

Central sensitization in photophobic and non-photophobic migraineurs: possible role of retino nuclear way in the central sensitization process

Carlo Lovati · C. Mariotti · L. Giani ·
D. D'Amico · A. Sinelli · F. De Angeli ·
E. Capiluppi · G. Bussone · C. Mariani

© Springer-Verlag Italia 2013

Abstract The aim of the present study was to investigate the possible relationships between the presence of headache-related photophobia and migraine-associated allodynia—a hallmark of central sensitization—among patients with different migraine types. A sample of 456 migraineurs was studied. Our results showed that photophobia was present in a high proportion of patients, with similar figures in patients with episodic migraine or CM, and confirmed that the prevalence of allodynia was higher among CM patients than in those with episodic migraine. We found a clear association between migraine-related allodynia and photophobia only in CM patients. Overall, these findings suggest that light stimulation may contribute to central sensitization of pain pathways in migraineurs, possibly contributing to progression into chronic forms. The possible connections underlying this type of sensitization is offered by the recently published data on a non-image-forming visual retino-thalamo-cortical pathway which may allow photic signals to converge on a thalamic region which is selectively activated during migraine headache.

Keywords Episodic migraine · Chronic migraine (CM) · Allodynia photophobia · Central sensitization

Introduction

Central sensitization is the process that underlies migraine-associated allodynia. It is an increased response to stimulation that is mediated by amplification of signaling in the central nervous system (CNS) with a consequent noxious sensation in presence of a non-noxious stimulus caused by a recruitment mechanism. In fact, central sensitization is a state in which neurons activated by noxious mechanical and chemical stimuli are sensitized by such stimuli and become hyper-responsive to all subsequent stimuli delivered to the neurons' receptive fields [1]. Neuroplasticity and subsequent CNS sensitization include altered function of chemical, electrophysiological, and pharmacological systems, involving intricate changes in both the peripheral and CNSs. In the case of migraine-associated allodynia, it is thought that the stimulus able to sensitize pain matrix nuclei is the frequent recurrence of migraine attacks. In fact, allodynia, that in turn is an hallmark of sensitization, has been found to be more prevalent among chronic migraineurs with respect to episodic ones reinforcing the hypothesis of the necessity of frequent stimulation of central nuclei of the pain pathway to induce sensitization [2].

A visual pathway from the optic chiasm to the pulvinar, and from the pulvinar to several associative cortical brain regions, was recently described, which may allow photic signals to converge on a thalamic region which is selectively activated during migraine headache [3, 4]. This pathway is responsible for migraine-associated photophobia, i.e., worsening of pain induced by light exposition.

C. Lovati (✉) · L. Giani · E. Capiluppi · C. Mariani
Chair of Neurology, Department of Neurology,
Headache Unit, A.O. Luigi Sacco, University of Milan,
Via G.B Grassi 74, 20157 Milan, Italy
e-mail: lovati.carlo@hsacco.it

C. Mariotti · A. Sinelli · F. De Angeli
Faculty of Medicine, University of Milan, Milan, Italy

D. D'Amico · G. Bussone
Department of Clinical Neuroscience, Headache Unit,
C. Besta Neurological Institute and Foundation, Milan, Italy

Based on the above reported background, we designed a study to investigate the possible relationships between the presence of headache-related photophobia and migraine-associated allodynia among patients with different migraine types. The aims of the study were: (1) to evaluate the prevalence of photophobia and of allodynia in a clinical sample of migraineurs and (2) to evaluate the possible relationship between the presence of headache-related photophobia and migraine-associated allodynia in migraineurs in general and in specific subgroups with differences in attack frequency.

Materials and methods

A sample of 456 migraineurs consecutively attending the Headache Center of L. Sacco Hospital was studied. Mean age was 38.2 ± 13.2 , 65 were males and 391 females. All patients with a diagnosis of episodic or chronic migraine (CM) according to ICHD-II criteria [5, 6] were enrolled. Patients with a diagnosis of medication overuse headache were not included. A semi-structured ad hoc questionnaire was used to evaluate the presence of allodynia [2]. The presence of photophobia was assessed by specifically asking patients if light exposition during headache attacks was able to increase head pain.

Chi square test was used to compare frequency of each symptom in different groups while Student *t* test was applied to compare mean duration of illness among different groups.

Results

CM was present in 126 patients and episodic migraine in 330.

In the total sample, 248 patients had allodynia. The prevalence of allodynia was higher among CM patients than in those with episodic migraine (62.7 vs. 51.2 %, respectively; $p = 0.035$). A total of 385 patients were photophobic. Its prevalence was similar in patients with CM and with episodic migraine (84.1 vs. 84.5 %, respectively; $p = \text{NS}$). Among the photophobic patients, 216 were allodynic and 169 were not, and among the 71 without photophobia, 32 were allodynic and 39 were not allodynic. Comparing the two groups (photophobic and non-photophobic patients) for the presence of allodynia, we observed a trend of association between photophobia and allodynia, although not significant ($p = 0.08$).

Among the CM patients, 106 out of 126 were photophobic (among them, 71 were allodynic and 35 not), while the remaining 20 subjects were free from photophobia (among them, 8 with allodynia and 12 without). A significant higher prevalence of allodynia among photophobic CM patients

with respect to those without photophobia ($p = 0,029$) was found.

In the episodic migraine group, 279 out of 330 subjects were photophobic (among them, 145 were allodynic and 134 were not) and 51 were non-photophobic (among them, 24 were allodynic and 27 were not). No difference in allodynia prevalence was observed comparing these two groups ($p = 0.51$). An analogous result was obtained dividing patients in photophobic ($n = 385$) and non-photophobic ($n = 71$): among 385 photophobic migraineurs 106 had CM (among them, 71 were allodynic and 35 were not) and 279 had episodic migraine (among them, 145 were allodynic and 134 were not), with a significant prevalence of allodynia among photophobic CM patients ($p = 0.008$). When the 71 migraineurs who did not complain of photophobia were evaluated, 20 out of them had CM (8 allodynic and 12 not allodynic), while 51 had episodic migraine (among them, 24 were allodynic and 27 were not) without any significant difference ($p = 0.59$).

The above reported data are reported in terms of percentages and statistical evaluation in Table 1.

To avoid selection biases, we assessed that photophobia was equally distributed among episodic and chronic migraineurs ($p = 0.77$), and that no difference in migraine duration (years of illness history) was present between allodynic and non-allodynic patients in both photophobic and non-photophobic groups.

Table 1 Prevalence of allodynia and photophobia, and statistical evaluation of the relationships between these two variables in the studied patients with CM and episodic migraine

Allodynia			
Chronic migraine	62.7 %		$p = 0.035$
Episodic migraine	51.2 %		
Photophobia			
Chronic migraine	84.1 %		$p = 0.77$ (NS)
Episodic migraine	84.5 %		
Relationship allodynia/photophobia			
Photophobic			
Chronic migraine			$p = 0.008$
With allodynia	71	67 %	
Without allodynia	35	33 %	
Episodic migraine			
With allodynia	145	52 %	
Without allodynia	134	48 %	
Non-photophobic			
Chronic migraine			$p = 0.59$ (NS)
With allodynia	8	40 %	
Without allodynia	12	60 %	
Episodic migraine			
With allodynia	24	47 %	
Without allodynia	27	53 %	

Discussion and conclusion

The presence of photophobia is one of the items included in the current diagnostic criteria of migraine [5], and in clinical practice it is frequently reported both by episodic migraine and by CM patients.

Our results showed that photophobia was present in a high proportion of migraineurs, with similar figures in patients with episodic migraine or CM. Our data confirmed that the prevalence of allodynia was higher among CM patients than in those with episodic migraine. Furthermore, we found that the association between migraine-related allodynia and photophobia was correlated to the frequency of headache, as it was evident only in CM patients, while no significant association was found with the length of migraine history. Overall, these observations suggest that light stimulation may contribute to central sensitization of pain pathways in migraineurs with a high frequency of attacks. This sensitizing effect may be due to the recurring stimulation of nuclei in the CNS involved in pain processing in migraine patients by a specific non-image-forming visual pathway. An interesting insight into the possible connections underlying this type of sensitization is offered by the recently published data on a novel retino-thalamo-cortical pathway, which was studied in rats and

also in humans by MR tractography, and that was demonstrated to be able to transmit photic stimuli from the retina into the trigeminovascular neurons in the thalamus.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Mosby Inc. (2009) Mosby's Medical Dictionary, 8th edn. Elsevier, St. Louis
2. Lovati C, D'Amico D, Bertora P, Rosa S, Suardelli M, Mailland E, Mariani C, Bussone G (2008) Acute and interictal allodynia in patients with different headache forms: an Italian pilot study. *Headache* 48(2):272–277
3. Nosedà R, Kainz V, Jakubowski M, Gooley JJ, Saper CB, Digre K, Burstein R (2010) A neural mechanism for exacerbation of headache by light. *Nat Neurosci* 13(2):239–245
4. Maleki N, Becerra L, Upadhyay J, Burstein R, Borsook D (2012) Direct optic nerve pulvinar connections defined by diffusion MR tractography in humans: implications for photophobia. *Hum Brain Mapp* 33(1):75–88
5. Headache Classification Subcommittee of the International Headache Society (2004) The international classification of headache disorders. *Cephalalgia* 24(Suppl 1):24–36
6. Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ et al (2006) New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 26:742–746