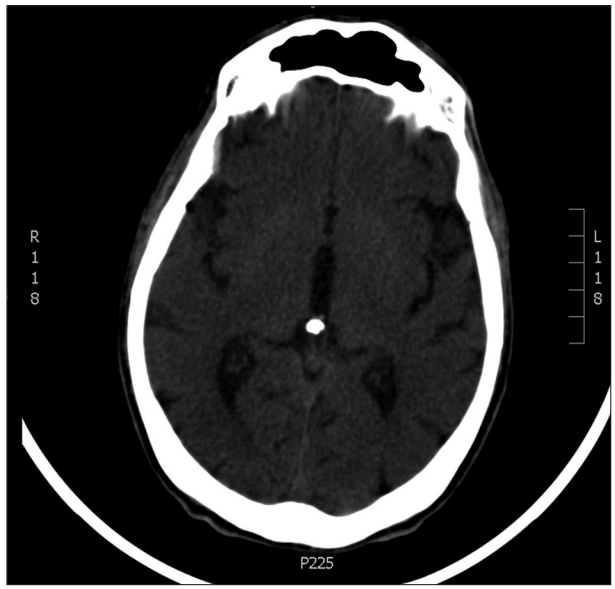
Érkezett: 2016. október 24. Elfogadva: 2017. január 4.

Magyarországon évente körülbelül 50 000 ember szenved el stroke-ot, melynek 80–85%-a ischaemiás eredetű. Az aortadissectio évi előfordulása 300–400 főre tehető. Ritkán ugyan, de előfordul, hogy ez a két súlyos betegség együtt jelentkezik és így a statisztikai adatok alapján 10 millió lakosra nézve hazánkban évente 15–20 ilyen beteggel számolhatunk. Ezen betegek nagy részénél a korrekt diagnózis később vagy sosem kerül felismerésre, mert típusos mellkasi fájdalom nem kíséri a dissectiót és/vagy a neurológiai tünetek elfedhetik az alapbetegséget. Az ezeknél a betegeknél jelentkező nyugtalanságot, halált a stroke-nak tulajdonítjuk, emiatt boncolás sok esetben nem történik. Esetismertetésünkben szeretnénk felhívni a figyelmet erre a ritka betegcsoportra, továbbá az ilyenkor fellépő diagnosztikai és terápiás kihívásokra, valamint szeretnénk rávilágítani a CT-angiográfia fontosságára is.



1. ábra. *Natív koponya-CT 24 órával a szisztémás thrombolysist követően*

Esetismertetés

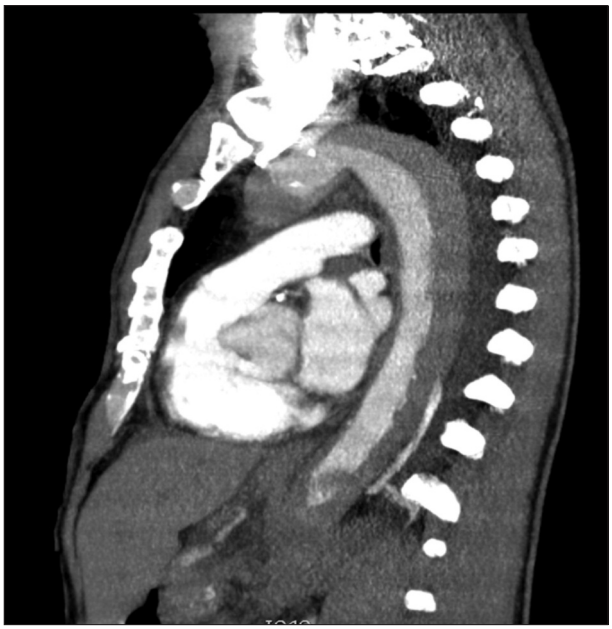
Ötvenkilenc éves férfi beteget szállítottak a sürgősségi betegellátó osztályunkra jobb féltekei stroke klinikumával, 90 perces időablakkal. Anamnézisében lényeges belgyógyászati megbetegedés nem szerepelt, gyógyszert rendszeresen nem szedett. Fizikális vizsgálata során vérnyomása mindkét felkaron mérve 140/70 Hgmm, pulzusa 50/min, oxigénszaturációja 100% volt. EKG-n sinusritmus, aVL-ben lapos T-hullám, a többi elvezetésben izoelektromos ST-szakasz, pozitív T-hullám ábrázolódott. Szívzörej nem volt hallható.

Neurológiai vizsgálata során jobbra irányuló bulbusdeviáció, bal oldali hemiplegia, bal centrális facialis paresis, bal oldali hemihypaesthesia, dysarthria volt észlelhető. Az NIHSS (National Institutes of Health Stroke Scale) 15 pont volt. A beteg nem jelzett mellkasi fájdalmat, laboreredményei, beleértve nekroenzimeket is (CK, CKMB, troponin) normáltartományon belül voltak. Koponya-CT-n friss denzitáseltérés nem ábrázolódott. Carotis-Doppler-ultrahangon mindkét arteria carotis internában normáláramlás mutatkozott. A beteg klinikuma és eszközös vizsgálata alapján akut jobb féltekei ischaemiás stroke-ra gondoltunk. Tekintettel arra, hogy az átvizsgálás alapján kontraindikáció nem igazolódott, 130 perces időablakkal szisztémás, intravénás thrombolysis történt. A beteg összesen 60 mg alteplázt (Actilyse) kapott, 6 mg-ot intravénás bolus formájában, 54 mg-ot egy óra alatt, infúziós pumpával. A vitális paramétereket lysis alatt és azt követően is folyamatosan monitorizáltuk, eltérést nem észleltünk. Thrombolysis alatt a beteg neurológiai státusza folyamatosan javult, lysis után két órával a beteg neurológiai gócjelei megszűntek.

Sikeres thrombolysis után hat órával a beteg nyugtalanná vált, fulladásérzetről számolt be, mellkasi fájdalmat továbbra sem jelzett, neurológiai státuszában gócjelet továbbra sem észleltünk. Spontán oxigénszaturációja 94% volt, EKG-n változás nem ábrázolódott, nekroenzimek normáltartományon belül voltak. Maszkon át történő oxigénadás mellett a beteg megnyugodott, fulladásérzete megszűnt. Kontroll-koponya-CT-n sem vérzéses transzformáció, sem friss hypodensitas nem ábrázolódott **(1. ábra)**.

Majd a thrombolysis után 36 órával a beteg ismét nyugtalanná vált, ekkor oxigénszaturációja maszkon át történő oxigénadás ellenére is csak 84% volt, EKG-n eltérés továbbra sem volt. Viszont laboreredményeiben emelkedett nekroenzimeket, laktát-dehidrogenázt (LDH) és D-dimert észleltünk és a beteg rákérdezésre háti fájdalomról számolt be. Ekkor aortadissectio gyanúja miatt sürgős kontrasztanyagos mellkas-CT-vizsgálat történt, ami Stanford A típusú aortadissectiót igazolt, mely ráterjedt a hasi aortára is **(2. ábra)**. A CT-vizsgálóból a beteg rögtön intenzív osztályra került, ahol analgoszedáció biztosítása mellett gépi lélegeztetést alkalmaztak. A beteget átszállították a Szegedi Tudományegyetem Szívsebészeti Centrumába életmentő műtét elvégzése céljából.

A műtét során heparinizálást követően a jobb arteria subclavián és a jobb pitvaron keresztül perfúziót indítottak. Az aortabillentyű felett átvágták



2. ábra. *Kontrasztanyagos mellkas-CT*

az aortát. Az aorta a noncoronalis szájadéktól a bal coronalis szájadékig dissecalt. A coronalis szájadékok nem voltak érintettek. A coronalis szájadékok feletti terület és az aorta descendens közé 26 mm-es egyenes graftot ültettek be, majd a proximalis anastomosis területén fellépő vérzés miatt Yacoub-műtét történt, saphenafolttal állították helyre a jobb arteria coronaria áramlását a graftról vezetve. A műtét végén mindkét kamrában csak renyhe mozgást észleltek, maximális inotrop szer támogatással is csak marginális keringés alakult ki, majd elektromechanikus disszociáció lépett fel, s a beteg exitált. A műtét során sem a pericardiumban, sem a mellüregben nem találtak vért.

Megbeszélés

A mellkasi fájdalom nélkül járó aortadissectio az összes dissectio 5–15%-ában fordul elő[1], és az ebbe a csoportba eső betegek felénél alakul ki neurológiai tünet[2]. A dissectiót követő neurológiai tünetek elfedhetik az alapbetegséget, emiatt a dissectio diagnózisa és ellátása sok esetben késik. A Stanford A típusú aortadissectio esetén a következő neurológiai tünetek fordulnak elő leggyakrabban: TIA (transient ischaemiás attack), stroke (dominálóan jobb féltekei), epilepsziás roham, Horner-szindróma, ischaemiás gerincvelő-szindrómák[1]. Betegünknél jobb féltekei ischaemiás stroke klasszikus tünettanát észleltük. Kórtörténetét visszatekintve az első nap csak a neurológiai tünetek domináltak, s az elsődleges vizsgálatok során semmiféle jel nem utalt aortadissectióra.

Az érvényben lévő irányelvek szerint a szisztémás thrombolysis mellkasröntgen, mellkas-CT és CT-angiográfia nélkül is elvégezhető, tehát a protokoll szerint[3] a szóban forgó betegcsoport esetében, tekintettel az elfedett cardialis tünetekre, a korrekt diagnózis nem állítható fel. *Flemming* és munkatársai[4] szerint a kiterjesztett eszközös vizsgálat (mellkasröntgen, mellkas-CT) csak abban az esetben mérlegelendő, ha fizikális vizsgálat során aortadissectióra utaló jelek észlelhetőek (például hipotenzió, szívzörej, elnyomható pulzus). Betegünknél ilyen tüneteket nem találtunk, emiatt kiterjesztett eszközös vizsgálat nem történt. A szisztémás thrombolysist követően a beteg neurológiai tünetei megszűntek, kontroll-koponya-CT-n sem vérzéses szövődmény, sem friss hypodensitas nem ábrázolódott. A lysis ellenére a betegnél csak 36 óra elteltével jelentkeztek cardialis tünetek.

Tekintettel arra, hogy betegünknél sem a kontroll-koponya-CT-vizsgálaton, sem műtét során nem találtak vérzésre utaló jelet, úgy véljük, hogy a thrombolysis a dissectiót nem rontotta, viszont neurológiai tüneteit megszüntette.

Esetünk alapján a következő kérdés merül fel: Mi a választandó eljárás, ha egyszerre igazolódik akut aortadissectio és ischaemiás stroke?

Erre a kérdésre az irodalomban nem található egyértelmű válasz: *Gaul* és munkatársai[2] tanulmánya szerint, azoknál a dissectiós betegeknél, akiknél a neurológiai tünetek elfedték a cardialis tüneteket, 62,5%-ban találtak szupraaortikus erekre terjedő dissectiót, tehát a betegek 1/3-ában a neurológiai tünetek hátterében thromboembolia vagy súlyos hipotenzió állhat. Betegünknél sem a carotis-Doppler-ultrahang, sem a mellkas-CT nem jelezte a carotisok érintettségét és hipotenzió sem állt fenn. Thromboemboliás eredet mellett szól, hogy altepláz (Actilyse) adása után két órával a beteg neurológiai tünetei megszűntek. *Hama* és munkatársai[5] közleményükben a carotis-Doppler-ultrahang fontosságára hívják fel a figyelmet, mely segítségével a carotisokra terjedő dissectio felismerhető, és ez alapján sürgős sebészi kezelést javasolnak. *Tsivgoulis* és munkatársai[6] szintén a carotis-Doppler-ultrahang fontosságát hangsúlyozzák: betegüknél mindkét arteria carotis internára terjedő dissectiót és ehhez társuló thrombust igazoltak, majd sürgős mellkas-CT-vizsgálatot követően a betegnél szisztémás thrombolysis nélkül, a dissectio műtéti megoldása mellett döntöttek. Bár betegünknél történt carotis-Doppler-ultrahangvizsgálat, az érvényben lévő protokoll szerint ez a vizsgálat sem kötelező szisztémás thrombolysis előtt[3].

Ugyanakkor *Mendes* és munkatársai[7] esetismertetésében 70 éves férfi betegüknél csak közvetlenül a szisztémás thrombolysis befejezése után jelentkezett háti fájdalom, illetve hipotenzió, s emiatt csak thrombolysis után került sor az aortadissectio diagnosztizálására és műtéti megoldására. A műtétet a beteg jól viselte, thrombolysisből származó szövődményt nem észleltek, ugyanakkor neurológiai tünetei már a thrombolysis alatt megszűntek. Hasonló a *Hong* és munkatársai[8] által közölt esetleírás: 69 éves nőbetegüknél akut jobb féltekei ischaemiás stroke-ot diagnosztizáltak, a beteg panaszkodott ugyan mellkasi diszkomfortérzésről, de nem volt sem EKG-eltérés, sem nekroenzim-emelkedés, s fizikális vizsgálata sem utalt aortadissectióra, emiatt betegüknél elindították a szisztémás thrombolysist. Protokolljuk alapján intravénás thrombolysis alatt CT-angiográfia történik nagy ér occlusio igazolása céljából, hogy szükség esetén intraarteriális thrombolysist is végezhessenek. CT-angiográfia során mindkét arteria carotis interna extracraniális szakaszán dissectio igazolódott, ekkor sürgős mellkas-CT-vizsgálat történt, mely Stanford A típusú aortadissectiót igazolt, és bár a beteg neurológiai státusza a lysis alatt folyamatosan javult, a vérzés veszélye miatt a thrombolysis leállítása mellett döntöttek (a szokásos dózis mintegy 60%-át kapta meg a beteg). A beteget ezt követően megoperálták, és 13 nappal később neurológiai státuszában már nem volt eltérés, kontroll-koponya-MRI-n a jobb féltekében kis kiterjedésű infarktus ábrázolódott.

Esetünk és az irodalom áttekintése alapján úgy véljük, hogy időablakon belüli ischaemiás stroke diagnózisával érkező betegeknél Hong[8] által ismertetett protokoll alkalmazása esetén van legnagyobb esély az esetleges aortadissectio felismerésére. Protokolljuk szerint natív CT- és laboreredmények után időveszteség minimalizálása céljából elindítják a szisztémás, intravénás thrombolysist, melynek ideje alatt készítenek CT-angiográfiát, melynek segítségével nemcsak a nagyér-occlusio, de a dissectio is igazolható. Amennyiben CT-angiográfián dissectio ábrázolódik, a thrombolysist leállítják és azonnal mellkas-CT-t készítenek. A Német Szakmai Kollégium[9] javaslata alapján, amennyiben a beteg NIHSS pontja 10 vagy a fölötti, CT-angiográfia elvégzése javasolt. A Magyar Szakmai Kollégium[3] szintén javasolja az extra- és intracranialis erek leképzésére a CT-angiográfia elvégzését, de annak indikációja és időzítése nem részletezett. Esetünkben a beteg kezelése időpontjában CT-angiográfia nem állt rendelkezésünkre, emiatt a carotisok megítélésére carotis-Doppler-ultrahangvizsgálatot végeztünk.

Időablakon belüli stroke esetén minden esetben indokolt a kezdeti képalkotás során CT-angiográfia végzése is a thrombectomiára történő alkalmasság megítélésére. Ha esetünk idején rendelkezésünkre állt volna CT-angiográfia, akkor a jelenlegi protokoll szerint a betegünknél a dissectiót jóval hamarabb tudtuk volna diagnosztizálni és a beteget Szívsebészeti Centrumba küldeni. Habár retrospektíve a thrombolysisnek dissectióra gyakorolt negatív következménye nem igazolódott, a vérzésveszély miatt thrombolysist nem indítottunk volna el.

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