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Improved identification of allodynic migraine patients using a questionnaire

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Running head: Diagnosis of allodynia

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INTRODUCTION

The occurrence of "scalp tenderness" during migraine was first described in 1832 (Liveing 1873) and then documented in greater detail during the 1950s-60s (Selby and Lance 1960; Wolff et al. 1953) and the 1980s (Blau 1987; Drummond 1987; Jensen 1993; Jensen et al. 1988; Jensen et al. 1993; Lous and Olesen 1982; Tfelt-Hansen et al. 1981; Waelkens 1985). Using quantitative sensory testing (QST), we found that many migraineurs exhibit decreased pain thresholds to thermal and mechanical stimulation of the skin during a migraine attack, a phenomenon we referred to as cutaneous allodynia (Burstein et al. 2000). Since the termination of migraine attacks that are associated with cutaneous allodynia requires early triptan treatment (within 20 min of attack onset) (Burstein et al. 2004), it is critical to determine whether or not the patient is allodynic during the attack .

Notwithstanding the scientific merits of QST, it is a rather impractical, cost-ineffective tool to be used routinely as it involves repeated 2-h testing in the doctor's office: once when the patient is free of migraine, and again during a migraine attack (Burstein et al. 2004; Burstein et al. 2000). In search for an alternative simple method for identifying allodynic migraine patients (Ashkenazi and Young, The effects of greater occipital nerve block and trigger point injection on brush allodynia and pain in migraine. Headache 2005;45:350-354, LoPinto et al. Cephalalgia 2006), we developed a questionnaire and tested its validity against QST. Used interictally, the questionnaire correctly identified 76% of the patients as allodynic or non-allodynic compared to QST performed during and between migraine attacks (Jakubowski et al. 2005).

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In this study we compared the incidence of markers of allodynia, as recollected interictally by the patients in the clinic, to the patients' own observation of allodynia during an actual migraine attack at home (4 h after the onset of headache).

METHODS

Patient selection

The study was carried out in accordance with the ethical standards of the Institutional Review Board for Studies with Human Subjects of Thomas Jefferson University Hospital and with the Helsinki Declaration of 1975, as revised in 1983. Included in the study were patients between the ages of 12 and 60 years who met the International Headache Society (IHS) criteria for episodic migraine with or without aura (Headache-classification-committee-of-the-International-Headache-Society 2004), had 1-6 migraine attacks per month, and were able to give an informed consent. Excluded from the study were patients with chronic daily headache or with chronic non-cephalgic pain and patients who had been treated with botulinum toxin for any indication.

Experimental protocol

Patients visited the clinic when they were free of migraine, at least 5 days from the conclusion of the last migraine attack. Patients were interviewed regarding migraine history (e.g., age of onset, number of years with migraine, frequency and duration of attacks, pain characteristics) and associated symptoms (e.g., nausea, vomiting, photophobia, phonophobia, osmophobia, muscle tenderness). During the interview,

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patients were asked to recall whether they had abnormal skin sensitivity during migraine attacks (see questionnaire below). Patients were sent home with a questionnaire that contained the same questions on skin sensitivity as the ones they were asked during the interview. They were instructed to fill it when having an acute migraine attack. When completed, the questionnaire was either mailed back to our clinic or given to the investigator during the patients' following office visit.

The questionnaire

Do you experience pain or unpleasant sensation *on your skin* during a migraine attack when you engage in ANY of the following activities (Yes, No, Not Applicable (N/A)):

(1) combing your hair; (2) pulling your hair back (example: ponytail); (3) shaving your face; (4) wearing eyeglasses; (5) wearing contact lenses; (6) wearing earrings; (7) wearing necklaces; (8) wearing anything tight on your head or neck (hat, scarf); (9) wearing anything on your arm or wrist (bracelet, watch); (10) wearing a finger ring; (11) wearing tight clothes; (12) being covered with a heavy blanket; (13) taking a shower (when shower water hits your face); (14) resting your face on the pillow on the side of the headache; (15) being exposed to heat (examples: cooking; placing heating pads on your face); (16) being exposed to cold (examples: breathing through your nose on a cold day; placing ice packs on your face).

Data analysis

In the absence of an objective measurement of allodynia such as QST, we applied the following criteria for allodynia: for the interictal interview, a single positive (Yes)

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answer was sufficient to classify a patient as allodynic, as we did in a previous study (Jakubowski et al. 2005). For the questionnaire filled by the patients during a migraine attack at home, a minimum of two positive answers were required to consider a patient as allodynic The number of allodynic patients as determined by these methods was analyzed using a simple χ^2 test (Zar 1998). The level of significance was set at 0.05.

RESULTS

The study included 151 patients (125 women, 26 men), with a mean (± SEM) age of 34.4±1.0 years. Mean age of migraine onset was 16.7 ± 0.7, and mean number of years with migraine was 17.5±1.0. Mean attack frequency was 3.5 ± 0.1 per month, mean attack duration was 38.1 ± 5.9 h, and mean number of headache days per month was 7.1 ± 0.3. Visual aura was reported by 34% of the patients. (*Rami, do you think we should add the data on the prevalence of other types of aura e.g. somatosensory? Alternatively, we can report the incidence of aura in general, not just visual.)* The prevalence of migraine –associated symptoms was as follows: photophobia – 94%; phonophobia – 86%, osmophobia – 58%; nausea – 84%, vomiting – 44%; muscle tenderness – 53% (16% before and 37% after attack onset).

During the interictal interview, 137/151 (91%) patients recalled having one or more symptom of skin hypersensitivity during migraine attacks, and were presumed to be allodynic. The remaining 14 patients were unaware of having any skin hypersensitivity during migraine attacks and were thus presumed to be non-allodynic.

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Data from the questionnaires filled by the patients during a migraine attack showed that 117/151 (77%) of the patients fulfilled our allodynia criterion of having two or more symptoms of skin hypersensitivity. The remaining 34 (23%) patients reported either one symptom of skin hypersensitivity (14%) or no such symptoms at all (9%). *(Rami, I think it will be clearer to present the data as percentages of the total study population. I changed the numbers accordingly).*

Using the criteria for allodynia described above, Tables 1 and 2 show the incidence of positive answers for the 16 items in the questionnaire among allodynic vs. non-allodynic patients. Among non-allodynic patients, the incidence of allodynia diminished between the interictal interview and the questionnaire they filled during a migraine attack. However, among allodynic patients, the incidence of individual positive answers did not differ between the two settings. .

Rami, according to Table 3, the number of allodynic patients, as defined by the interictal interview criteria, was different from that number as defined by the attack questionnaire criteria. I corrected the numbers in Tables 1 and 2 accordingly.

Table 1: Incidence of positive responses to individual questions during interictal interview

	Allodynic	Non-allodynic

Number of patients	137	14
	(%)	(%)
Combing	58	17
Pony tail	68	18
Shaving	20	13
Eye glasses	53	21
Contact lenses	32	0
Earring	18	6
Necklace	16	6
Headband	74	36
Arm-wrist	18	3
Ring	14	0
Tight cloth	56	21
Blanket	29	0
Shower	36	6
Pillow	50	19
Heat	49	24
Cold	36	6

Table 2: Incidence of positive responses to individual questions during migraine attack

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	Allodynic	Non-allodynic
Number of patients	117	34
	(%)	(%)
Combing	62	3
Pony tail	71	3
Shaving	4	0
Eye glasses	48	6
Contact lenses	32	0
Earring	24	0
Necklace	26	0
Headband	84	9
Arm-wrist	22	0
Ring	23	0
Tight cloth	62	6
Blanket	29	9
Shower	32	3
Pillow	59	18
Heat	54	9
Cold	35	3

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Patient-by-patient analysis indicated that of the 137 patients initially presumed to be allodynic based on the interview, 21 (16%) were false-positives who were classified as non-allodynic based on their answers during migraine. Of the 14 patients initially presumed non-allodynic based on the interview, only 1(7%) was false-negative who was classified as allodynic based on her answers during migraine.

Increasing the threshold for allodynia from 1 to 2 positive answers during the interictal interview yielded minimal change in the classification of patients (Table 3) based on the interview alone. On the other hand, decreasing the threshold for allodynia from 2 to 1 positive answers as recorded during migraine yielded significant change in the classification of patients (Table 3) based on their answers during migraine.

Table 3. Classification of patients according to number of positive answers in the interview/questionnaire

	Threshold	Allodynic	Non-allodynic
Interview			
	≥1 criterion[a]	137	14
	≥2 criterion[b]	133	18
During migraine			
	≥1 criterion[c]	133	18
	≥2 criterion[a,b,c]	117	34

[a]$\chi^2 = 5.95$, $p<0.02$; [b,c]$\chi^2 = 9.91$, $p<0.002$

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The consistency and inconsistency of responses between the interview and the migraine attack questionnaire confirmed that a threshold of two or more positive answers during migraine attack is necessary for classifying patients as allodynic (Table 4).

Allodynic patients. Between the interview and the migraine-attack, allodynic patients responded positively in a consistent way to four items. During migraine attack, they responded positively to one *additional* item that they failed to recall during the interview (false negative). Conversely, they responded positively to one additional item during the interview which they failed to confirm during migraine (false positive).

Non-allodynic patients. During the interview, non-allodynic patients showed negligible number of positive responses that were confirmed during a migraine attack, or negative responses that reversed to positive during attack . However, they did respond positively to one item in the interview which they failed to confirm during migraine attack.

Table 4. Consistent and inconsistent responses of allodynic and non-allodynic patients.

Responses in interview vs. response during migraine	Number of questionnaire items		
	Allodynic (n=117)	Non-allodynic (n=34)	*p*
Yes - Yes	3.97±0.24	0.12±0.06	<0.0001

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No - Yes	1.17±0.14	0.18±0.07	<0.0001
Yes - No	0.98±0.11	1.21±0.29	>0.9

History of triptan efficacy

Eighty-three of the 151 patients (55%) had experience with triptan therapy. They were asked whether triptan therapy typically rendered them pain-free. All twenty one (25%) patients who reported on consistently using triptans early in the attack, said that triptans always rendered them pain-free. Sixty two (75%) patients reported on using triptans at various times during the attack. Among those, the most common answers were 'always' (20%), 'never' (20%), and 'sometimes' (35%). The incidence of claiming that triptans *always* terminate migraine attacks was twice as high in non-allodynic compare with allodynic patients. Conversely, the incidence of claiming that triptans terminate migraine attacks *sometimes* (especially if treated early) or *never* was twice as high in allodynic compared with non-allodynic patients.

DISCUSSION

Using a minimum of two markers of allodynia during a migraine attack, 77% of the patients were classified as allodynic migraineurs, in agreement with QST measurements

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during and between migraine attacks (Burstein et al. 2000). A significantly higher proportion of patients were classified allodynic during the interview using either a single marker of allodynia (91%) or a minimum of two markers (88%). Of the 137 patients who were classified as allodynic in the interview using a single marker, 21 (15%) failed to record a minimum of two markers during a migraine attack at home, perhaps representing false-positive identification of allodynia in the interview. We found similar incidence of false-positive cases (16%) by comparing single-marker classification of allodynia during an interictal interview to QST classification of allodynia during and between migraine attacks (Jakubowski et al. 2005).

In agreement with our previous studies (Burstein et al. 2004; Burstein et al. 2000; Jakubowski et al. 2005), there was no difference between allodynic and non-allodynic patients in the prevalence of aura (37 *vs*. 41%), photophobia (94 *vs*. 94%), phonophobia (88 *vs*. 79%) or osmophobia (56 *vs*. 62%). If these symptoms are initiated and mediated by neuronal hyperexcitability in the visual, auditory, olfactory, sensory and motor cortices (Bolay and Moskowitz 2005), our findings suggest that the initiation or maintenance of allodynia does not depend on cortical hyperexcitability.

As a practical approach for identifying allodynic migraineures, we now propose to rely on a questionnaire filled by the patient at home during acute attack, rather than interictally in the doctor's office. Indeed, markers of skin hypersensitivity are more likely to be reliably documented by the patient during migraine attack than by recollection when the patient is headache-free. We recommend that the threshold for allodynia be based on a minimum of two markers of skin hypersensitivity because allodynic and non-allodynic patients each had a positive response to *one* item in the

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interview that was not confirmed during migraine. Thus, a threshold of one item is inadequate for two reasons: first, it is insuffient for identifying the allodynic patients and, second, it is highly likely to mislabel non-allodynic patients as allodynic.

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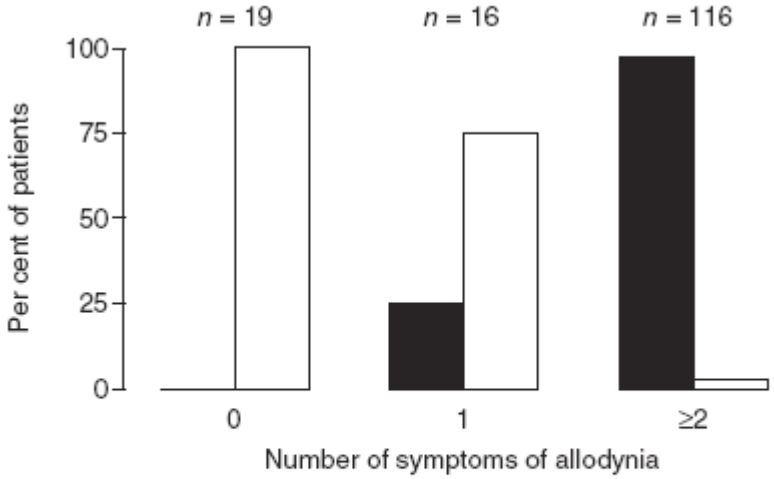

Figure 2 Distribution of allodynic (■) and non-allodynic (□) patients according to the number of symptoms of skin hypersensitivity cited during a migraine attack. Note that 75% of patients citing a single symptom were non-allodynic.

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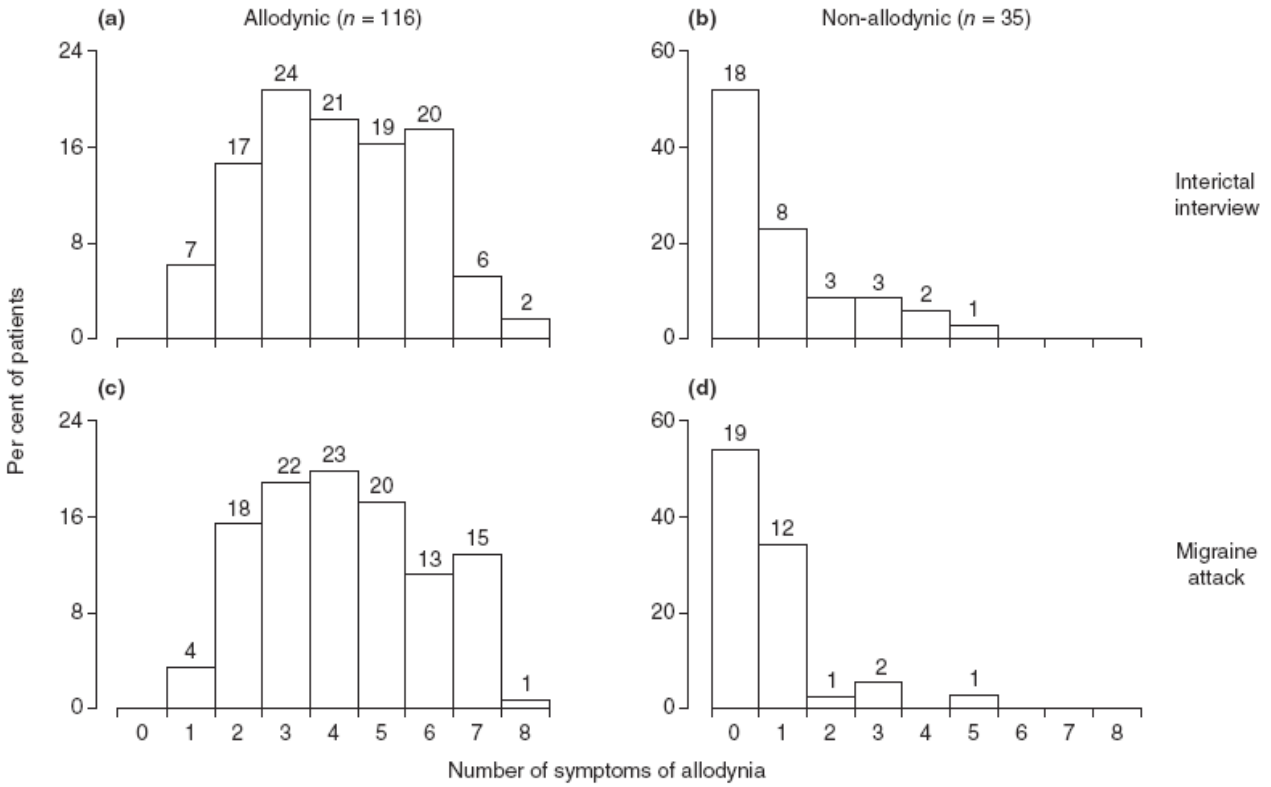

Figure 1 Percentage of allodynic (a,c) and non-allodynic (b,d) patients citing symptoms of skin hypersensitivity in the interictal interview and during an attack. Numbers above bars indicate actual number of patients. (a) vs. (b) or (c) vs. (d): $P < 0.0001$, Mann–Whitney *U*-test. (a) vs. (c) or (b) vs. (d): $P > 0.22$, Wilcoxon matched-pairs signed-rank test.

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