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Avi Ashkenazi

Thomas Jefferson University, avi.ashkenazi@jefferson.edu

Melissa Sholtzow

Thomas Jefferson University

Rami Burstein

Beth Israel Deaconess Medical Center and Harvard University

James W. Shaw

Thomas Jefferson University

William B. Young

Thomas Jefferson University

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Identifying Cutaneous Allodynia in Chronic Migraine using a Practical Clinical Method

Avi Ashkenazi M.D.¹, Melissa Sholtzow B.S.¹, Rami Burstein Ph.D.²,
James W. Shaw Ph.D., Pharm.D.¹, M.P.H., and William B. Young M.D.¹

¹Department of Neurology
Thomas Jefferson University
and
Jefferson Headache Center
Jefferson University Hospital
Philadelphia, PA

²Department of Anesthesia and Critical Care
Beth Israel Deaconess Medical Center
and
Program in Neuroscience,
Harvard Medical School
Boston, MA

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Address all correspondence to:

Avi Ashkenazi, M.D.
Department of Neurology
Jefferson Headache Center
Jefferson University Hospital
111 South 11th Street, Suite 8130
Philadelphia, PA 19107
E-mail: avi.ashkenazi@jefferson.edu

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Abstract

Background: Cutaneous allodynia is common in migraine. Since the presence of allodynia during an acute migraine attack is associated with poor response to triptans, a clinically practical method to test migraine patients for allodynia would be useful to the clinician. Objective: To assess the prevalence of dynamic mechanical (brush) allodynia in chronic migraine, using a clinically practical method. Methods: Eighty-nine chronic migraine patients were prospectively recruited. Patients were given a structured questionnaire regarding migraine characteristics and skin sensitivity. Allodynia testing was performed by lightly brushing a 4x4-inch gauze pad on various areas of the skin. The prevalence of brush allodynia in the entire study population and in different patient sub-groups was calculated. Results: Brush allodynia was present in 38 of 89 patients (42.7% of the entire study population). The presence of allodynia was unrelated to the occurrence of an acute migraine attack at the time of testing. Allodynia was positively associated with a history of migraine aura ($p=0.03$). It was most common in the cephalic area, but it was also often seen in cervical dermatomes. The intensity of allodynia was positively correlated with the intensity of headache pain at the time of testing ($p=0.048$). However, the laterality of allodynia was unrelated to that of the headache pain. Conclusion: Allodynia is common in chronic migraine patients and is not significantly affected by the occurrence of an acute migraine attack. This suggests a state of ongoing neuronal sensitization in chronic migraine. We present a clinically practical method of testing migraine patients for cutaneous allodynia that may help physicians identify and make appropriate treatment decisions for allodynic migraine patients in a clinical setting.

Introduction

Cutaneous allodynia is the perception of pain when a non-noxious stimulus is applied to normal skin.¹ Scalp and muscle tenderness have been recognized in migraine, and 60%-80% of migraine patients have cutaneous allodynia during an acute attack.²⁻⁶ The underlying mechanism of cutaneous allodynia in migraine is thought to be sensitization of neurons in the trigeminal ganglion, which in turn results in sensitization of second-order neurons in the trigeminal nucleus caudalis (TNC).⁷⁻¹⁰ Migraine patients have been found to experience allodynia in response to stimuli of various sensory modalities: thermal (heat or cold allodynia), dynamic mechanical (brush allodynia), and static mechanical (pressure allodynia). The prevalence of the different types of allodynia in migraine is not the same, suggesting that they result from sensitization of different sensory neurons.^{5,11} Allodynia in migraine is usually found in cephalic areas; however, it may also occur in extra-cephalic regions, suggesting sensitization of higher order sensory neurons, possibly in the thalamus.^{10,12}

The presence of cutaneous allodynia during an acute migraine attack is associated with significantly reduced efficacy of treatment with the 5HT_{1B/1D} agonists known as triptans.⁶ In allodynic patients, triptans were significantly more effective in relieving headache when given before, rather than after, cutaneous allodynia was established. In non-allodynic patients, however, treatment with triptans was equally effective when given early (1 hour after the onset of headache) or late (4 hours after headache onset) during an acute attack. This observation was supported by an electrophysiologic study in a rat model of migraine. After the dura was irritated by applying inflammatory mediators, sumatriptan prevented the sensitization of neurons in the TNC when given early, but failed to do so when given late (i.e. two hours after the dura was

irritated).¹³ Cutaneous allodynia is therefore an important phenomenon not only from the pathophysiological aspect but also clinically. Recognizing allodynia can help clinicians select the optimal treatment for migraine patients. In most studies to date, allodynia in migraine patients was evaluated by using either quantitative sensory testing (QST)⁵ or a questionnaire.^{14,15} QST is a lengthy process that requires sophisticated equipment and a questionnaire is a subjective rather than an objective measure. A practical objective tool is therefore needed to assess cutaneous allodynia in migraine in a clinic setting. Recently, we developed a method to examine patients for dynamic mechanical (brush) allodynia in the clinic and tested it in a small number of patients.^{16,17} We found this method to be both practical and reliable, and we used it in the current study to assess the prevalence and spatial distribution of cutaneous allodynia in chronic migraine patients attending a tertiary headache clinic.

Methods

This study was approved by the Institutional Review Board for Studies in Human Subjects of Thomas Jefferson University Hospital. We recruited patients with International Headache Society (IHS)-defined chronic migraine from the Jefferson Headache Center outpatient clinic.¹⁸ Included patients were 16 years of age or older. We excluded patients with neurologic diseases that could cause sensory abnormalities (e.g. peripheral neuropathy, multiple sclerosis) and patients with dermatologic diseases that could cause abnormal skin sensation. All patients provided informed consent prior to enrollment in the study.

Included patients were given a structured questionnaire to obtain demographic data, migraine history (age of onset, disease duration), average attack frequency and duration, headache

characteristics (severity, location, pain character), associated symptoms, and type and duration of aura, if present. The questionnaire also included a seven-item scale that we had used and validated previously, designed to evaluate the presence of allodynia.¹⁷

Brush allodynia (BA) was tested by lightly brushing a 4x4-inch gauze pad over the skin at a rate of 2/sec, ten times consecutively.¹⁷ Six skin areas were stimulated: right frontal (V_1), left frontal, right posterior cervical (C_2 - C_3), left posterior cervical, right medial forearm (C_8) and left medial forearm. For each site, patients were asked to assess the degree of pain (if any) evoked by the gauze pad application to the skin, using a 100 mm visual analog scale (VAS). Allodynia score at each site ranged from zero to 100. Patients who recorded a VAS score greater than zero at one or more sites were considered to be allodynic. A total allodynia score was calculated as the sum of the six site-specific VAS scores (maximum total score: $6 \times 100 = 600$). The prevalence of allodynia in the entire study population, as well as in different patient sub-groups, was calculated. Sub-groups were defined based on the presence or absence of a history of aura and on the presence or absence of an acute migraine attack at the time of allodynia testing. The intensity of headache pain at the time of testing (current headache pain), as measured using an 11-point verbal scale, was documented.

Statistical analysis: Chi Square tests were used to compare the prevalence of allodynia among different sub-groups of chronic migraine patients. Spearman correlation was used to evaluate the association between the total allodynia score and current headache pain. Fisher's exact test was used to study the relationship between the laterality of allodynia and the laterality of the current headache pain. For those patients who had allodynia at all three dermatomes (at either right or left, or both) (i.e., V_1 , C_2 - C_3 , and C_8), the Friedman test was used to compare the median

maximal allodynia score among dermatomes. For a given dermatome, the median maximal score was defined as the median of the maximum allodynia scores at that dermatome. All statistical tests were performed using Stata/SE 9.0 and with two-tailed $\alpha=0.05$.

Results

Eighty nine patients (75 women and 14 men) were included in the study. Their mean (\pm SD) age was 44.5 ± 11.9 years. Thirty five patients (39%) were tested for allodynia while they were having an acute migraine attack and 54 patients (61%) were tested between attacks, when they had their baseline headache. Thirty five patients (39%) reported experiencing auras in the past with their migraine attacks, while 54 patients (61%) did not.

Allodynia during an acute attack and in between attacks:

Overall, 38 patients (42.7%) had BA. The prevalence of BA in patients who had an acute migraine attack during allodynia testing versus those who did not is shown in figure 1. Sixteen (45.7%) of the 35 patients who were tested during an acute attack were allodynic, compared with 22 (40.7%) allodynic patients of those who were tested between attacks. There was no significant difference in the prevalence of allodynia between these two groups ($\chi^2_1 = 0.21$, $p=0.64$).

Cutaneous allodynia and a history of aura:

Figure 1 also depicts the relationship between a history of migraine aura and the prevalence of allodynia. Twenty (57.1%) of the 35 patients who reported a history of aura had BA. By comparison, 18 (33.3%) of the 54 patients who did not report a history of aura, were allodynic.

The difference in the prevalence of allodynia between these two groups was statistically significant ($\chi_1^2 = 4.92$, $p=0.03$).

The spatial distribution of allodynia:

Table 1 presents the distribution of cephalic and extra-cephalic allodynia in the study population. Cephalic allodynia was found in 33 patients (86.8% of allodynic patients, 37.1% of the entire study population), while extra-cephalic allodynia was found in 25 patients (65.8% of allodynic patients, 28.1% of the entire study population). Of those patients with extra-cephalic allodynia, all had allodynia at the C₂-C₃ area, while 14 (56.0% of patients with extra-cephalic allodynia; 36.8% of allodynic patients; 15.7% of the entire study population) had allodynia at the C₈ area.

Table 2 presents the different patterns of spatial distribution of allodynia in the study population. The most common distributional pattern was cephalic with extra-cephalic, which was found in 20 patients (52.6% of allodynic patients; 22.5% of the entire study population). Twelve of these patients (31.6% of allodynic patients; 13.5% of the entire study population) had allodynia at all three sites. Thirteen patients (34.2% of allodynic patients; 14.6% of the entire study population) had cephalic allodynia alone. Only five patients (13.2% of allodynic patients; 5.6% of the entire study population) had extra-cephalic allodynia with no cephalic allodynia.

Allodynia scores by site:

Figure 2 shows the median maximal allodynia scores (as measured on a VAS scale) by dermatome for those patients who experienced allodynia at all three dermatomes (n=12).

Allodynia scores (mean±SD) tended to be higher at the V₁ (38.7± 35.6) and C₂-C₃ (37.3 ± 37.1)

and lower at the C₈ (21.0± 30.2). The median maximal allodynia scores were 25.5, 23.5, and 7.0 at the V₁, C₂–C₃, and C₈ sites, respectively. However, there were no significant differences among the sites ($\chi^2 = 2.33$, p=0.34).

Allodynia score in relation to headache and to other migraine symptoms:

Figure 3 presents a scatterplot of total allodynia scores against current headache pain ratings along with a fitted linear regression line and confidence interval for the mean. A positive correlation was found between the total allodynia score and current headache pain as measured on an 11-point scale ($\rho = 0.21$, p=0.048). No association was found between the laterality (right, left, or bilateral) of allodynia and the laterality of current headache pain (p=0.09).

In this study, no significant difference was found in the prevalence of allodynia between men and women ($\chi^2 = 0.05$, p=0.82). Similarly, no significant association was found between photophobia/phonophobia (categorized as neither, either, or both) and allodynia ($\chi^2 = 3.38$, p=0.19).

Discussion

In most previous studies, allodynia in migraine was assessed using either time-consuming quantitative sensory testing (QST) or a questionnaire alone.^{5,14,15} In this study, we used a clinically practical method to evaluate chronic migraine patients for the presence of allodynia.

There is little data in the literature regarding the prevalence of allodynia in chronic (or transformed) migraine. Creach et al found that extra-cranial, but not facial, allodynia was

significantly more common in patients with transformed migraine compared with those with episodic migraine (EM).¹⁹ Sorbino used a questionnaire to identify CM patients with cutaneous allodynia. Of 135 patients with CM in his study, 56% were allodynic.²⁰ This figure is somewhat higher than ours. However, no sensory testing was used in that study to verify the presence of allodynia. Kitaj and Klink tested patients with transformed migraine (TM) and EM for pain thresholds, using QST. They found that patients with TM had lower pain thresholds compared with those with EM.²¹

This study demonstrated a high prevalence of cutaneous allodynia in patients with CM, both during an acute attack and between attacks. In contrast to the findings in studies of patients with EM, allodynia prevalence in patients with CM was not significantly affected by the presence of an acute attack at the time of testing. These observations support the hypothesis that a state of ongoing sensory neuronal sensitization in the trigeminal, and possibly extra-trigeminal, pain pathways exists in CM. Sensory neurons in the trigeminovascular system that are chronically sensitized may not be affected by the physiologic and chemical events that occur during an acute migraine attack to the same degree as neurons that are not chronically sensitized. Our results may also explain why patients with CM are more difficult to treat than those with EM. Burstein et al have shown that the presence of allodynia is associated with a dramatically reduced efficacy of triptans in migraine treatment.⁶ The high prevalence of allodynia in CM patients may offer an explanation for the refractoriness to triptans that many of these patients exhibit. This observation and the hypothesis it raises require further evaluation.

In a recent study, we found that patients with chronic cluster headache (CH) were more likely to be allodynic compared with those with episodic CH (67% vs. 29%). This suggests that ongoing neuronal sensitization may be a common process associated with chronicity in different primary headaches.

We found that cutaneous allodynia was 1.7 times as common in patients who had a history of aura with their migraine attacks compared with those who did not. This data is consistent with results of previous studies.^{5,6} There is currently no satisfactory explanation for the association between cutaneous allodynia and a history of aura. Since there was no correlation between the presence of aura and the likelihood of being tested during an acute attack (data not shown), the higher prevalence of allodynia in migraine with aura (MA) compared with migraine without aura could not be explained by a higher proportion of MA patients being tested during an acute attack. It may be speculated that patients with MA have a state of higher cortical neuronal excitability that spreads to central trigeminal neurons via peripheral trigeminal fibers, thereby enhancing cutaneous allodynia. This theory remains to be tested.

We found that allodynia was most common in the V₁ area, followed by the C₂-C₃ dermatome, and it was least common at the C₈ dermatome. Allodynia scores tended to be higher at the V₁ area compared to scores at extra-cephalic areas. These results confirm data from a previous smaller study, in which migraine patients were tested for brush allodynia.^{12,17} The most common spatial distribution of allodynia in the present study was cephalic + extra-cephalic. Similar results were found in studies using QST.. Burstein et al found that allodynia was always present at the referred head pain area, and it was also found in extra-cephalic areas in the majority (28/33) of

allodynic patients.⁵ This spatial distribution supports the hypothesis that allodynia initially occurs at the referred head pain area and then spreads to extra-cephalic areas as a result of sequential sensitization of higher order neurons. This pattern of allodynia spread has been shown clinically in a patient with MA who was tested for allodynia at several time points during an acute migraine attack.¹⁰ Five patients in our study (13.2 % of allodynic patients) had allodynia at extra-cephalic areas only. This uncommon pattern may occur when patients are tested for allodynia at a time point when cephalic allodynia had subsided, while extra-cephalic allodynia was still maintained. Since we tested the patients for allodynia at a single time point in this study, we can not verify this assumption.

Allodynia and headache intensities were positively correlated in this study. The correlation between allodynia and headache severity has not been extensively studied before. In a smaller preliminary study, we found a correlation between allodynia score and migraine score (a measure of migraine severity and duration), that was not statistically significant.¹⁷ This correlation is expected, since allodynia is a manifestation of neuronal sensitization in pain pathways that are responsible for the headache generation. The laterality of headache and that of allodynia were not correlated in this study, suggesting a more complex relationship between the two. Indeed, we recently reported on a migraine patient who exhibited cephalic allodynia that was contralateral to the side of head pain, a phenomenon we called referred allodynia.²²

The results of this study should be interpreted with the following reservations: 1. This was a clinic-based study. Our results regarding allodynia prevalence may not be applicable to the general migraine population. 2. Many patients were taking migraine preventive drugs during the

study period. This could have affected their skin sensitivity to mechanical stimuli. For example, there is both experimental and clinical evidence that gabapentin, which is occasionally used for migraine prevention, reduces cutaneous allodynia in humans and in a rat model of postherpetic neuralgia.^{23,24} 3. The effect of acute medication intake on the occurrence of allodynia was not assessed in this study. Sumatriptan can cause transient, short-lasting allodynia in migraine patients.²⁵ This may have affected the results of allodynia testing in patients who were in an acute attack.

In summary, we used a clinically-practical test to assess chronic migraine patients for cutaneous allodynia. Our findings suggest a high prevalence of BA in CM that may interfere with patients' response to acute migraine treatment. Our proposed method for allodynia testing can help clinicians identify patients with allodynia and select the appropriate treatment for them.

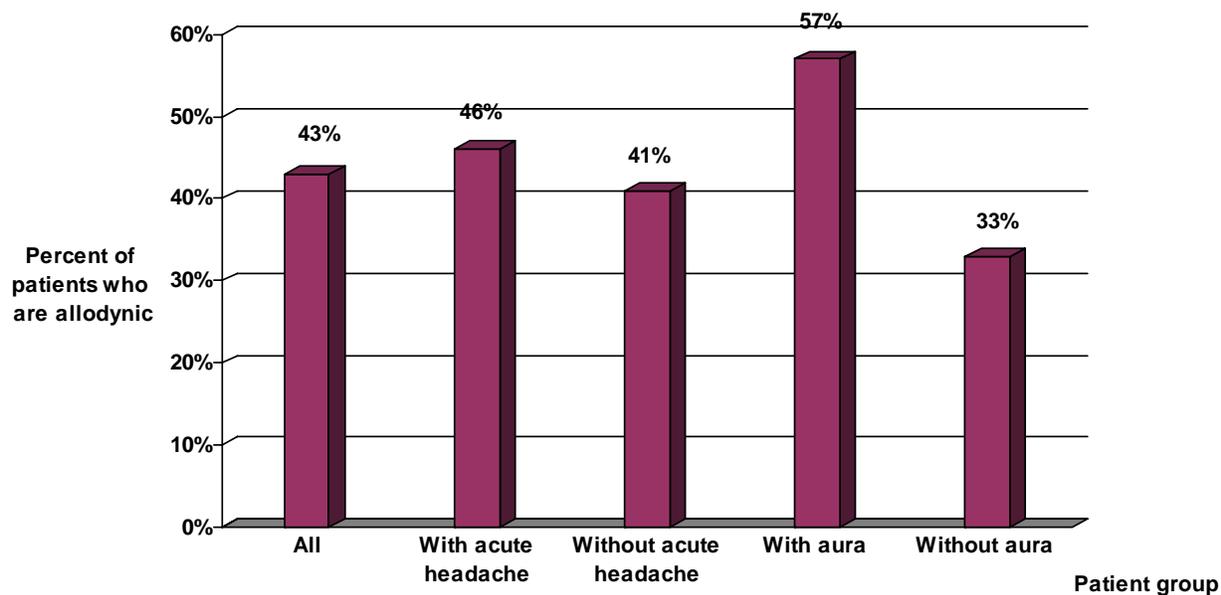


Figure 1: Allodynia prevalence in the entire study population and in the different patient sub-groups.

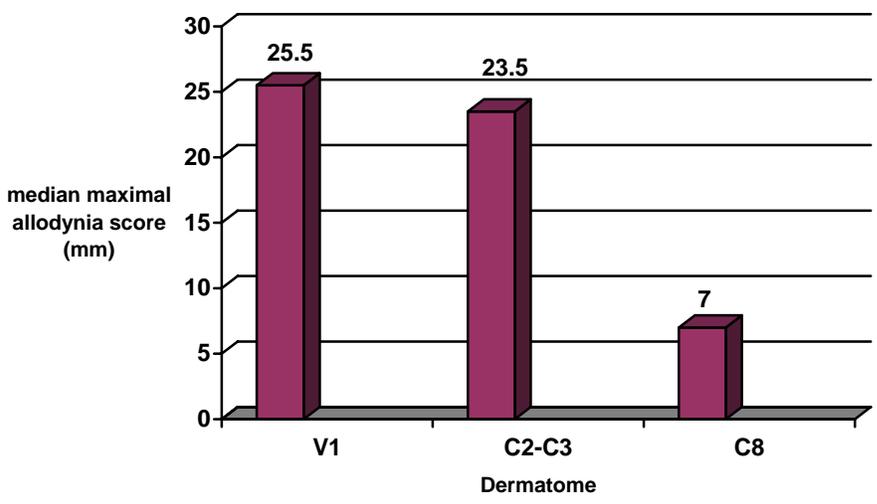


Figure 2: Median maximal allodynia scores (measured as mm on VAS scale) by dermatome in patients who had allodynia at all three dermatomes.

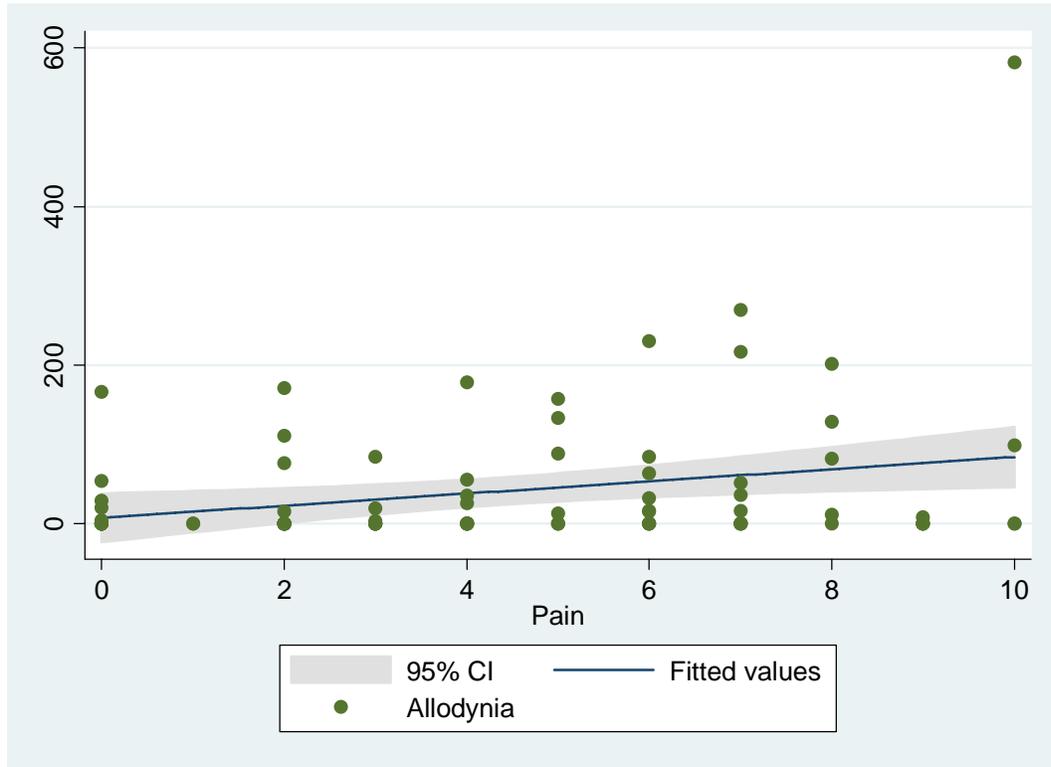


Figure 3: Correlation between total allodynia score and current headache pain rating

Site	No. of Patients	Percent of Allodynic Patients	Percent of Total Study Population
Cephalic	33	86.8	37.1
Extra-cephalic - all	25	65.8	28.1
Extra-cephalic (C ₂ -C ₃)	25	65.8	28.1
Extra-cephalic (C ₈)	14	36.8	15.7
Total	38	100.0	42.7

Table 1: No. (%) of patients with cephalic or extra-cephalic allodynia ^a

^a Numbers in columns do not add to 100% since patients may have had allodynia at more than one site

Site	No. of Patients	Percent of Allodynic Patients	Percent of Total Study Population
Cephalic and extra-cephalic (V ₁ with C ₂ -C ₃ and/or C ₈)	20	52.6	22.5
Cephalic only (V ₁)	13	34.2	14.6
All tested sites (V ₁ and C ₂ -C ₃ and C ₈)	12	31.6	13.5
Extra-cephalic only (C ₂ -C ₃ and/or C ₈)	5	13.2	5.6
Total	38	100.0	42.7

Table 2: No. (%) of patients with allodynia at single and multiple sites ^a

^a Numbers in columns do not add to 100% since patients with allodynia at all three sites are a subset of those with cephalic and extra-cephalic allodynia

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