An Association between Migraine and Cutaneous Allodynia

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Recent animal studies on the mechanism of migraine show that intracranial pain is accompanied by increased periorbital skin sensitivity. These findings suggest that the pathophysiology of migraine involves not only irritation of meningeal perivascular pain fibers but also a transient increase in the responsiveness (ie, sensitization) of central pain neurons that process information arising from intracranial structures and skin. The purpose of this study was to determine whether the increased skin sensitivity observed in animal also develops in humans during migraine attacks. Repeated measurements of mechanical and thermal pain thresholds of periorbital and forearm skin areas in the absence of, and during, migraine attacks enabled us to determine the occurrence of cutaneous allodynia during migraine. Cutaneous allodynia is pain resulting from a nonnoxious stimulus to normal skin. In 79% of the patients, migraine was associated with cutaneous allodynia as defined, and in 21% of the patients it was not. The cutaneous allodynia occurred either solely within the referred pain area on the ipsilateral head, or within and outside the ipsilateral head. Cutaneous allodynia in certain well-defined regions of the skin during migraine is an as yet unreported neurological finding that points to hyperexcitability of a specific central pain pathway that subserves intracranial sensation.

Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol 2000;47:614–624

Recent studies in our laboratory show that a brief chemical irritation of the dura in rats (1) temporarily changes the physiological properties of meningeal perivascular nociceptors, lowering their thresholds and causing them to respond to dural indentation with forces that previously induced minimal or no responses[1]; and (2) temporarily changes the physiological properties of central trigeminal neurons that receive convergent input from the dura and the skin, lowering their thresholds, increasing their excitability, and causing them to respond to stimulation of the periorbital skin with forces (ie, brush) and temperatures ($<42°C$) that previously induced minimal or no responses.[2,3] These data were interpreted as follows: (1) sensitization of meningeal perivascular nociceptors can explain the intracranial hypersensitivity (ie, the worsening pain during coughing, bending over, or any head movement) and the throbbing element in the pain of migraine; and (2) sensitization of central trigeminal neurons that receive convergent input from the dura and the skin can explain the extracranial tenderness and cutaneous allodynia (pain resulting from a nonnoxious stimulus to normal skin) that often accompany migraine.

Because these studies suggested an association between increased periorbital skin sensitivity and intracranial pain in the animal model, we hypothesized that it may also be present during migraine attacks in humans. The purpose of this study was to determine whether cutaneous allodynia (in addition to muscular tenderness) is associated with migraine in humans, and if so, to what territorial extent. We further hypothesized that, as in the animal model, the presence of cutaneous allodynia in migraineurs points to central sensitization; from this, it would follow that, because many antimigraine drugs do not address central sensitization, its presence would indicate a need for appropriate therapeutic approaches.

Materials and Methods

Selection of Patients

Patients were recruited from the clinical caseload of the pain management center and the Neurology Service at Beth Israel Deaconess Medical Center. Women and men who were 18 to 70 years old, who met the criteria of the International Headache Classification Committee for migraine with or without aura,[4] who had one to

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Received Oct 19, 1999, and in revised form Dec 22. Accepted for publication Dec 29, 1999.

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six migraine attacks each month in the past 3 years, and who were able to communicate in English and give an informed consent were included in this study. Exclusion criteria included peripheral nervous system injuries and the use of opiates or other analgesic drugs for reasons other than migraine.

To increase the sensitivity of detecting cutaneous allodynia and to reduce measurements variance, patients in this study were compared with themselves (before vs during migraine) rather than with control subjects because the large normative range of pain thresholds[5] reduces the sensitivity of detecting allodynia in reference to the normal range. This study was carried out in accordance with the ethical standards of the Committee on Clinical Investigation on Human Experimentation at Beth Israel Deaconess Medical Center and with the Helsinki Declaration of 1975, as revised in 1983.

Experimental Protocol

Sixty patients were initially scheduled for a 2-hour session to classify their migraine type and to document the symptoms that usually accompany their migraine. These sessions were held when the patients were migraine-free and when at least 7 days had elapsed since the last migraine attack. In the sessions, patients lay in a quiet room and Quantitative Sensory Testing (QST) was performed to determine pain thresholds to cold, warm, and mechanical stimuli. Thresholds were measured in the following locations in a randomized order: left periorbital skin, right periorbital skin, left forearm ventral skin and right forearm ventral skin. Patients were instructed to return to the pain clinic 3 to 4 hours after the onset of a moderate to severe migraine attack (pain intensity $\geq$7 on a 0–10 visual analogue scale [VAS]) during which they did not take any antimigraine or analgesic medications. (We chose to examine the patients 3 to 4 hours into their attack because this period was needed to show increased skin sensitivity in the animal model.) Forty-four of the 60 patients (73%) that were initially recruited for this study returned during their migraine attack. History relevant to the attack was taken, and QST repeated. Changes in skin sensitivity were determined by comparing pain thresholds obtained in the absence of migraine with pain thresholds obtained during migraine at each skin location.

Thermal and Mechanical Stimulation

Heat and cold skin stimuli were delivered through a 30×30 mm^2 thermode (Thermal Sensory Analyzer-2001, Medoc, Ramat Yishai, Israel) attached to the skin at a constant pressure and their pain thresholds were determined by using the Method of Limits.[6,7] To determine pain thresholds, the skin was allowed to adapt to a temperature of 32°C for 5 minutes and then cooled down or warmed up at a slow rate (1°C/sec) until pain sensation was perceived, at which moment the subject stopped the stimulus by pressing a button on a patient response unit. Cold and heat stimuli were repeated three times each, and the mean of recorded temperatures was considered threshold. Pain threshold to mechanical stimuli was determined by using a set of 20 calibrated von Frey hairs (VFH; Stoelting, Wood Dale, IL). Each VFH monofilament was assigned a scalar number in an ascending order (1 = 0.0045*g*, 2 = 0.023*g*, 3 = 0.027*g*, 4 = 0.07*g*, 5 = 0.16*g*, 6 = 0.4*g*, 7 = 0.7*g*, 8 = 1.2*g*, 9 = 1.5*g*, 10 = 2.0*g*, 11 = 3.6*g*, 12 = 5.4*g*, 13 = 8.5*g*, 14 = 11.7*g*, 15 = 15.1*g*, 16 = 28.8*g*, 17 = 75.0*g*, 18 = 125.0*g*, 19 = 281.0*g*). Because a linear relationship exists between the log force and the ranked number, mechanical pain thresholds are expressed as VFH numbers rather then their forces (*g*). Each monofilament was applied to the skin three times for 2 seconds, and the smallest VFH number capable of inducing pain in two of three trials was considered threshold. Skin sensitivity was also determined by recording patient's perception of soft skin brushing, which is a dynamic mechanical stimulus, as distinguished from the VFH, which is a static mechanical stimulus.

Criteria for Cutaneous Allodynia

Cutaneous allodynia is defined as pain resulting from a nonnoxious stimulus such as heat, cold, or pressure to normal skin. In this study, the presence of cutaneous allodynia was determined using the values of the pain thresholds for heat, cold, and pressure measured as described earlier at the bilateral periorbital and forearm skin areas of patients, both in the absence of and during migraine attacks in the same patients. If, during a migraine attack in a given patient, the pain threshold of one or more modalities (heat, cold, pressure), measured on the ipsilateral head alone or on the ipsilateral head and one or more of the other three skin locations, was reduced by 1 or more standard deviations (SD) of the respective baseline control threshold (implying increased sensitivity to one or more modalities in the respective skin areas), the presence of cutaneous allodynia was inferred. Alternatively, patients did not have cutaneous allodynia if none of their pain thresholds for any of the modalities in the head or the head and other skin areas was reduced by 1 SD or more from baseline control during a migraine attack.

In the absence of migraine, mean pain thresholds on the head and forearms were as indicated in Table 1. Accordingly, on the head, the critical values of these standard deviations were $>$6.8°C for cold pain, $-$3.8°C or less for heat pain, and $-$3 or less VFH numbers for mechanical pain ($-$3 or less VFH numbers is a stricter criterion than 1.7 or less VFH numbers to accommodate the nonlinearity of the mechanical stimulus paradigm). Similarly, on the forearms,

Table 1. Mean Pain Thresholds of Skin Areas on the Head and Forearms in Absence of Migraine

	Head	Forearm
Cold (°C)	16.3 ± 6.8	11.6 ± 8.6
Heat (°C)	44.3 ± 3.8	45.2 ± 3.5
Mechanical[a]	17.8 ± 1.7	18.1 ± 2.1

[a]Number of von Frey hairs.

these critical values were >8.6°C for cold pain, −3.5°C or less for heat pain, and −3 or less VFH numbers for mechanical pain. These critical values were based on 88 separate measurements in the head and forearms.

The primary outcome measures, accordingly, were the proportions of patients with and without cutaneous allodynia during migraine.

Statistical Analysis

The data base consisted of pain threshold measurements in 44 patients, taken before and during migraine attacks. The resulting distributions were tested for normality, and their descriptive statistics computed. The differences between during and before attack (during − before) were computed on a pairwise basis, and the criteria for allodynia were applied, yielding two groups of migraine patients—those without cutaneous allodynia and those with cutaneous allodynia (Groups A and B). These proportions were tested for statistical significance using the Fisher Exact Test and verified by the Fleiss Method for comparing proportions. Differences in mean pain threshold between the respective nonallodynic and allodynic groups (A and B) were performed using appropriate two-sample (*t* test and rank sum tests) and pairwise multiple sample comparison (Newman-Keuls, Kruskal-Wallis, Friedman's) tests. Comparisons between symptoms expressed as proportions were performed using a Tukey-type pairwise multiple comparison procedure.

Results

The application of the criteria for cutaneous allodynia to the 44 subjects yielded a very clear-cut pattern of behavior for 42 subjects, as shown in Table 2. Two subjects that did not exhibit cutaneous allodynia on the ipsilateral head but that scored with one modality of allodynia on the contralateral head or the ipsilateral forearm were excluded from further analysis because, in the absence of cutaneous allodynia in the ipsilateral head, these changes were judged as unrelated to the migraine attack.

Table 2. The Prevalence of Allodynia during Migraine

	Allodynia		
Migraine	Yes (%)	No (%)	
Yes	33 (79)	9 (21)	42
No	0	42 (100)	42

Sensitivity = 79%; specificity = 100%; predictive value of positive test = 100%; predictive value of negative test = 82%.

During migraine, 9 of 42 (21%) of the patients (Group A) did not exhibit cutaneous allodynia in any of the four sites, and 33 of 42 (79%) experienced cutaneous allodynia on the facial skin ipsilateral to the migraine pain (Group B). The difference in proportions was statistically significant at $p < 0.0001$.

Examination of the distribution of cutaneous allodynia in the 33 Group B patients over the respective skin areas revealed further clear-cut patterns of behavior (Table 3).

The appearance of these consistent patterns of cutaneous allodynia constituted an unexpected but not unreasonable finding. In the spirit of John Tukey's "Explorative Data Analysis,"[8] it was decided to evaluate the findings in terms of the 5 groups (A, B1, B2, B3, B4) that emerged from the analysis as distinct patient categories.

These results were found to be reproducible in patients from each of these groups (total number = 15) who were re-examined during more than one attack and found to exhibit consistent sensory patterns (ie, absence, presence, and distribution of cutaneous allodynia).

Demographic Data and Clinical Symptoms

Forty-two of the 44 patients who completed the two QST sessions were included in the subsequent data analysis. The demographic information on each patient and the symptoms that usually accompanied their migraines are summarized in Table 4. Nonallodynic patients (Group A) were significantly younger than allodynic patients (Group B mean ± SD, 34 ± 5 vs 42 ± 10; $p = 0.006$). They also experienced migraine fewer years (the number of years each patient experienced

Table 3. Distribution of Cutaneous Allodynia in Group B Patients

Group B Patients	No. of Patients	No. of Sites	Location of Allodynia
B1	5	1	1 site within the ipsilateral head
B2	7	2	1 site within and 1 site beyond ipsilateral head
B3	7	3	1 site within and 2 sites beyond the ipsilateral head
B4	14	4	1 site within and 3 sites beyond the ipsilateral head
Total	33		

Table 4. Demographic Data and Symptoms[a]

Patient	Sex/Age	Age at Onset (yr)	Family History	Days per Month	Aura				During Migraine			
					Visual	Somatosensory	Motor	Speech	Phonophobea or Olfactophobea	Mental	Autonomic	Gastric
Group A—no cutaneous allodynia												
BR	F/25	12	X	3	X	X	X	X	X	X	X	X
DM	F/37	31	X	6		X	X	X	X	X	X	X
FS	M/39	35	X	10	X				X	X	X	X
GM	F/33	25	X	8					X	X		X
LB	F/37	10		2					X	X	X	X
ML	F/37	15	X	6					X			
PC	F/34	8	X	1					X	X	X	X
SS1	F/39	22	X	4		X	X	X	X	X	X	X
SL	F/26	14	X	30[b]					X	X	X	X
Group B1—cutaneous allodynia, ipsilateral head only												
BK	F/25	19		6	X				X			X
CJ	F/38	8	X	1	X	X	X	X	X	X	X	X
NJ	F/33	23	X	4	X	X	X	X	X	X	X	X
RE	F/25	18	X	1					X			X
SA	F/41	31	X	3	X	X	X	X	X		X	X
Group B2—cutaneous allodynia, ipsilateral head and 1 site												
DC	F/44	18	X		X			X	X	X	X	X
KR	M/49	27	X	20[b]	X	X	X	X	X	X	X	X
RM1	F/53	25	X	8	X	X		X	X	X	X	X
RM2	F/44	15	X	8	X			X	X	X	X	X
SR	M/51	19	X	8			X	X	X		X	X
SS2	F/50	35	X	10					X		X	
WK	F/51	32	X	6	X			X	X	X	X	X
Group B3—cutaneous allodynia, ipsilateral head and 2 sites												
CD1	F/67	9	X	12	X		X		X	X	X	X
CD2	M/42	20		9	X		X	X	X	X	X	X
CM1	M/42	14	X	2	X	X	X	X	X	X	X	X
EM	F/40	20		1					X			X
MC	F/37	7	X	2			X	X	X	X	X	X
MA	F/42	32	X	4	X	X	X		X	X	X	X
RC	F/31	29	X	1	X	X	X	X	X	X	X	X
Group 4—cutaneous allodynia, ipsilateral head and 3 sites												
AM	F/67	11	X	3					X			
BG	M/32	10	X	2		X	X		X	X	X	
BJ	F/28	13	X	8	X	X			X	X	X	X
CG	F/46	33		30[b]	X	X	X	X	X	X	X	X
CM2	F/45	15	X	3		X			X	X	X	X
DN	F/49	19	X	16	X	X	X	X	X	X	X	X
FL	F/50	25	X	2					X	X	X	X
GN	F/47	15	X	30[b]						X	X	X
HL	F/25	15	X	5	X	X	X		X	X	X	X
MB	F/43	8	X	8		X	X	X	X	X	X	X
PM	F/30	25		20[b]				X	X			
RM3	F/35	29	X	1	X	X	X	X	X	X	X	X
VB	F/40	8	X	12	X			X	X	X	X	X
YC	F/34	4	X	6	X			X	X	X	X	X

[a]X denotes the following symptoms:
Visual, auditory, olfactory—increased sensitivity.
Somatosensory—numbness, tingling.
Motor—weakness, tremor, clumsiness.
Speech—expressive or receptive aphasia, dysarthria.
Mental—irritability, depression, reduced concentration, fatigue, sleepiness.
Autonomic—conjunctival injection, lacrimation, nasal congestion, ptosis, excessive salivation, frequent yawning or urination.
Gastric—anorexia, diarrhea, nausea, vomiting.

[b]Indicates number of days per month patients experience headache (these are tension-type headache patients that experience migraine 2–4 times a month).

migraine was calculated by subtracting age at onset from patient's age), but the differences did not reach statistical significance with this sample size: nonallodynic patients experienced migraine 15 ± 9 years and allodynic patients experienced it 23 ± 13 years ($p = 0.112$). The sample size required to achieve statistical significance, as determined from power analysis, was 36 patients per group.

Regarding symptoms that usually accompany migraine attacks, nonallodynic patients differed from allodynic patients in the occurrence of visual (flashes of lights and scotoma; $p = 0.02$), speech (expressive or receptive aphasia, dysarthria; $p = 0.08$), motor (weakness, tremor, clumsiness; $p = 0.18$), and somatosensory auras (numbness and tingling; $p = 0.22$), but they did not differ in the occurrence of auditory, olfactory, or gustatory hallucinations or in increased sensitivities. They also did not differ in the changes they exhibited in mental (irritability, depression, reduced concentration, fatigue, sleepiness), autonomic (conjunctival injection, lacrimation, nasal congestion, ptosis, excessive salivation, frequent yawning or urination), and gastric (anorexia, diarrhea, nausea, vomiting) functions (see Table 4).

Pain Threshold Characteristics of Nonallodynic Patients during Migraine

Nine of the 42 patients (21%) experienced no cutaneous allodynia within the referred pain area on the ipsilateral head or any of the other skin areas during migraine (Table 5). An example of an individual patient from this group is illustrated in Figure 1. The mean (n = 3) pain thresholds to cold, heat, and mechanical stimulation of the four sites changed minimally. They were within normal range before the migraine attack and during the full-blown headache (pain severity = 10). A comparison between the respective threshold means of the 9 patients in this group revealed no changes in their pain threshold (t test vs zero).

Pain Threshold Characteristics of Allodynic Patients during Migraine

Thirty-three patients (79%) exhibited cutaneous allodynia during migraine (Table 6). While cutaneous allodynia was always present within the referred pain area on the ipsilateral head, it was not restricted to this area. In fact, most allodynic patients (28/33) exhibited cutaneous allodynia outside the referred pain area. The variety of spatial distributions found in these patients is illustrated in Figure 2. As shown in the four examples, cutaneous allodynia was restricted to the ipsilateral head (Patient SA), the ipsilateral and contralateral sides of the head (Patient WK), both sides of the head and ipsilateral forearm (Patient CM1), and the head and forearms, bilaterally (Patient RM3). Grouping of patients according to the spatial distribution of their cutaneous allodynia produced the patterns of allodynic distribution tabulated above.

Pattern of Changes in Pain Thresholds

A summary of the changes in pain thresholds of the three modalities at the four examined sites of the 33 allodynic patients is given in Table 6 for the four subgroups. In this table, pain threshold changes that fulfill the criteria for cutaneous allodynia (ie, ≥1 SD) are marked by the shaded boxes, and the means ± SD of the changes for all nonallodynic (lightface) and allodynic (boldface) sites are shown in the bottom four rows. As depicted, in the *presence of cutaneous allodynia*, mean cold pain threshold decreased by an average of 12.7°C (from 16.3 to 29.0°C), heat pain threshold decreased by 7.4°C (from 44.3 to 36.9°C), and mechanical pain threshold decreased by 7.1 VFH numbers (from 17.8 to 10.7) for the ipsilateral head, with the

Table 5. Changes in Pain Threshold for Cold, Heat, and Mechanical Stimulation (Mech) of Head and Forearms in Nonallodynic Patients

	Ipsilateral Head			Contralateral Head			Ipsilateral Forearm			Contralateral Forearm		
Patient	Cold	Heat	Mech	Cold	Heat	Mech	Cold	Heat	Mech	Cold	Heat	Mech
BR	−5.1	5.3	−2	−8.5	0.1	0	−4.1	−0.4	0	−2.1	1.4	0
DM	6.2	0	0	−2.2	−2.2	0	1.3	1.4	0	0.3	−0.2	0
FS	0.1	0.4	0	−0.9	−1.1	2	6.5	2	0	1.1	8.3	0
GM	0.5	2.9	0	2	0.5	0	−14.5	1.6	0	0.8	0.8	0
LB	−11.3	10.8	0	−2.2	8	0	2	1.9	0	0.7	−0.7	0
ML	−2.4	0.2	0	−3	3.9	1	0.6	0.2	0	4.5	0	0
PC	−8.5	2.7	−1	−6.7	1.7	−1	−19.6	2.5	1	−5.9	2.5	0
SS1	−20.7	10.3	−1	−0.1	2.3	2	−2.6	7	0	−7	3	0
SL	−2.8	−0.4	1	1.3	−1.6	2	−5.1	−1.1	−1	−2.2	−0.7	0
Mean	**−4.89**	**3.58**	**−0.33**	**−2.26**	**1.29**	**0.67**	**−3.94**	**1.68**	**0.00**	**−1.09**	**1.60**	**0.00**

All numbers indicate changes in pain threshold as determined by the following equation: (during-migraine pain threshold) − (before-migraine pain threshold) = pain threshold change. Mean pain thresholds recorded in the absence of migraine were used as baseline, and 1 SD of these means was used as the criteria for allodynia (see text).

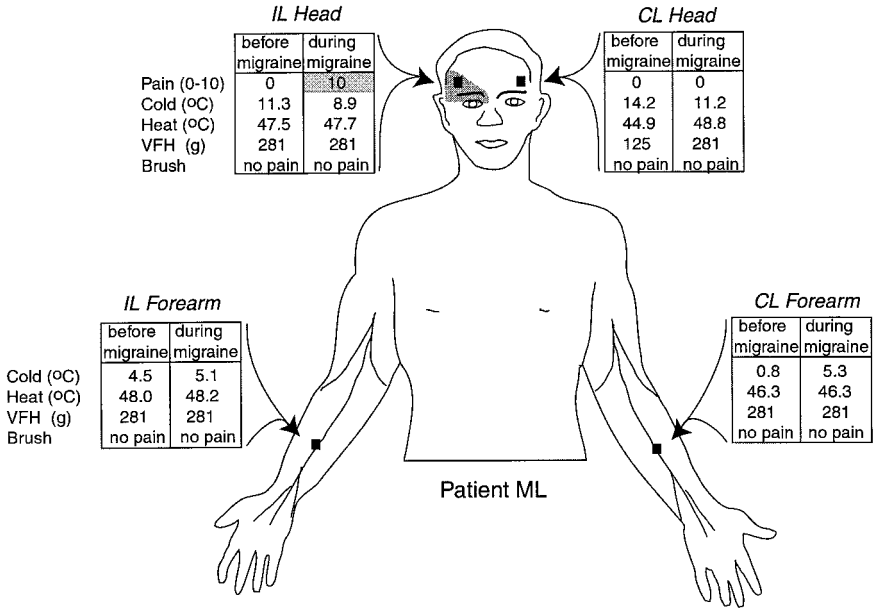

Fig 1. Spatial distribution of pain and sensory testing of a nonallodynic patient. The tables show pain scores; mean pain thresholds (n = 3) to cold, heat, and mechanical stimulation (von Frey hairs [VFH] and brush; see text for g *to VFH number conversion) of the four skin sites* (black squares) *before and during migraine. Shaded areas depict referred pain distribution on the face and pain intensity score in the table. IL = ipsilateral; CL = contralateral.*

other three locations showing very similar values, thereby demonstrating that regardless of site, the magnitude of change is 12°C for cold, 7°C for heat, and 7 VFH numbers for mechanical pain. Similarly, in the *absence of cutaneous allodynia*, intersession variability of cold, heat, and mechanical pain thresholds over the four locations were 2.2°C or less, 1.0°C or less, and 1.0 or less VFH number, respectively. Further examination of Tables 5 and 6 shows that the expression of cutaneous allodynia consists of fewer modalities in Group B1 and more modalities in Group B4 patients.

Regarding the need to examine all three modalities to detect the presence of cutaneous allodynia, we found the following: allodynic changes within the referred pain area included one modality in 16 patients, two modalities in 12 patients, and all three modalities in only 5 patients. For the ipsilateral head, these modalities were cold allodynia in 16 of 33 (48%), heat allodynia in 18 of 33 (55%), and mechanical allodynia in 21 of 33 (64%) patients. Thus, using cold, heat, or mechanical pain thresholds alone, 52%, 45%, and 36% of the patients, respectively, would have been misdiagnosed. On the other hand, 12% of the patients would have been misdiagnosed with cold and mechanical pain thresholds, 12% with heat and mechanical pain thresholds, and 26% with cold and heat pain thresholds. These findings indicate that skin testing cannot be limited to only one modality (eg, heat) to detect the presence of cutaneous allodynia during a migraine attack.

Discussion

This study extends previous reports on extracranial tenderness in migraine patients.[9–15] It demonstrates that during migraine, 21% of the 42 patients experienced no changes in skin sensitivity, and 79% experienced various distributions of cutaneous allodynia. These clinical data, by complementing findings in the animal model,[1,2] raise new hypotheses on the neuronal mechanism that underlies migraine pain. We hypothesize that the difference between allodynic and nonallodynic patients is that the pathophysiology of migraine in nonallodynic patients involves peripheral sensitization of meningeal pain fibers alone; in allodynic patients, it involves central sensitization of second-order brainstem trigeminal neurons as well. We further hypothesize that the difference between patients in Group B1 and Groups B2 to B4 is that the pathophysiology of migraine in Group B1 involves peripheral sensitization of first-order neurons and central sensitization of second-order neurons, and in Groups B2 to B4, it involves central sensitization of third-order trigeminal neurons in the thalamus as well. These hypotheses are presented in Figure 3 and discussed in detail below.

We propose that the aggravation of migraine pain by physical activities such as climbing stairs, bending over, and coughing,[16] together with its pulsating quality, occurs when normally silent and unresponsive dural mechanosensitive nociceptors[17–19] become responsive to even the mildest intracranial mechanical stimulus.[1] Thus, they are suggested to represent a source of increased *intracranial hypersensitivity*. Theoretically, any increase in the pressure exerted on the dura by the brain or the cerebrospinal fluid as a result of normal arterial pressure pulsation, coughing, or bending over could be sufficient to activate sensitized mechanosensitive nociceptors that supply the dura and induce pain.

Table 6. Changes in Pain Threshold for Cold, Heat, and Mechanical Stimulation (Mech) of the Head and Forearms in Allodynic Patients

	IL Head			CL Head			IL Forearm			CL Forearm		
Patient	Cold	Heat	Mech	Cold	Heat	Mech	Cold	Heat	Mech	Cold	Heat	Mech
IL head only (B1)												
BK	−8.1	3.4	−5	−5.5	2.6	−1	0.5	1.8	−2	−11	1.3	0
CJ	6.9	−2.5	−2	−6.8	6.1	0	4.3	1.3	1	−0.6	0.2	0
NJ	7.6	−0.2	1	−1.4	0.4	1	5.5	0	0	2.3	0.1	0
RE	−1.1	−4	−1	6.1	2.3	0	−5.9	2.6	0	5.7	0.4	0
SA	−3.2	0.2	−10	−4.3	−0.4	−2	2.5	−1.8	0	3.2	−0.6	0
IL head and 1 site (B2)												
DC	2.8	−1.6	−7	16.1	−6.3	−4	4.3	−2.8	0	4.1	−2.3	0
KR	−1.9	0.8	−9	−2.1	−1	−9	−5	0.4	−1	−0.9	0.7	2
RM1	23.6	−3.9	−2	3.4	0.1	0	7.5	−3	0	15.4	−3	0
RM2	−2.2	−4.5	−2	5.8	−1.5	−1	3.8	−0.4	−3	2.9	−3.3	0
SR	−16.2	1	−6	−18.7	1.4	0	−1.3	0.7	−3	1.2	3.4	−2
SS2	9.0	−0.3	0	12.2	−1.6	0	−0.5	−0.1	0	4.4	−0.8	0
WK	14.7	−8.2	−6	9.5	−5.9	0	6.8	−0.2	0	0	−0.4	0
IL head and 2 sites (B3)												
CD1	1	−5.3	−2	3.1	−7.1	0	−0.4	−3.2	0	2.1	−3.6	0
CD2	0.3	−3.9	−8	−2.7	−2.5	−2	9.6	−6.4	−2	3.9	−5.9	−2
CM1	11.3	−3.2	−9	9.3	−5.2	−8	9.3	−3.7	−1	0	1.1	−1
EM	4	−5.2	−4	4.1	0.1	0	17	1.4	0	27.1	−0.3	−1
MC	11.4	−3	−2	0.3	0.7	−2	9.6	−5.1	−2	10.2	−2.7	−2
MA	3.4	1	−3	5.6	1	0	−8	−7.2	−3	8.7	0.3	−2
RC	3.5	−2.7	−7	0.9	−2.5	−8	0.5	2	2	12.2	−0.2	−1
IL head and 3 sites (B4)												
AM	10.5	−13	−2	4.1	−8.7	−2	16.4	−11.3	−1	7.3	−9	−1
BG	13.7	−10	0	16.5	−9.5	0	14.2	−6.1	−2	19.6	−3.1	−2
BJ	3.7	−3.3	−3	−1.2	−2	−3	−1.4	−5.5	0	6.5	−3.7	0
CG	11.7	−10.6	−7	8.5	−4.1	−2	5.5	−6.5	0	8.3	−4.8	0
CM2	1.6	−5.5	−10	13.4	−5.1	−5	6.8	−1.2	−6	2	−0.5	−5
DN	4.4	−11.6	−7	4.8	−11.9	−2	11.6	−1.7	−2	8.6	−1.5	−2
FL	4	−6.4	0	8.6	−8.5	0	18.1	−2.2	0	5.9	−5.6	0
GN	11.9	−3.4	−5	14.2	−2.1	−5	9.5	−0.3	−1	9.9	−2.6	−1
HL	1.1	−4	−6	5.4	−6.6	−7	7.4	−4.9	−7	8.8	−2.7	−7
MB	15	−12.8	−1	15.3	−12.8	−1	20.4	−2.6	1	15.5	−3.9	1
PM	18.4	−1.3	−8	7.9	−1.8	−2	8.4	−4	−2	24.7	−1.2	−11
RM3	8.5	−10.5	−10	10.5	−11.1	−10	16.1	−11.9	−10	18.6	−10.1	−10
VB	16.5	−10.1	−8	14.8	−10.9	−2	11.4	−5.9	−2	9.6	−6.3	0
YC	12	−4.3	−11	4.9	−4.1	−9	10.8	−0.9	−7	3.7	−8.2	−3
Mean	−0.17	−1.00	−1.00	0.29	−0.03	−0.78	2.23	−0.63	−0.53	1.96	−0.76	−0.50
SD	5.30	2.05	1.08	6.04	2.21	1.00	5.72	1.74	1.10	3.92	1.69	1.00
Mean	12.67	−7.43	−7.1	12.06	−7.85	−6.8	12.34	−6.54	−5.57	13.63	−6.11	−7.2
SD	4.30	3.36	2.30	3.15	2.87	2.39	4.00	2.57	2.70	6.30	2.30	3.35

All numbers indicate changes in pain threshold as determined by the following equation: (during-migraine pain threshold) − (before-migraine pain threshold) = pain threshold change. Mean pain thresholds recorded in the absence of migraine were used as baseline, and 1 SD of these means was used as the criteria for allodynia (see text).

Numbers on white background depict pain threshold changes that are smaller than 1 SD of baseline mean (ie, nonallodynic). Numbers on gray background depict pain threshold changes that are larger than 1 SD of baseline mean (ie, allodynic). The bottom four rows depict the mean and SD of the changes in pain thresholds for all nonallodynic and allodynic sites.

IL = ipsilateral; CL = contralateral.

Sensitization of intracranial nociceptors, therefore, would seem to be a feature common to all migraine patients and was indeed present in all the patients in this study. This peripheral sensitization is sufficient to account for those patients experiencing intracranial hypersensitivity without cutaneous allodynia (see Fig 3A).

In 79% of the patients (Groups B1–B4), cutaneous allodynia to mechanical or thermal stimulation, or

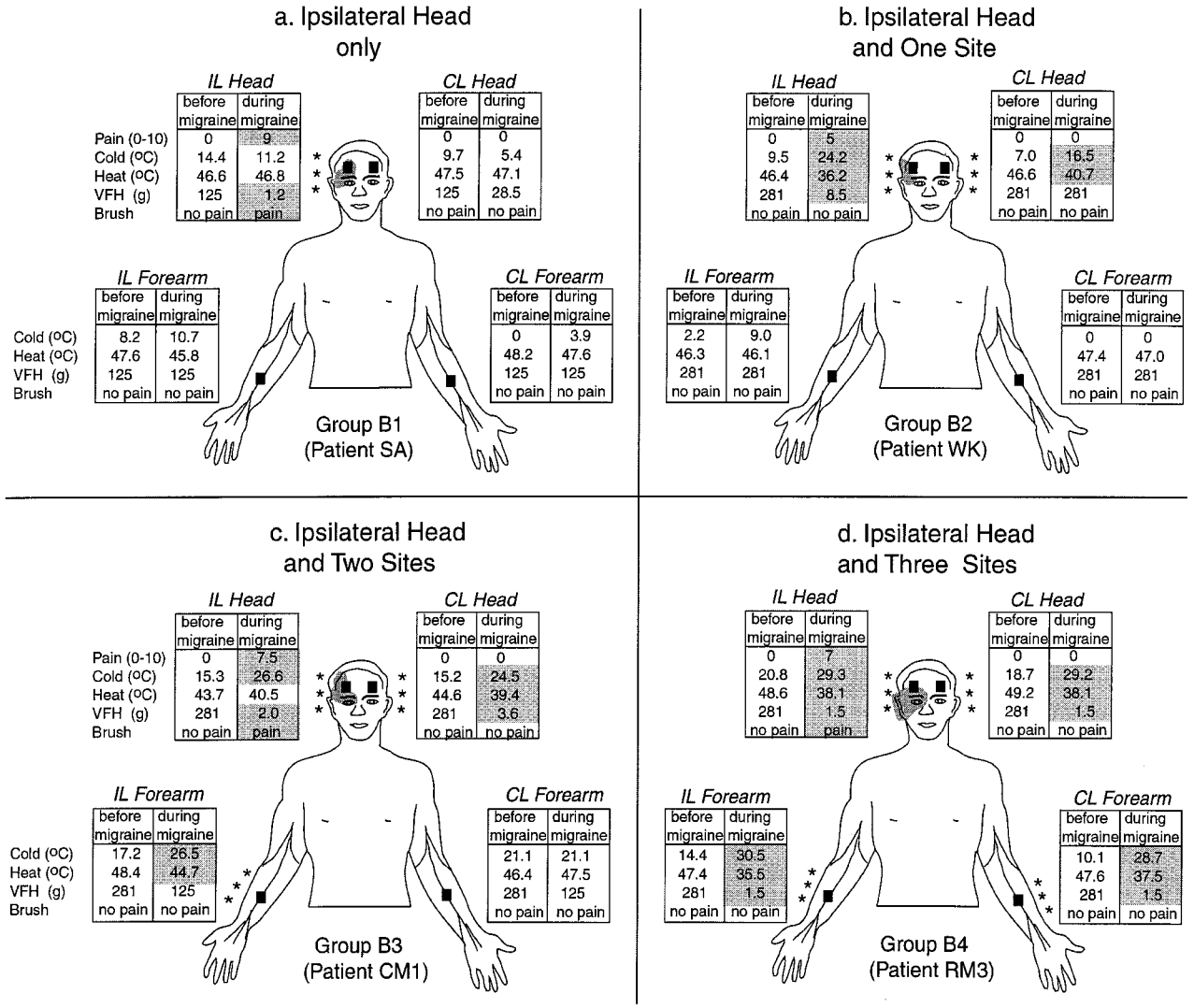

Fig 2. Spatial distribution of pain and sensory testing of allodynic patients. Each of the four cases represents a subgroup of patients (Groups B1, B2, B3, B4). As in Figure 1, the tables with each patient show pain scores and mean pain thresholds (n = 3) to cold, heat, and mechanical (von Frey hairs [VFH] and brush; see text for g *to VFH number conversion) stimulation of the skin sites* (black squares) *before and during migraine.* Triple asterisks *indicate skin regions that became allodynic during migraine attacks.* Shaded areas on the face *depict referred pain distribution, and* shaded areas in the tables *depict pain intensity scores and changes in pain thresholds that fulfilled the criteria for allodynia (≥1 SD).*

both, affected the referred pain area on the ipsilateral head. In these patients, innocuous stimulation of the periorbital skin was perceived as nonpainful in the absence of migraine but painful during migraine. We hypothesize that this cutaneous allodynia reflects a temporary increase in the sensitivity of central (second-order) trigeminal neurons that receive convergent input from intracranial structures such as blood vessels and meninges and from extracranial structures such as skin and hair follicles (see Fig 3B). This hypothesis is based on the notion that continuous activity of peripheral nociceptors could induce sensitization in second-order spinal cord neurons.[20]

In 67% of the patients (Groups B2–B4), cutaneous allodynia extended beyond the referred pain area on the ipsilateral head. Theoretically, *extracephalic* allodynia could result from hyperexcitability that develops along a specific pain pathway in response to its continuous activation or from a "general hyperexcitability" that is not stimulus dependent. Extracephalic allodynia caused by "general hyperexcitability" could result either from hyperexcitability of cortical and subcortical brain regions, which could also account for symptoms such as photophobia and phonophobia, or from general deficiency of central pain-modulating circuits. Because nonspecific general hyperexcitability predicts the pres-

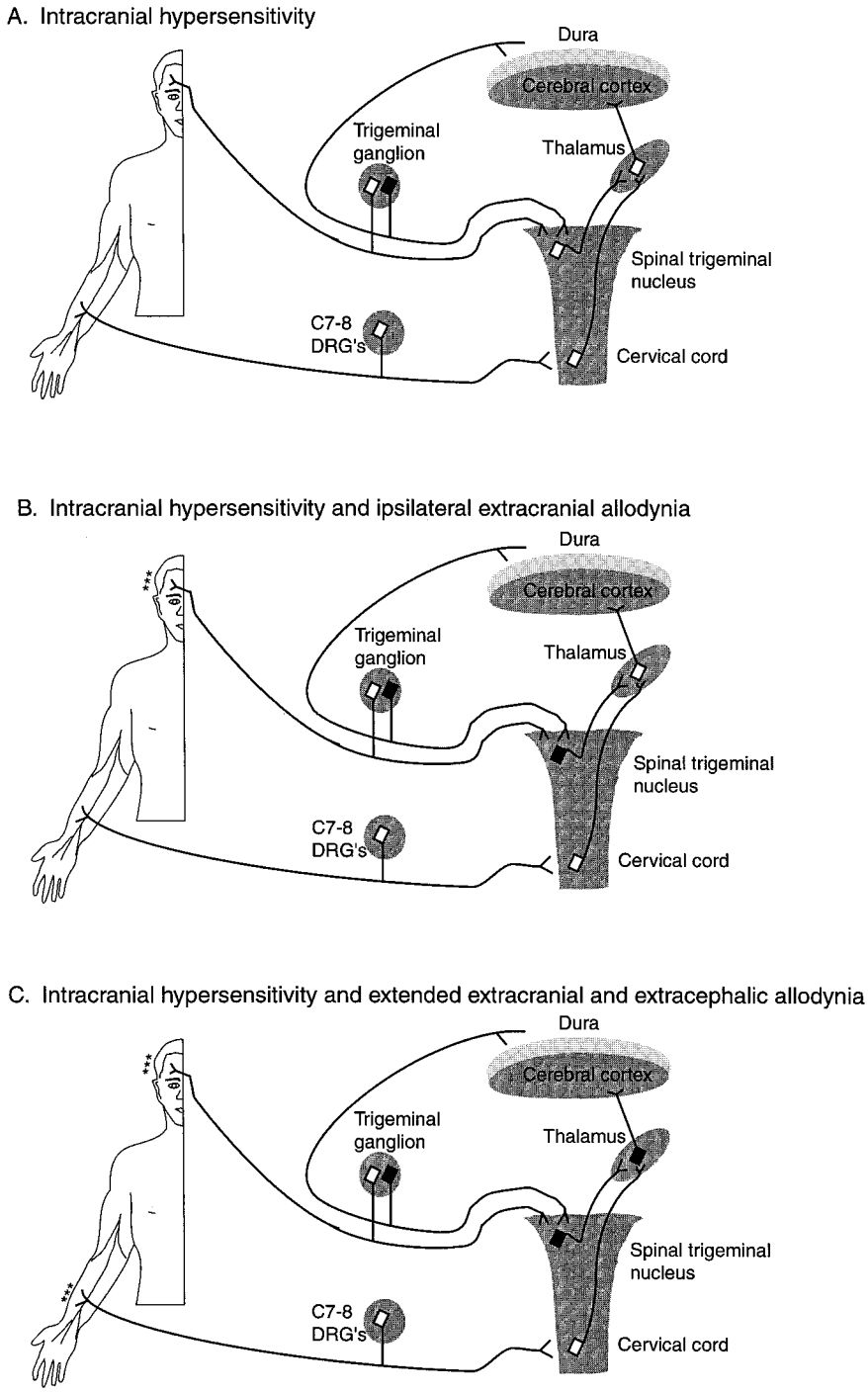

Fig 3. Proposed mechanism for cutaneous allodynia during migraine. A. Intracranial hypersensitivity is explained by sensitization of dural nociceptors (first-order neurons) in the trigeminal ganglion. B. Intracranial hypersensitivity and cutaneous allodynia within the referred pain area are explained by the subsequent sensitization of central (second-order) trigeminal neurons in the brainstem. C. Intracranial hypersensitivity and extracephalic allodynia are explained by additional sensitization of third-order neurons that receive convergent information from the head and forearms. Black diamonds *represent sensitized pain sensitive neurons. DRG = dorsal root ganglion.*

ence of cutaneous allodynia all over the body, this mechanism can account for only the 33% of the patients who exhibit cutaneous allodynia at all tested sites (Group B4). Forty-three percent of the patients (Groups B1–B3), however, exhibited cutaneous allodynia in some but not all tested sites. The spatial distribution of cutaneous allodynia in these patients cannot be explained by the general hyperexcitability theory. Rather, hyperexcitability that develops along the trigeminovascular pain pathway following its activation during a migraine attack is considered a more likely hypothesis. Accordingly, a temporary increase in the sensitivity of at least third-order neurons that receive convergent input from the dura, periorbital skin, and skin areas at different body sites[21,22] can explain the different distributions of allodynia in Group B2 to B4 patients (see Fig 3C). In animals, for example, third-order thalamic neurons become hypersensitive to

stimulation of large skin areas on both sides of the body following a small unilateral injury.[23,24]

Previous reports on scalp and muscle tenderness in migraine[9–15] and tension-type headache[25–31] contributed to the notion that muscle tenderness provides a component of an extracranial pathophysiology to migraine pain. The hypothesized mechanism, however, implies that intracranial pathophysiology alone can be sufficient to induce such muscle and scalp tenderness. The presence of second-order dorsal horn neurons that innervate skin, muscles, and intracranial structures can provide the neural substrate for this mechanism. As is the case during acute myocardial infarction, in which the muscle ache in the left arm is caused by visceral rather than somatic pathology, the pericranial muscle tenderness of migraine could also be visceral in origin.

It is generally believed that migraine patients are more sensitive on the headache side even between migraine attacks. This study demonstrates that, in the absence of migraine, there are no differences in the pain thresholds between the two sides of the head, which suggests that cutaneous allodynia that develops during migraine is reversible. Otherwise, pain thresholds on the ipsilateral head would be significantly lower than on the contralateral head in the absence of migraine.

Conclusion

This study points to the importance of identifying the presence and the extent of cutaneous allodynia during migraine. Since most physicians are unlikely to see their patients during a migraine attack, they may be able to elicit a history of increased skin sensitivity through relevant questioning that inquires whether activities such as brushing hair, touching the scalp, shaving, and wearing glasses, contact lenses, earrings, or wearing tight clothes hurt patients during migraine attacks.

Supported by NIH grants DE-10904 (National Institutes of Dental and Craniofacial Research) and NS-35611-01 (National Institutes of Neurological Disorder and Stroke) to Dr Burstein, by the Education Fund of the Department of Anesthesia and Critical Care at Beth Israel Deaconess Medical Center, and by the Goldfarb family, the Fink family, and the Boston Foundation. Data organization and analysis were done on the Prophet System (Release 4.1), a national computing resource for life science research sponsored by the NIH, Division of Research Resources.

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