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Palinopsia in patients with migraine: A case-control study

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Abstract

Objectives: This study was aimed at investigating the frequency of the visual phenomenon of palinopsia (visual perseveration) in patients with migraine.

Methods: We interviewed 63 patients with migraine with aura (MwA), 137 patients with migraine without aura (MwoA) and 226 sex-age-matched healthy control subjects using an *ad hoc* structured interview/questionnaire. The interview was divided into four classes of variables for statistical testing.

Results: Palinopsia occurred in 19/200 patients (9.5%); of them 10/63 had MwA and 9/137 MwoA (14.2% vs 6.6%, chi = 9.7, degrees of freedom = 1, $p = 0.002$). Patients with palinopsia had a significantly lower migraine attack frequency than those without this visual phenomenon (4.3 ± 0.3 vs 14.4 ± 0.2, $z = 7.1$, $p < 0.0001$). No healthy control subjects complained of palinopsia according to the structured interview/questionnaire.

Discussion: Palinopsia is probably under-diagnosed in patients with migraine. Further investigations are needed to assess whether migraineurs are particularly susceptible to the development of recurrent episodes of visual perseveration.

Keywords

Palinopsia, migraine, aura, visual hallucinations

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Introduction

Visual hallucinations are found in several neurological conditions and migraine is well recognized as a cause of simple visual hallucinations (1,2). The experience of retaining a visual image of objects remaining in the field of view after the patient has looked away or returning after a short delay is known as palinopsia (Greek palin, again and opsis, vision) (3). Palinopsia has numerous aetiologies and associations, including seizures (4), focal cerebral lesions (5), multiple sclerosis (5), psychiatric disease (5) and Charles Bonnet syndrome (4,5). Occurrence of palinopsia in subjects using psychoactive drugs (6–9) and topiramate (5,10) has been reported.

Palinopsia can also occur in otherwise healthy individuals although its prevalence is unknown in the general population and the literature is currently limited to the description of clinical cases of patients reporting symptoms attributable to palinopsia (11).

Palinopsia is probably under-diagnosed in patients with migraine because the patient's visual perception might easily be dismissed as atypical aura.

This study was aimed at investigating the frequency of this visual phenomenon in patients with migraine with and without aura.

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Subjects and Methods

The study was conducted from April 2009 to July 2010 at the outpatient Headache Centres of Como (S. Anna Hospital), Perugia (S. Maria della Misericordia Hospital), and Rome (S. Eugenio Hospital). The final protocol was approved by the local Institutional Review Boards and ethics committees of each centre and informed consent was signed by each patient and healthy control subject.

Patients

Patients with episodic migraine with aura (MwA) and migraine without aura (MwoA) according to the International Classification of Headache Disorders 2nd ed. criteria (12) were consecutively recruited.

All patients underwent a detailed interview about the history of the primary headache and a clinical evaluation by an experienced neurologist. All details regarding day and time of migraine and aura onset, duration, associated symptoms, symptomatic drugs used and the relief after 2 hours following drug intake were recorded into a headache diary for a period of 3 months before inclusion in the study.

Patients were excluded from the study if: i) there was a history of stroke or epilepsy; ii) palinopsia occurred in relation to sleep onset or on waking; iii) the visual disturbance was accompanied by auditory hallucinations; iv) palinopsia was accompanied by symptoms suggestive of complex partial seizures; v) there were symptoms or history suggestive of alcohol withdrawal syndrome; vi) previously or currently under treatment with medications associated with palinopsia (i.e. trazodone (6), mirtazapine (7), maprotiline (8), nafazodone (9) or topiramate (5,10); or there was a history of vii) psychiatric diseases or viii) ophthalmologic diseases. Moreover, patients who referred to visual perseveration only after looking at a bright object were excluded because this visual phenomenon was considered as prolonged retinal after-image.

Patients were assessed in the outpatient departments using an *ad hoc* questionnaire. This semi-structured interview/questionnaire covers patient demographics, medication history, current health and questions in which patients are asked to describe the characteristics of their visual disturbances (i.e. palinopsia) (see Appendix).

Two skilled investigators carried out all the assessments (VB and LMC). EEG, brain MRI, neuropsychometric assessment and a complete ophthalmologic examination were performed on patients diagnosed with palinopsia disclosed during the structured interview/questionnaire.

Analysis

The interview was divided into four classes of variables for statistical testing.

(i) Presence or absence of palinopsia and verbal description of the visual phenomenon;
(ii) Temporal variable: this variable was divided into three categories: a) the duration, b) the recurrence of the visual disturbance and c) the temporal relationship with migraine;
(iii) Phenomenological variable: the emotional content variable was recorded into emotional (pleasant and unpleasant) or neutral;
(iv) Conditions in which palinopsia was likely to occur.

Our agreement between and within investigators was 0.8.

The items in the above specified interview were combined into a single dummy variable (presence/absence of palinopsia) that was used in the statistical analysis.

Preliminary analyses of the demographic and clinical features of our sample were performed grouping the patients according to their clinical diagnosis (MwoA and MwA). Distribution of sex and occurrence of palinopsia were summarized as frequencies, and comparisons were made using the Pearson chi-square test. Age and migraine frequency were indicated as geometric mean and standard error and were investigated using Mann Whitney U test and Kruskal-Wallis analysis of variance when appropriate. Within patients, the relationship between frequency of migraine attacks and presence of palinopsia was explored using a logistic regression model with a 'robust' estimation of standard errors, adjusting for age, sex and presence of aura. Subsequently, a Hosmer-Lemeshow test was performed to confirm the compatibility of the regression model. All values were considered statically significant if $p < 0.05$. All statistics were implemented using STATA version 10.0 (StataCorp, Texas, USA).

Results

Of the 275 patients investigated, 200 met entry criteria and were interviewed to assess the occurrence of palinopsia, as were 226 healthy subjects, matched for age and sex, that were used as controls. Drug-free control subjects without a history of migraine were recruited from among the staff working at the hospitals.

Demographic and clinical details of patients and controls are given in Table 1. No difference was found regarding sex distribution ($\chi^2 = 1.76$, degrees of freedom (df) = 1, $p = 0.2$) and age ($Z = 0.9$ $p = 0.3$) between patients and controls and between MwA patients and MwoA patients (sex: chi = 2.1, df = 2

Table 1. Demographic and clinical features of patients and controls

	MwA (n = 63)	MwoA (n = 137)	Overall (n = 200)	Controls (n = 226)
Sex (M/F)	11/52	19/118	30/170	45/181
Age (years)*	37.9 (1.2)	36.7 (1.1)	37 (0.8)	37.4 (0.8)
Migraine attacks per year*	11.2 (0.6)	13.6 (0.3)	12.8 (0.3)	Not applicable
Palinopsia (n)	10	9	19	0

*Values are given as geometric mean and standard error (SE). Abbreviations: MwoA: migraine without aura, MwA: migraine with aura.

$p = 0.3$; age: chi = 0.27, df = 2, $p = 0.9$). Moreover, no difference was found between MwA and MwoA patients regarding the frequency of migraine attacks ($Z = 1.57$, $p = 0.1$).

Palinopsia occurred in 19 patients (9.5%); of them 10/63 had MwA and 9/137 MwoA (14.2% vs 6.6%, chi= 9.7, df = 1, $p = 0.002$). There was a tendency for palinopsia to last for seconds, rather than minutes or hours (data not shown). No patients had an emotional response to the visual phenomenon and they found the experiences neutral (Appendix, item 3); moreover, palinopsia could occur at any time and it was not related to specific conditions (Appendix, item 4). Visual perseveration (palinopsia) consisted of real objects or patterns (Table 2) that were located in the peripheral visual field after looking away, and these were unlikely to be associated with the onset of migraine attacks or an aura.

67.8% of the patients reported that their visual disturbance occurred monthly, whereas 32.2% of the patients said that it occurred only periodically. The Mann-Witney test showed that patients with palinopsia had a significantly lower migraine attack frequency than those without palinopsia (4.3 ± 0.3 vs 14.4 ± 0.2 attack/year), $Z = 7.1$, $p < 0.0001$).

Logistic regression showed a significant inverse relationship between frequency of migraine attacks and the occurrence of palinopsia, even after adjustment for sex, age and presence of aura (wald $\chi^2 = 20.3$ df = 4, $p = 0.0004$, pseudo $R^2 = 0.77$, Table 3). The Hosmer-Lemeshow test demonstrated that the regression model used in this analysis provided an adequate description of the data (chi = 1.13, df = 8 $p = 0.99$). Because of the small sample size the product term 'sex × presence of aura' was not included in this analysis.

EEG and brain MRI were unremarkable in all patients with palinopsia. Neuropsychometric assessment was entirely normal with no visuospatial deficit. No healthy control subjects complained of palinopsia.

Discussion

To the best of our knowledge this is the first study aimed at investigating the frequency of the visual phenomenon of palinopsia in patients with migraine. We confirm previous data showing that visual hallucinations are common in patients with migraine (1,2). Although in these patients complex visual hallucinations are rare (2), in our study we found that recurrent episodes of visual perseveration were referred to by about 10% of patients interviewed. In particular, palinopsia was seen more frequently in MwA patients than in MwoA patients, and patients overall reported that palinopsic events lasted for seconds, were located in the peripheral visual field and consisted of real objects or patterns (Table 2). Moreover, we found that palinopsic events were unlikely to be associated with the onset of migraine attacks or an aura, and that there was a significant inverse relationship between frequency of migraine attacks and the occurrence of palinopsia.

Palinopsia bears a resemblance to retinal after-images. If one looks at a bright object and then at a bland background the after-image persists for about 20 s and it can be revived by blinking and appears to move in the direction of eye movements (3). The duration is related to the intensity and time of exposure to the stimulus (3). In our patients, the images in visual perseveration did not have these characteristics and patients with prolonged retinal after-image were excluded from the analysis.

The mechanism of visual perseveration is not fully understood (13,14). A range of symptoms collectively termed palinopsia have been linked to dysfunction within parietal-lobe coordinate systems (13,14). They include: i) polyopia (perceiving multiple copies of the same object, often arranged in rows and columns; ii) visual perseveration (an object remaining fixed in retinal coordinates with eye movements); iii) delayed palinopsia (an object returning to field of view); and iv) illusory visual spread (the spread of a pattern from an object to its surroundings).

There are currently no studies that have clearly defined which cerebral areas and connections are involved in the pathogenesis of these symptoms. Functional MRI data showed that the onset of palinopsia is associated with activation of occipito-temporal region of the non-dominant hemisphere, in particular activation of some connections between parietal and occipital cortex (15,16). The mechanisms of these rare

Table 2. Demographic and clinical features regarding the nature of the visual phenomenon in patients with palinopsia

Age (years)	Sex	ICHD-II	Frequency (attacks/year)	Type of object
46	F	MwoA	5	Appliances, plants, cars
32	F	MwoA	7	Shrubs, plants
57	F	MwoA	4	Landscapes
46	F	MwA	5	Books, trees, desks
54	F	MwA	5	Road signs, plants, trees, cars
25	F	MwA	3	Vehicles, road maps
47	F	MwA	3	Chairs, tables, desks, musical instruments
32	F	MwA	5	Rows, text, multiple particles
38	F	MwoA	6	Musical notes, text
35	F	MwA	5	Vehicles, books
35	F	MwA	4	Trees, landscapes
36	F	MwA	3	Plants, figures, vehicles
35	M	MwoA	4	Musical notes, books, text
57	F	MwA	3	Road maps, vehicles, text
46	F	MwA	3	Tables, chairs, trees
28	F	MwoA	6	Trees, vehicles, landscapes
23	F	MwoA	6	Landscapes, tables, chairs
32	F	MwoA	3	Figures
24	M	MwoA	5	Landscapes

Abbreviations: F: female, M: male, MwoA: migraine without aura, MwA: migraine with aura.

Table 3. Relationship between migraine attacks frequency and palinopsia after adjustment for sex, age and migraine subtypes

	OR (95%CI)	Robust SE	Z	p
Sex	0.6 (0.1–2.7)	0.52	–0.65	0.5
Age	0.96 (0.92–1.0)	0.02	–1.47	0.1
Aura	0.4 (0.04–4.2)	0.48	–0.03	0.5
Frequency of migraine attacks	0.4 (0.25–0.70)	0.11	–3.3	0.001

Abbreviations: OR: odds ratio, CI: confidence interval, SE: standard error.

visual phenomena remain uncertain; the most likely pathogenetic possibilities are visual seizures (17), cerebral hyperperfusion adjacent to areas of cortical damage (18), or hallucination in cases of visual loss (19).

Topological disorders of visual perception are localized within a particular cortical area and result in a loss (deficit) or an increase in function (hyperfunction). In migraine aura, the same region of cortical spreading depression may result in a hyperfunctional symptom at its margins (teichopsia) and a deficit in its centre (scotoma) (20).

We can only speculate about the physiopathological link between palinopsia and migraine since there are no clearly defined pathological changes, as revealed by brain MRI and EEG, in our patients. In our study, palinopsia was seen more frequently in MwA patients than in MwoA patients and we found that palinopsic events were unlikely to be associated with the onset of migraine attacks or an aura.

Cortical spreading depression (CSD) is a term coined to describe a transient 'depression' of electrocorticographic activity that lasts up to several minutes and slowly 'spreads' in all directions in cortex by way of grey matter contiguity (21). Today, CSD is known as an intrinsic electrophysiological property of central nervous systems (21). Although evidences supports a causal relationship between CSD and migraine aura and headache, CSD may also be involved in migraine attacks without a 'perceived' aura (21).

For this reason, we argue that spreading depression of cortical activity, as well as in the generation of the aura, may be also involved in the generation of visual

perseveration in patients with migraine when the CSD activity is nearby confined to the parietal projections of the dorsal visual pathway (13,14).

The novel finding derived from the present investigation is that palinopsia could be a common visual disturbance in patients with migraine and that this phenomenon could probably be underdiagnosed or misdiagnosed as an atypical aura in patients with migraine. It is important to be aware of the potential occurrence of this visual phenomenon in patients with migraine in order to avoid uncorrected diagnosis and, consequently, unnecessary diagnostic tests. Further investigations are needed to confirm our observations and to assess whether migraineurs are particularly susceptible to the development of recurrent episodes of visual perseveration.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix: Questionnaire about the frequency of palinopsia in migraine patients

Definition of palinopsia: the persistence of recurrent visual images following removal of the exciting stimulus.
Patient Number €€€ Name _____ Surname _____

Patient Record_____Type of headache[1] _____

Question for the patient

1. Have you ever seen the image of an *object* or a *scene* that you had previously viewed?
   € Yes € No
2. If the answer to question 1 is yes, ask:
   - Are the visions like whole scenes, or individual objects/figures

- How long did the phenomena last? _____ *Second/minutes*
- How often do they occur?_____*Episodes/month*
- Do you see them in front of you, or out of the corner of your eye?
- Do you have more than one episode per day? € *Never* € *Occasionally* € *More often*
- Do you experience the palinopsia before a headache? € *Never* € *Sometimes* € *Always*
- Do you experience the palinopsia after a headache? € *Never* € *Sometimes* € *Always*
- Do you experience the palinopsia independently? € *Never* € *Sometimes* € *Always*

3. During the episode, how do you feel?
   € Neutral
   € Pleasant
   € Unpleasant
4. When does these phenomena normally happen?
   € When relaxing
   € At work
   € During periods of stress

[1]Migraine with Aura – Migraine without Aura