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## Značenje transkranijalne sonografije mozga u sindromu pekućih usta: Pilot studija

### The Significance of Brain Transcranial Sonography in Burning Mouth Syndrome: a Pilot Study

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#### Sažetak

**Uvod:** Sindrom pekućih usta (SPU) kronični je poremećaj koji uglavnom zahvaća žene u postmenopauzi, a svojstven mu je osjećaj pečenja u usnoj šupljini unatoč potpuno zdravoj oralnoj sluznici. Rezultati dosadašnjih istraživanja sugeriraju moguću ulogu centralnih i/ili perifernih neuroloških poremećaja. **Ispitanici i postupci:** U skupini od 20 ispitanika sa SPU-om ( $64,7 \pm 12,3$  godina) i njih 20 u kontrolnoj skupini ( $61,5 \pm 15$  godina) s bolovima u lumbosakralnom dijelu leđa, transkranijalnom sonografijom evaluirani su moždani parenhim, crna tvar (*substantia nigra*), središnji niz stanica smješten u *formatio reticularis* lateralno od *rapha medulla oblongata* (*nucleus raphe*) i crvena jezgra (*nucleus ruber*). Statistička analiza obavljena je Studentovim t-testom sa značajnošću od  $p < 0,05$ . **Rezultati:** Rezultati ovog istraživanja pokazuju da se kod oboljelih od SPU-a ( $p < 0,05$ ), u usporedbi s kontrolnom skupinom, pojavljuje hipoehogenost *substantia nigra* i *nuclei raphe*, a hiperehogenostaje *nucleus ruber*. **Zaključak:** Možemo zaključiti da promijenjeni nalazi transkranijalne sonografije moždanoga parenhima, *nucleus raphe* i crvene jezgre (*nucleus ruber*) kod bolesnika sa SPU-om mogu odražavati centralne poremećaje u sklopu ovog sindroma.

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sindrom pekućih usta; transkranijalna sonografija; crna tvar; midbrain raphe jezgre; crvene jezgre

#### Uvod

Sindrom pekućih usta (SPU) kroničan je i bolan poremećaj čija se etiologija još istražuje. Simptomi povezani sa SPU-om mogu biti različiti i uglavnom negativno utječu na bolesnikovu kvalitetu života (1). Nadalje, vrlo je malo terapijskih opcija za SPU. McMillan i suradnici (2) zaključili su kako je malo dokaza o tome treba li poduprijeti ili odbaciti bilo koju dosadašnju terapiju u liječenju SPU-a. Danas se zna da u slučaju pekućih usta nastaje poremećaj u perifernom i/ili središnjem živčanom sustavu (3, 4). Postoje tri podskupine pacijenata sa SPU-om: podskupina koja ima perifernu neuropatiju malih vlakana (50 – 65 %), podskupina koja ima supkliničku patologiju lingvalnoga, mandibularnoga ili trigeminalnoga sustava (20 – 25 %), te podskupina s poremećajem u središnjem živčanom sustavu koji je posljedica poremećaja u dopaminergičkom ili serotoninergičkom sustavu (20 – 40 %) (5). Istraživanja s pomoću 6-(18F) fluorodopa-fDO-PA pozitronske emisijske tomografije bolesnika sa SPU-om

#### Introduction

Burning mouth syndrome (BMS) is a chronic pain disorder the etiology of which has remained unclear. Symptoms associated with BMS vary and may have a negative impact on oral health-related quality of life in patients with BMS (1). McMillan et al. (2) reported that, so far, no therapy has been proven to be effective or ineffective in patients with BMS. To date, there is no clear evidence that there is dysfunction of central and/or peripheral nervous system in patients with BMS (3, 4). There are 3 subgroups of BMS patients: subgroup with peripheral small diameter fiber neuropathy of intraoral mucosa (50-65%), subgroup with subclinical lingual, mandibular or trigeminal system pathology (20-25%), subgroup with presentation of central pain pattern which can be attributed to dysfunction of central dopaminergic or serotonergic pathways (20-40%) (5). Functional studies using 6-(18F) fluorodopa (FDOPA) positron emission tomography in BMS patients have shown a dysfunction of striatal do-

pokazala su disfunkciju strijatalnog dopaminergičkog sustava koju obilježava smanjena presinaptička aktivnost strijatalnih dopaminergičkih neurona i promjene u dostupnosti dopaminskih receptora D2 (6). Nedavno su Sinding i suradnici (3), uz uporabu vokselne morfometrije, ustanovili promjene u koncentraciji sive tvari kod 12 bolesnika sa SPU-om. Bilo je zahvaćeno šest područja od ukupno osam [anteriorni i posteriorni *cingulate gyrus*, *cerebellum*, *insula*/*frontal operculum*, inferiorno temporalno područje, primarna motorna kora i dorzolateralna prefrontalna kora (DLPFC)]. Nadalje, Liu i suradnici (7) zaključili su da je bolesnicima sa SPU-om smanjen lokalni protok krvi u lijevom temporalnom i parijetalnom režnju, što je možda povezano s depresijom.

Cilj ovog istraživanja bio je analizirati pacijente sa sindromom pekućih usta uz uporabu transkranijalne sonografije.

### Ispitanici i metode

Ovo istraživanje odobrilo je Etičko povjerenstvo Stomatološkog fakulteta Sveučilišta u Zagrebu. Prije nego što je počelo, svaki je ispitanik potpisao informirani pristanak u skladu s Drugim helsinškim dokumentom. Za 20 bolesnika sa SPU-om ( $64,7 \pm 12,3$  godina) i 20 u kontrolnoj skupini koji su imali bolove u lumbosakralnom dijelu ( $61,5 \pm 15$ ), transkranijalnim ultrazvukom evaluiran je moždani parenhim.

Evaluacija moždanog parenhima obavljena je standardno – sondom od 3,5 MHz (Aloka 5500 Prosound) na akustičnom prozoru temporalne kosti (transducer je bio postavljen na preaurikularnom mjestu) u položaju s elevacijom glave na  $45^\circ$  stupnjeva i okretom od  $30^\circ$  zdesna ulijevo. Evaluacija je napravljena na razini srednjeg mozga (aksijalni presjek).

Različite anatomske strukture unutar moždanoga debla i bazalnih ganglija opisane su kao hiperehogene ako su planimetrijski mjerena područja ehogenog signala bila veća kod pacijenata u odnosu na opću populaciju, ili ako je vizualni intenzitet signala ultrazvuka bio pojačan u odnosu na okolno moždano tkivo (*thalamus*, *lenticular nucleus*, *caudate nucleus*) izoehogeni su u odnosu na okolna tkiva; normalna, umjerena i izražena hipoehogenost – stupnjevi 1, 2, 3). Različita struktura mozga opisana je kao hipoehogena ako je planimetrijski mjereno ehogeno područje bilo manje kod pacijenata u odnosu na opću populaciju, ili ako je ehogenost bila visoka (npr. *midbrain raphe*) te je riječ o niskoj ehogenosti koja uzrokuje prekid ili nevidljivost eho-signala. Ehogene veličine na jednoj strani, ako su manje od  $0,20 \text{ cm}^2$ , klasificiraju se kao normalno ehogene. Veličine između  $0,20 \text{ cm}^2$  i  $0,25 \text{ cm}^2$  kategorizirane su kao umjereno hiperehogene, a one veće od  $0,25 \text{ cm}^2$  (10 % opće populacije) smatraju se značajno hiperehogenima. Hipoehogenost se može razlikovati ovisno o različitim sustavima ultrazvuka. Laboratoriji trebaju odrediti standardne vrijednosti za normalne i poremećene vrijednosti ehogenosti.

Normalan nalaz za *substantia nigra* slabo je ehogen – ehogeno područje  $< 0,20 \text{ cm}^2$ , za crvenu jezgru i *nuclei raphe*, značajno ehogen (stupanj 2).

Statistička analiza obavljena je Studentovim t-testom, a značajnost je bila  $p < 0,05$ .

paminergic system characterized by reduced presynaptic activity of striatal dopamine neurons and changes in dopamine D2 receptors availability (6). Recently, Sinding et al. (3) have found grey matter changes in 12 subjects with BMS using voxel-based morphometry. The anterior and posterior cingulate gyrus, lobules of the cerebellum, insula/frontal operculum, inferior temporal area, primary motor cortex, and dorsolateral pre-frontal cortex were affected. Furthermore, Liu et al. (7) found lower regional cerebral blood flow in the left temporal and parietal lobes, which might correlate with depression in patients with BMS.

The aim of this study was to analyze patients with burning mouth syndrome using transcranial sonography.

### Material and methods

This study was approved by the Ethics Committee of the School of Dental Medicine, University of Zagreb, Croatia. All participants gave their informed consent in writing prior to inclusion in the study, according to Helsinki II. An evaluation of brain parenchyma using transcranial ultrasonography was performed in 20 patients with BMS ( $64.7 \pm 12.3$  years) and 20 controls with chronic lumbosacral pain ( $61.5 \pm 15$ ) (Figure 1).

The evaluation of brain parenchyma was performed by 3,5 MHz probe in a standardized manner (Aloka Prosound SSD-5500, Hitachi Medical Corporation, Japan) at acoustic temporal bone windows (the transducer placed at the preauricular site) in supine position with head elevation of up  $45^\circ$  and side tilt of  $30^\circ$  to the right and to the left. The evaluation was performed at midbrain level (axial section). A distinct brain area was described as hyperechogenic if the planimetrically measured area of the echogenic signal was larger in the patient than in the general population (*substantia nigra*-SN) or when the increased intensity of the ultrasound signal was visually seen in that area compared to the surrounding brain tissue (*thalamus*, *lenticular nucleus*, *caudate nucleus*) were isoechoic to surrounding tissue; normal, moderate or pronounced hyperechogenicity - grade 1, 2, 3). Certain areas of brain were noticed as hypoechogenic when the planimetrically measured echogenic region was smaller in the patient than in the general population. Furthermore, if the area known to have high echogenicity (e.g. *midbrain raphe*) had a low echogenicity, this was also measured as hypoechogenic due to discontinuity or "invisibility" of echo signal. The echogenic sizes on one side, which were smaller than  $0.20 \text{ cm}^2$ , were classified as normally echogenic. The sizes ranging between  $0.20 \text{ cm}^2$  and  $0.25 \text{ cm}^2$  were categorized as moderately hyperechogenic, whereas sizes of  $0.25 \text{ cm}^2$  and larger (10% of the general population) were classified as markedly hyperechogenic. A normal finding for *substantia nigra* was weakly echogenic, echogenic area  $< 0.20 \text{ cm}^2$ , for *red nucleus* and *nuclei raphe*, markedly echogenic (grade 2).

The t-test with significance set at  $p < 0.05$  was used for statistical analysis.

## Rezultati

Nalaz transkranijalne sonografije moždanoga parenhima pokazuje da kod bolesnika sa SPU-om postoji značajna razlika u ehogenosti tvari *substantia nigra*, *nuclei raphe* i *nucleus ruber*. Ustanovili smo hipoehogenost *substantia nigra* i *nuclei raphe* te hiperehogenost *nucleus ruber* kod bolesnika sa SPU-om ( $p < 0,05$ ) (tablica 1.).

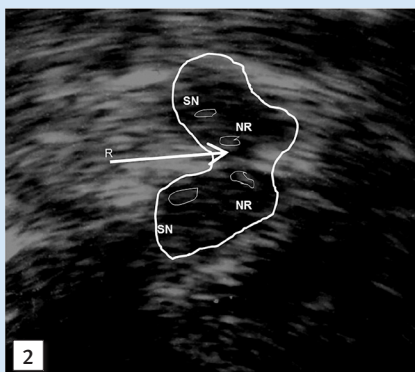
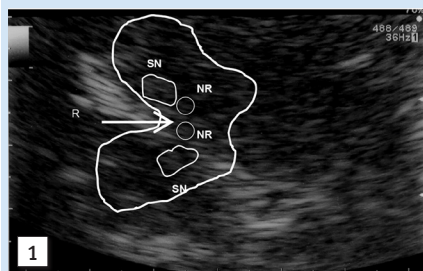
## Results

Clinical findings of the transcranial sonography of the brain parenchyma have shown that there was a significant difference in echogenicity of *substantia nigra*, *midbrain raphe* and *brain nucleus* in patients with BMS. Hypoechoogenicity of the *substantia nigra* and *midbrain nuclei* as well as hyper-echoogenicity of the *brain nucleus* were found in BMS patients ( $p < 0.05$ ) (Table 1) (Figure 1) when compared to controls (Figure 2).

**Tablica 1.** Morfološki nalazi transkranijalne sonografije (TKS) moždanog parenhima kod bolesnika sa SPU-om – I. kontrola  
**Table 1** Morphological findings of the transcranial Doppler sonography (TCS) of the brain parenchyma in BMS patients and controls.

TKS • TCS	SPU • BMS	Kontrole • Controls
<i>Substantia nigra</i> - normalan nalaz • normal finding	8*	13
<i>Substantia nigra</i> - hiperehogenost • hyperechogenicity	2	3
<i>Substantia nigra</i> - hipoehogenost • hypoechoogenicity	10*	3
<i>Nucleus ruber</i> - normalan nalaz • normal finding	10*	15
<i>Nucleus ruber</i> - hipoehogenost • hypoechoogenicity	2	2
<i>Nucleus ruber</i> - hiperehogenost • hyperechogenicity	8*	3
<i>Nuclei raphe</i> - normalan nalaz • normal finding	9*	16
<i>Nuclei raphe</i> - hipoehogenost • hypoechoogenicity	9*	4
<i>Nuclei raphe</i> - hiperehogenost • hyperechogenicity	2	0

\* $p < 0.05$



**Slika 1.** Promjene u ehogenosti evaluiranih struktura u bolesnika sa sindromom pekućih usta: hipoehogenost supstancie nigre i nukleus ruber, diskontinuitet nukleus raphe.

**Figure 1** Changes in echogenicity of the evaluated structures in patient with burning mouth syndrome: hypoechoogenicity of the SN-*substantia nigra* and NR-*nucleus ruber*, discontinuation in R-*nuclei raphe*.

**Slika 2.** Normalan nalaz transkranijalne sonografije.

**Figure 2** Normal transcranial sonography finding: SN-*substantia nigra*, NR-*nucleus ruber*, R-*nuclei raphe*.

## Rasprava

Nalazi transkranijalne sonografije moždanog parenhima pokazuju da između bolesnika sa SPU-om postoji razlika u ehogenosti *substantia nigra*, *nuclei raphe* i *nucleus ruber*. Dopaminergički neuroni uglavnom potječu iz *substantia nigra* i kontroliraju inhibiciju silaznog puta boli. Poznato je da su poremećaji u dopaminergičkoj neurotransmisiji unutar ovih putova povezani s različitim bolnim sindromima, pa tako i sa SPU-om. U dosadašnjim istraživanjima to je potvrđeno EMNG-om, odnosno s pomoću hiperaktivnosti refleksa treptaja koji je pod inhibitornom kontrolom mezencefaličnog dopamina (8). Pozitronska emisijska tomografija kod bolesnika sa SPU-om pokazuje smanjenu presinaptičku aktivnost strijatalnih dopaminskih neurona i promjene u dostupnosti dopaminskih receptora D2 (9).

Istraživanja neuroendokrine uloge serotonina pokazala su da *nuclei raphe* ima važnu ulogu u regulaciji sekrecije kor-

## Discussion

Transcranial sonography findings of the brain parenchyma have shown that there was a difference in echogenicity of *substantia nigra*, *midbrain raphe* and *brain nucleus* in patients with BMS. Most of the dopaminergic neurons of the brain originate in the midbrain and are found in the *substantia nigra* and they control descending pain inhibition pathways. It is a well-known fact that abnormalities in dopaminergic neurotransmission within these pathways are connected with different painful syndromes as well as other conditions associated with BMS. In previous studies, those abnormalities were confirmed by EMNG blink reflex hyperactivity which is under inhibitory control of mesencephalic dopamine (8). Positron emission tomography in BMS patients is characterized by reduced presynaptic activity of striatal dopamine neurons and changes in dopamine D2 receptors availability (9).

tikotropnog otpuštajućeg hormona i adenokortikotropnog hormona na hipotalamičkoj i pituitarnoj razini, a možda i na adrenalnoj. Ovi mehanizmi uključeni su u silazne serotonske i norepinefrinske inhibitorne putove boli. Ova istraživanja obavljena su *in vivo* na eksperimentalnim životinjama (štakorima) sa stereotaktičnim lezijama ciljnih puteva (10). Ovi neurotransmiteri također su uključeni kod ljudi i utječu na depresiju zbog bliske povezanosti *nuclei raphe* s dorzo-kaudalnim limbičkim sustavom. U nekim dosadašnjim istraživanjima autori su (11, 12) pokazali, koristeći se transkranijalnim ultrazvukom moždanoga parenhima, smanjenu ehogenost *nuclei raphe* kod pacijenata s velikim depresivnim poremećajem i suicidalnim sklonostima. U ovom istraživanju također smo ustanovili hipoehogenosti *nuclei raphe* kod bolesnika sa SPU-om. Nadalje, ustanovili smo značajno povećanu depresivnu simptomatologiju kod oboljelih od SPU-a u usporedbi s kontrolnom skupinom.

Dieb i suradnici (13) izvijestili su da deplecija nigrostrijalnog dopaminergičkog sustava rezultira trigeminalnom neuropatskom boli koja u najmanju ruku uključuje segmentalni model, barem kad je riječ o štakorima. Khan i suradnici (14) predložili su mnoge dokaze o poremećenoj strukturi i funkciji medijalnog prefrontalnog korteksa i hipokampusa kod bolesnika sa SPU-om, a koji mogu djelovati na raspoloženje i depresivne simptome ovih bolesnika.

Tri sonografske abnormalnosti pronađene su kod oboljelih s tipičnim sindromom nemirnih nogu (15 – 17): hipoehogenost *substantia nigra* kod njih 17 posto, hipoehogenost *nuclei raphe* kod 26 posto bolesnika, a hiperehogenost *nucleus ruber* kod 26 posto. Naši bolesnici sa SPU-om imali su hipoehogenost *substantia nigra* u 50 posto slučajeva, hipoehogenost *nuclei raphe* iznosila je 45 posto, a hiperehogenost *nucleus ruber* 40 posto, što može upućivati na sličan mehanizam u podlozi ovih dvaju sindroma. Naime, možda je SPU oralna varijanta sindroma nemirnih nogu.

Posljednje, ali ne i najmanje važno jest da je transkranijalni ultrazvuk neinvazivan i lako ga se može ponoviti, a to omogućuje brzu i dobru evaluaciju struktura moždanoga debla koje su zahvaćene kod bolesnika sa SPU-om. Jedini nedostatak ove metode jest uzak ili zadebljan akustični prozor.

### Sukob interesa

Nije bilo sukoba interesa.

Studies of the neuroendocrine role of serotonin have shown that *nuclei raphe* play an important role in the regulation of secretion of the corticotrophin releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH), both at the hypothalamic, pituitary portal and pituitary gland level and possibly also at the adrenal level. These mechanisms are involved in descending serotonin and norepinephrine inhibition of descending pain pathways. These studies were performed *in vivo* on experimental animals (rat model) with stereotactic lesions of target pathways (10). These neurotransmitters are also involved in humans and they affect depression due to close association of the brainstem *raphe nuclei* with dorso-caudal limbic system. In some previous studies, the authors (11, 12) used transcranial ultrasonography of the brain parenchyma, thus revealing reduced raphe echogenicity in patients with major depressive disorder and, also, with suicidal tendencies. In the present study, hypoechogenicity of the midbrain raphe was found in BMS patients.

Dieb et al. (13) reported that nigrostriatal dopaminergic depletion produces trigeminal neuropathic pain that at least involves a segmental mechanism in a rat model. Khan et al. (14) showed multiple lines of evidence of disturbed structure and function in the medial prefrontal cortex and hippocampus in BMS patients, which might also affect mood.

Three sonographic abnormalities were found in patients with typical restless legs syndrome (13-15): *substantia nigra* hypoechogenicity (17%), *nuclei raphe* hypoechogenicity (26%) and *red nucleus* hyperechogenicity (26%). These results suggest similar underlying mechanism of both conditions. It seems that BMS could be analyzed as an oral variant of restless legs syndrome.

In conclusion, transcranial ultrasonography is a non-invasive, reproducible method which enables visualization and evaluation of stem structures and their environment of patients with brain BMS. The only disadvantage of this method is a narrow or thickened acoustic window.

### Conflict of interest

Non declared



**Abstract**

**Objective:** Burning mouth syndrome (BMS) is a chronic disorder which is affecting mostly postmenopausal women and is characterized by burning symptoms in the oral cavity on the clinically healthy oral mucosa. The results of previous studies suggested a possible role of peripheral and/or central neurological disturbances in these patients. The aim of this study was to analyze patients with burning mouth syndrome using transcranial sonography. **Methods:** By use of transcranial sonography of the brain parenchyma, *substantia nigra*, midbrain raphe and brain nucleus were evaluated in 20 patients with BMS (64.7±12.3 years) and 20 controls with chronic pain in the lumbosacral region (61.5±15). Statistical analysis was performed by use of Student t test with significance set at p<0.05. **Results:** The results of this study have shown hypoechoogenicity of the *substantia nigra* and *midbrain raphe* as well as hyperechoogenicity of the *brain nucleus* in BMS patients (p<0,05) as compared to controls. **Conclusions:** Altered transcranial sonography findings of the *brain parenchyma*, *midbrain raphe* and *brain nucleus* in patients with burning mouth syndrome might reflect central disturbances within this syndrome.

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**Key words**

Burning Mouth Syndrome; Transcranial Sonography; substantia nigra; Midbrain Raphe Nuclei; Red Nucleus

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