

Syncope in migraine

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Abstract. Syncope, defined as transient loss of consciousness and postural tone, is a frequent symptom due to an abrupt reduction in cerebral flow and by multiple etiological causes including migraine; of great emotional impact on the patient, it is of high social cost both for the diagnostic difficulties and for the cure of its consequences. Numerous factors can contribute to the pathogenesis of migraine, including dysfunction of the sympathetic nervous system and endothelial dysfunction that causes abnormal vascular reactivity. A clinical study using standardized and validated diagnostic methods will allow further knowledge on the association between migraine, symptoms of orthostatic intolerance and vasovagal syncope.

Key words: vasovagal syncope, migraine, sympathetic nervous system

SINCOPE NELL'EMICRANIA

Riassunto. La sincope, definita come transitoria perdita di coscienza e del tono posturale, è un sintomo frequente dovuto a una brusca riduzione del flusso cerebrale e da più cause eziologiche fra cui l'emicrania; di grande impatto emotivo sul paziente, risulta di alto costo sociale sia per le difficoltà diagnostiche che per la cura delle sue conseguenze. Numerosi fattori possono contribuire alla patogenesi dell'emicrania, tra cui la disfunzione del sistema nervoso simpatico e la disfunzione endoteliale che causa una reattività vascolare anormale. Uno studio clinico che utilizza metodi standardizzati e validati per la diagnosi, consentirà ulteriori conoscenze sull'associazione tra emicrania, sintomi di intolleranza ortostatica e sincope vasovagale.

Parole chiave: sincope vasovagale, emicrania, sistema nervoso simpatico

SÍNCOPE EN MIGRAÑA

Resumen. El síncope, definido como pérdida transitoria de conciencia y tono postural, es un síntoma frecuente debido a una reducción abrupta en el flujo cerebral y por múltiples causas etiológicas, incluida la migraña; De gran impacto emocional en el paciente, tiene un alto costo social tanto por las dificultades de diagnóstico como por la cura de sus consecuencias. Numerosos factores pueden contribuir a la patogénesis de la migraña, incluida la disfunción del sistema nervoso simpático y la disfunción endotelial que causa una reactividad vascular anormal. Un estudio clínico que utilice métodos de diagnóstico estandarizados y validados permitirá un mayor conocimiento sobre la asociación entre la migraña, los síntomas de intolerancia ortostática y el síncope vasovagal.

Palabras clave: síncope vasovagal, migraña, sistema nervoso simpático

Background information

Migraine is a complex polygenic neurovascular brain disorder characterized by episodes of unilateral or bilateral head pain, accompanied with autonomic manifestations and in some patients with aura symptoms. Several factors may contribute to pathogenesis of migraine including sympathetic nervous system dysfunction and endothelial dysfunction causing abnormal vascular reactivity. During the crisis the following autonomic symptoms may occur:

1. *Cranial autonomic symptoms*: facial flushing/sweating, lacrimation, conjunctival injection, ptosis, scratchiness in eye, periorbital edema, nasal congestion and rhinorrhea, caused by activation of trigeminal-autonomic reflex. (Gelfand 2013) Cranial autonomic symptoms in migraine are bilateral, while in cluster headache are unilateral (Lai 2009, Gelfand 2013).

2. *Gastrointestinal symptoms*: nausea, vomiting, abdominal pain, diarrhea. A delayed gastric emptying may occur during the crisis. It may be caused by increased sympathetic and decreased vagal activity (Aurora SK 2013)

3. *Orthostatic intolerance symptoms*: Patients with migraine may present vasovagal (VV) syncope episodes during the migraine-free periods. A population-based study showed a high prevalence of VV syncope and orthostatic intolerance in patients with migraine compared with controls (Thijs et al 2006). Likewise studies of patients with VV syncope showed high prevalence of migraine

Syncopal migraine: patients report a migraine headache closely preceding or following a VV syncope episode, these patients may also present typical migraine episodes without syncope. (Nappi 1984, Curfman 2012).

Autonomic function in patients during migraine-free period has been studied using different techniques:

1. *Cardiovascular autonomic function tests*: sympathetic tests had shown increased blood pressure (BP) and heart rate (HR) reactivity to mental stress (Domingues 2009). No abnormal reactivity has been also reported (Shechter 2002, Leistad 2007). Decreased BP response to isometric handgrip exercise (Mosek 1999, Benjelloun 2004). BP and HR responses to orthostatic stress had shown no significant dif-

ferences between migraine and control subjects (Thijs 2006). Increased vasomotor reactivity to isometric handgrip, Valsalva maneuver and cold test was found (Babayán 2017). Parasympathetic tests: normal HR response to deep breathing and Valsalva maneuver was shown (Mosek 1999, Shechter 2002), also abnormal immediate HR response on standing was reported (Shechter 2002).

2. *Biochemical studies*: there is evidence of abnormal sympathetic neurotransmission in migraine patients: low plasma norepinephrine levels, pharmacological tests that found adrenergic receptors supersensitivity and unbalanced levels of dopamine and noradrenaline (Peroutka 2004, D'Andrea 2012)

3. *Brain functional imaging*: studies in patients with migraine had shown several findings: MRI showed enhanced connection between the amygdala and viscerosensitive cortex (Hadjikhani 2013), voxel-based morphometry showed reduced grey matter volume in brainstem structures (midbrain periaqueductal gray matter, pons and medullary raphe) (Marciszewski 2013), abnormal activation of the anterior and posterior hypothalamus (Schulte 2017)

The mechanisms responsible for syncopal migraine are not clear; Curfman et al (2012) suggested that syncope occurring in a migraine episode is caused by a mechanism related with the migraine pathophysiology. Functional imaging in migraine patients had shown compromise of the hypothalamus and brainstem areas, which are related with autonomic function.

Patients with migraine showed biomarkers of endothelin activation (Tietjen 2009), association of endothelin type A receptors polymorphism with migraine was shown (Miao 2012). Patients with and syncope showed upregulated expression microRNAs showing an endothelial dysfunction, which could be associated with impairment of sympathetic control of blood flow (Cheng 2017).

A clinical study using standardized and validated methods for: diagnosis of migraine, diagnosis of VV syncope with an assessment of cardiovascular autonomic function, plasma and urinary biomarkers of endothelial dysfunction and functional imaging will allow further knowledge about the association between migraine and VV syncope.

Objectives

1. To describe different groups of migraine patients in relation to occurrence of VVS: patients with migraine without VV syncope, patients with migraine and presence of VV syncope during migraine-free period and patients with syncopal migraine
2. To explore clinical autonomic function, endothelial dysfunction and autonomic functional imaging in different groups of migraine patients

Study design: cross sectional study in of patients with from outpatient clinic

Methodology: Population: Consecutive patients with clinical diagnosis of migraine according to the International Classification of Headache Disorders, 3rd edition (beta version). Sociodemographic, medical, and migraine characteristics were assessed by a medical history and neurological examination. VV syncope diagnosis was obtained according to the 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope (Shen 2017).

Methods: 1. Questionnaires: 1.A. Autonomic symptoms, 1.B. VVS Syncope.

2. Cardiovascular autonomic function tests: 2.1. orthostatic stress: blood pressure (BP) and heart rate (HR) change on standing, 2.2. Cardiovagal, deep breathing HR change 2.3. Valsalva maneuver. 2.4. Isometric handgrip exercise: BP and HR change during handgrip. 2.5. Cold pressor test: BP change. 3. plasma and urinary biomarkers of endothelial dysfunction and 4. brain functional imaging studies

Ethical approval by local committee.

Literature search

- Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. *Neurology*. 2013;81:431-6.
- Lai TH, Fuh JL, Wang SJ. 3-7. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. *J Neurol Neurosurg Psychiatry*. 2009;80:1116-9
- Aurora SK, Papapetropoulos S, Kori SH, Kedar A, Abell TL. Gastric stasis in migraineurs: etiology, characteristics, and clinical and therapeutic implications. *Cephalalgia*. 2013;33:408-15
- Nappi G, Sances G, Martignoni E, Micieli G, Sandrini G, Bono G. L'emicrania sincopale. *Giornale di Neuropsicofarmacologia* 1984;4:211-213
- Curfman D, Chilungu M, Daroff RB, Alsheklee A, Chelimsky G, Chelimsky TC. Syncopal migraine. *Clin Auton Res*. 2012;22:17-23
- Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine: the population-based CAMERA study. *Neurology*. 2006;66(7):1034-7
- Bandinelli G, Cencetti S, Bacalli S, Lagi A. Disease-related syncope. Analysis of a community-based hospital registry. *J Intern Med*. 2000;247:513-6.
- Babayan L, Mamontov OV, Amelin AV, Bogachev M, Kamshilin AA. Arterial hypertension in migraine: Role of familial history and cardiovascular phenotype. *Auton Neurosci*. 2017;203:103-107.
- Domingues RB, Fonseca KB, Ziviane LF, Domingues SA, Vasalo D. Altered cardiovascular reactivity to mental stress but not to cold pressure test in migraine. *Headache*. 2010;50:13
- Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. *Neurology*. 2002;58:422-7.
- Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache*. 2004;44:53-64
- D'Andrea G, D'Arrigo A, Dalle Carbonare M, Leon A. Pathogenesis of migraine: role of neuromodulators. *Headache*. 2012 Jul-Aug;52(7):1155-63
- Leistad RB, Sand T, Nilsen KB, Westgaard RH, Stovner LJ. Cardiovascular responses to cognitive stress in patients with migraine and tension-type headache. *BMC Neurol*. 2007;7:23 .
- Mosek A, Novak V, Opfer-Gehrking TL, Swanson JW, Low PA. Autonomic dysfunction in migraineurs. *Headache*. 1999;39:108-17.
- Benjelloun H, Birouk N, Slaoui I, Coghlan L, Bencheikh BO, Jroundi I, Benomar M. Autonomic profile of patients with migraine. *Neurophysiol Clin*. 2005;35:127-34
- Hadjikhani N, Ward N, Boshyan J, Napadow V, Maeda Y, Truini A, Caramia F, Tinelli E, Mainero C. The missing link: enhanced functional connectivity between amygdala and viscerosensitive cortex in migraine. *Cephalalgia*. 2013;33:1264-1268.
- Marciszewski KK, Meylakh N, Di Pietro F, Macefield VG, Macey PM, Henderson LA. Altered brainstem anatomy in migraine. *Cephalalgia*. 2017;33:102417694884.
- Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: Evidence from high-resolution fMRI. *Neurology*. 2017;88:2011-2016
- Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. *Stroke*. 2009;40:2977-82
- Miao J, Wang F, Fang Y. Association of 231G>A polymorphism of endothelin type A receptor gene with migraine: a meta-analysis. *J Neurol Sci*. 2012;323:232-5
- Cheng CY, Chen SP, Liao YC, Fuh JL, Wang YF, Wang SJ. Elevated circulating endothelial-specific microRNAs in migraine patients: A pilot study. *Cephalalgia*. 2017 Jan 1:333102417742375
- Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2017;136(5):e25-e59