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Autonomic responses to tooth clenching in migraineurs - augmented trigeminocardiac reflex?

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ABSTRACT

Background. **–** Systemic autonomic changes are well-known in migraineurs. Also, masticatory dysfunctions including tooth clenching are reported to be associated with migraine. However, if those phenomena are interrelated, and how, is unclear. Moreover, the knowledge on the autonomic responses to masticatory stimuli in migraineurs is limited.

Objective. - To investigate tooth clenching-related cardiac autonomic regulation in migraineurs.

Methods. - We compared maximal tooth clenching-induced systemic autonomic responses, indicated by heart rate variability and blood pressure changes, in headache-free migraineurs (n=17) and control subjects (n=22).

Results.- Levels of high-frequency power, reflecting vagal activity, were lower in migraineurs at baseline but increased after tooth clenching whereas in controls they returned to baseline ($p<0.05$, Mixed model analysis). In multivariate regression model, the presence of migraine predicted the baseline levels of low- and high-frequency power and sympathovagal balance, and the post-test increase of high-frequency power, with the attack frequency and side of headache as the modifiers of the measured changes in migraineurs. The painful signs of temporomandibular disorders, found in clinical oral examination, enhanced both maximal maximal changes in RR intervals and post-test vagal responses to tooth clenching only in migraineurs.

Conclusion.- The enhanced post-clenching vagal activation may represent a marker of the augmented trigeminocardiac reflex to stimulation of trigeminal area, sensitized in migraineurs. Our results support an involvement of autonomic mechanisms in migraine pathophysiology and are interesting in terms of interactions between migraine and masticatory disorders, elucidating one potential way how masticatory disorders may aggravate migraine.

Keywords: Autonomic nervous system; heart rate variability; migraine; oral physiology; parasympathetic; trigeminal

1. INTRODUCTION

Migraine is a common neurovascular disorder but the triggering mechanisms for the activation of the trigeminovascular system, playing a key role in the development of migraine headache (1) and sensitized in migraineurs (2), are poorly understood. Migraineurs have autonomic dysfunctions (3) with interictal parasympathetic hypofunction (4, 5) but hyperfunction during the headache attacks (6). On the other hand, migraineurs are known to have more temporomandibular disorders (TMD, 7, 8) and Didier et al. (9) reported the possible cause–effect relationship between masticatory parafunctions, such as teeth clenching and grinding and the presence of chronic migraine. The mechanisms of the relations between autonomic and masticatory disorders in migraine are unclear but Peroutka (3) proposed earlier that a loss of inhibitory effects on the trigeminal system due to an imbalance of sympathetic co-transmitters may lead to trigeminal activation in migraine. However, responses to stimuli related to masticatory structures e.g. to tooth clenching are limited in migraineurs.

In the present study we compared autonomic responses to the maximal tooth clenching (MTC) in migraineurs and control subjects by measuring of heart rate variability (HRV) and blood pressure changes and identified modifiers of these responses.

2. METHODS

The study plan was approved by the Research Ethics Committee, Hospital District of Northern Savo. All participants provided a written consent.

2.1. Subjects

The study group consisted of 17 headache-free episodic migraineurs (13 women) and 22 control subjects (16 women). Patients fulfilled the diagnostic criteria of migraine according to the International Classification of Headache Disorders (10). The headache was restricted to the right side in six, to the left in three and was either bilateral or varied between attacks in eight of the migraineurs. Thirteen patients had migraine with aura. The subjects did not have other pain conditions or any other neurologic or cardiovascular diseases, or prophylactic treatment and were non-smokers.

2.2. Measurements

Clinical oral examination was performed by a TMD specialist, using the diagnostic Research Criteria for TMD (RDC TMD, 11). Of the TMD signs, pain in masticatory muscles or temporomandibular joints during palpation and jaw movements was particularly recorded (painful signs of temporomandibular disorders, pTMD) and their pain intensity was evaluated by scale 0-3. Only three migraineurs reported history of TMD but the clinical oral examination revealed painful signs in eleven migraineurs (painful muscle palpation in seven and both muscle- and joint-related pain in four patients) and in eleven controls (muscle palpation pain in all of them). There were no differences between the groups as regards to the presence of pTMD or its intensity,

Mood (0-21, 12) and autonomic disorder (0-39) scores and, in migraineurs, the intensity of the headache (0-10) and annual number of migraine attacks were self-reported.

The protocol of MTC included two series of 5 s clenching + 5 s break, followed by maximal clenching until volitional exhaustion, with cotton swabs between the teeth for their protection. The subjects were instructed to stop the test if they started to feel pain. However, the subjects did not report pain during MTC, except for one migraineur.

The systolic (SBP) and diastolic (DBP) blood pressures were measured using a Portapres device (Finapres Medical Systems, Amsterdam, the Netherlands). The electrocardiogram was recorded using a modified chest lead V5 with Biopac MP150 system (V5Biopac Systems Inc., Goleta, CA, USA). The built-in QRS detector of Kubios HRV software (Kubios Ltd., Kuopio, Finland) was used to extract the inter-beat-intervals (RR intervals) for HRV analysis. Before HRV analysis, the baseline changes in RR interval data were removed using a smoothness priors method with cut-off frequency at 0.03 Hz (13). HRV was analyzed by computing mean RR interval, root-mean-square of successive RR interval differences (RMSSD), and LF (low frequency, 0.04-0.15 Hz) and HF (high frequency, 0.15-0.4 Hz) band powers using a 2-min window. Muscular activity from both masseter muscles was controlled with surface electromyography with ME6000 biosignal monitor (Mega Electronics Ltd, Kuopio, Finland).

2.3. Statistical analysis

LF and HF powers of HRV were computed in absolute units (ms^2) and in normalized units (n.u.), and the base-10 logarithm transformation was applied for absolute power values to guarantee normality. For all parameters, averaged values were calculated two minutes before and after the test. For blood

pressure and RR, the 5s averaged values of maximal increase and decrease during or after the test were defined. The SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Mann-Whitney U-test, t-test and Fisher's Exact test were used to examine differences in characteristics between the groups. MTC-induced changes (baseline levels compared to post-test levels) in the mean values of HRV parameters and blood pressure were compared between the groups with a Linear mixed model. A stepwise linear regression analysis was used to identify the predictors of the measured changes. The level $p<0.05$ was considered significant.

3. RESULTS

The study groups did not differ as regards to age or sex or anthropometric characteristics apart of more family history of migraine ($p<0.001$) and a tendency for higher autonomic scores in migraineurs than in controls.

Before the test, mean levels of HF power and RMSSD ($p<0.005$ for both), and LF power ($p<0.05$, Fig. 1) were lower in migraineurs than in controls. Such a difference existed for RMSSD and LF/HF ratio ($p<0.05$ for both, Mann-Whitney U-test) also in post-test values.

However, the values of HF power, reflecting vagal activity, in migraineurs increased after the test whereas in controls HF power returned to the baseline levels (Mixed model analysis, $p<0.05$, Fig. 1). This increase compared to the baseline (maximally 27.8 %, mean 6.8, SEM 2.9 %) was seen in the majority of migraineurs except for one female patient with pTMD, who reported pain during MTC and showed a 17.9 % decrease in HF power, and three young patients with rare migraine attacks (1-4 annually) and absence of pTMD in two of them showing slight HF power decrease. In controls, consequently, the mean HF change was -0.9, SEM 1.5 %. The maximal DBP decrease was greater in controls than in migraineurs ($p<0.05$, Mann-Whitney U-test).

The possible determinants of the MTC-induced HRV and blood pressure changes (age, sex, migraine, pTMD and its intensity, mood and autonomic scores, duration of MTC, the baseline values of measured parameters and, in migraineurs, also duration of migraine, frequency of attacks, aura, side and intensity of headache, and, in controls, a family history of migraine) were entered stepwise into the model to study, whether they were independently associated with the measured changes. Presence of migraine was found to predict the baseline levels of LF, HF and LF/HF ratio, with the duration of disease, aura and the frequency of migraine attacks as a modifiers of the baseline HRV

levels (Table 1). Self-reported autonomic scores were related to baseline values of HF power and RR intervals. In all subjects, test-induced HF changes were predicted by the presence of migraine and also by duration of MTC. In migraineurs, in addition to the frequency of attacks and side of headache, also the intensity of pTMD was found to predict the magnitude of HRV changes (Table 1). The changes were also related to baseline HRV levels, different in migraineurs. There was not any relationship between HRV findings and pTMD in controls. In controls, however, presence of family history of migraine predicted the baseline levels and changes of RMSSD and the magnitude of maximal DBP changes (Table 1). Maximal changes in blood pressure were associated with mood state but, in migraineurs, maximal changes in RR intervals were dependent on both the frequency of attacks and intensity of pTMD.

4. DISCUSSION

In the present study, MTC-induced autonomic responses differed between migraineurs and controls. In line with the previous studies (4, 5), we found in migraineurs lower baseline vagal activity. However, we showed for the first time that, in migraineurs, MTC increased this activity as indicated by increase in HF power. Migraine and MTC duration were the main modifiers of this increase. The observed changes in vagal activity likely occurred due to trigeminocardiac reflex (TCR), induced by irritation of the trigeminal-innervated structures and well-known as an inducer of bradycardia and hypotension (14). According to Lapi et al. (15), TCR may influence the regulation of the cerebral blood flow. However, the effect of this reflex is a result of increased vagal activation combined with the state of sympathetic activity (14). Thus, impaired autonomic regulation in migraineurs may influence the responses to masticatory irritation, too. Thus, the present findings may indicate that in migraine stimuli from masticatory apparatus may play a role via the cardiac autonomic regulation. Earlier, Yarnitsky et al. (16) have shown the role of cranial parasympathetic outflow in the migraine pain induction. Indeed, the opposite roles of the sympathetic and trigeminovascular systems in the pathophysiology of migraine was claimed to be under-appreciated (3).

Previously, Takeuchi et al. (17) reported a decrease in the heart rate during a prolonged low-level tooth-clenching task. The authors suggested that there "*may be other necessary factors, such as mental stress or a sensitized or predisposed vulnerable pain system, besides tooth clenching to induce pain such as TMD or headache*" (17). In migraineurs all such factors are present. Their stress

sensitivity is higher than that of healthy individuals (18) and, in the present study, blood pressure increase was associated with mood scores, with stress and unpleasantness affecting autonomic reactions. In addition to underlying autonomic dysfunction, there is sensitization of nervous system, both central and peripheral, in migraine (2). Among migraineurs, cutaneous allodynia, reflecting central sensitization (19), and cortical hyperexcitability (20) have been shown to be associated with headache frequency, which was associated with the autonomic imbalance also in our patients. However, the causal connections between painful masticatory muscles and severity of migraine are not completely clear. A recent systematic review (21) reported that the pressure pain thresholds values over the craniofacial muscles were lower in headache patients including migraineurs, masseter being the most sensitive muscle. It has been claimed that tension-type headache frequency correlated with the muscle tenderness with continuous nociceptive input from peripheral myofascial structures as one of the possible causes of the central sensitization (22). The impact of myofascial trigger points in peripheral sensitization has also been considered (22). Thus, increased sensitivity of masticatory muscles may reflect sensitization due to alteration of pain processing (21). However, according to Buchgreitz et al. (23), the increased pain sensitivity is a consequence of frequent headache, not a risk factor. In migraineurs, Sandrini et al. (24) reported that the thresholds to trigeminal stimulation were lowered and lowest on the symptomatic side, suggesting trigeminal sensitization and hyperexcitability of the trigeminal pain pathway.

In myofascial TMD, tooth clenching induced an increase in serotonin levels and decrease in masseter muscle blood flow, both being sources of muscular pain (25). In a previous study, heart rate increase was found to correlate with pain ratings (26). Thus, clenching-related pain may possibly play a role in altered autonomic responses, but because of short and heterogeneous clenching time, our on-test HRV parameters were not reliable. However, our subjects, except for one, did not report pain during tooth clenching. Still, more than half of them in both groups had painful findings during oral examination. However, only in migraineurs these findings were related to enhanced post-test vagal responses to MTC. Indeed, in experiments with tooth clenching, development of attack in migraineurs was not dependent on the task intensity suggesting that muscle ischemia and strain on muscle insertions are unlikely a cause of the attack (27). Further, in migraineurs, HF increase occurred regardless of the presence or absence of pTMD, and both higher attack frequency, predisposing for trigeminal sensitization and allodynia, and possibly consequent, pTMD predicted RR

intervals changes in migraineurs. It is important to note that TMD pain severity is associated with migraine attack frequency (8). Indeed, both migraineurs and TMD patients may have similar biopsychosocial risk factors for the development of pain conditions (28) and the involvement of the central sensitization has been suggested also in myofascial TMD (29). Overall, the mechanisms of the relationship between migraine and tenderness of masticatory muscles, so far, are waiting for explanation.

With HRV measurements during cluster pain, induced by sphenopalatine ganglion stimulation, parasympathetic activity has been shown to increase, indicating the involvement of cardiac autonomic regulation, specifically TCR, in cluster headache mechanisms (30). Previously, beneficial effect of vagal stimulation in migraine has been reported (31). Taking into account the baseline autonomic imbalance and enhanced vagal effect of experimental clenching, the augmented TCR may play a significant role in the multifactorial pathophysiology of migraine, since increase in vagal activity results in cerebral vasodilation. Anyway, the results call for future investigations and larger studies are needed to clarify the nature of the cardiac autonomic responses to tooth clenching.

Limitations: Duration of the MTC varied between the subjects when every subject determined individually the clenching duration and the force, which was maximal for him/her. Therefore, we concentrated in the examination of the post-test values. The breathing was not controlled but ECG derived respiratory rate was computed and it was within the HF frequency band for all subjects.

5. CONCLUSION

The enhanced post-clenching vagal activation may be a marker of augmented trigeminocardiac reflex to masticatory stimuli affecting the sensitized trigeminal area in migraineurs. It supports an involvement of autonomic mechanisms in migraine pathophysiology and is interesting in terms of interactions between migraine and masticatory disorders.

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DISCLOSURE

The study plan was approved by the Research Ethics Committee, Hospital District of Northern Savo. All participants provided a written consent. The authors have stated explicitly that there are no conflict of interests in connection with this article. No additional funding was received.

ABBREVIATIONS

DBP, diastolic blood pressure; HF, high frequency; HR, heart rate; HRV, heart rate variability; LF, low frequency; MTC, maximal tooth clenching; pTMD, painful signs of temporomandibular disorders; RR, inter-beat-intervals; SBP, systolic blood pressure; TCR, trigeminocardiac reflex; TMD, temporomandibular disorders.

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TABLES

Table 1. Predictors of changes in HRV parameters and blood pressure compared to baseline values in all studied subjects (n=39) and separately in controls (n=22) and in migraineurs (n=17) with the clinical characteristics of migraine added into the model.

Parameter	All subjects	Controls	Migraineurs
	Predictor, *β;* Sign.	Predictor, β; Sign.	Predictor, β; Sign.
Baseline levels (2min mean):			
LF power	Migraine, -0.427 **	ns	Migraine duration, -0.504 *
HF power	Migraine, -0.375 *	ns	Aura, 0.696 **
	Autonomic scores, -0.347 *		Autonomic scores, -0.518 **
RMSSD	Age, -0.466 ***	FHM, 0.485 *	Migraine duration, -0.570 *
	Sex, -0.342 *		
	Autonomic scores, 0.301 *		
LH/HF ratio	Sex, 0.374 *	Autonomic scores, -0.497 *	Attack frequency, 0.586 *
	Migraine, 0.333 *	Sex, 0.496 *	
RR intervals	Autonomic scores, -0.678 ***	Sex, -0.475 *	ns
	Mood scores, 0.432 *		
	pTMD, 0.343 *		

Post-test changes compared to baseline levels:

LF power	Baseline levels, -0.497 ***	Baseline levels, -0.468 *	ns
HF power	Migraine, 0.445 **	ns	ns
MTC duration, 0.333 *			
RMSSD	ns	FHM, 0.609 *	ns
Sex, -0.511 **			
RR intervals	ns	Baseline levels, 0.463 *	Baseline levels, -0.597 ***
Headache side, -0.522 ***			
pTMD intensity, 0.499 ***			
LF/HF ratio	Baseline levels, -0.605 ***	ns	Attack frequency, -0.625 ***
Headache side, 0.383 *			
SBP	ns	Mood scores, -0.621 *	ns

Maximal increase compared to baseline levels:

SBP	Mood scores, 0.403 *	Mood scores, 0.652 **	Baseline levels, 0.546 *
Baseline levels, 0.357 *		Attack frequency, 0.497 *	
DBP	Mood scores, 0.395 *	Mood scores, 0.616 *	ns
RR intervals	ns	Baseline levels, 0.713 ***	MTC duration, 0.485 *
Age, -0.498 *			

Maximal decrease compared to baseline levels:

SBP	ns	ns	Sex, -0.650 *
DBP	Migraine, -0.451 *	ns	Sex, -0.667 *
RR intervals	Baseline levels, 0.575 ***	Baseline levels, 0.747 ***	Attack frequency, 0.556 ***
pTMD intensity, -0.294 *	Age, -0.423 *	Baseline levels, 0.535 ***	
pTMD intensity, -0.452 *			

Amplitude of maximal changes:

SBP	Mood scores, 0.496 **	Mood scores, 0.844 ***	Baseline levels, 0.752 ***
Age, 0.614 ***			
Sex, 0.428 *			
DBP	ns	Mood scores, 0.776 ***	ns

FHM, 0.536 ***

Baseline levels, 0.394 ***

RR intervals Baseline levels, 0.476 *** Baseline levels, 0.794 *** Attack frequency, 0.707 ***

Age, -0.497 *

Data were analyzed by logistic multivariate stepwise regression model.
LF: low frequency; HF: high frequency; RMSSD: root-mean-square of successive RR interval differences; MTC: maximal tooth clenching; SBP: systolic blood pressure; DBP: diastolic blood pressure; FHM: family history of migraine; pTMD: painful signs of temporomandibular disorders.
* $p<0.05$, ** $p<0.01$, *** $p<0.005$

Figure legends

Figure 1. Mean values of RR intervals, HF and LF powers in controls (n=22) and migraineurs (n=17) two minutes before and after maximal tooth clenching (mean values/SEM).