Migraine headache is present in the aura phase

A prospective study

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ABSTRACT

Objectives: Migraine aura is commonly considered to be a distinct phase of a migraine attack that precedes headache. The objective of the study was to examine a large number of prospectively recorded attacks of migraine with aura and determine the timing of headache and other migraine symptoms relative to aura.

Methods: As part of a clinical trial we collected prospective data on the time course of headache and other symptoms relative to the aura. Patients ($n = 267$) were enrolled from 16 centers, and asked to keep a headache diary for 1 month (phase I). They were asked to record headache symptoms as soon as possible after aura began and always within 1 hour of aura onset. A total of 456 attacks were reported during phase I by 201 patients. These patients were then randomized and included in phase II, during which a total of 405 attacks were reported in 164 patients. In total, we present data from 861 attacks of migraine with aura from 201 patients.

Results: During the aura phase, the majority of attacks (73%) were associated with headache. Other migraine symptoms were also frequently reported during the aura: nausea (51%), photophobia (88%), and photophobia (73%). During the first 15 minutes within the onset of aura, 54% of patients reported headache fulfilling the criteria for migraine.

Conclusion: Our results indicate that headaches as well as associated migraine symptoms are present early, during the aura phase of the migraine attack in the majority of patients.

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GLOSSARY

CSD = cortical spreading depression; **ICHD** = International Classification of Headache Disorders; **TMS** = transcranial magnetic stimulation.

Migraine is the most prevalent neurologic disorder, with more than 80 million patients in Europe and the United States alone.¹ Severe migraine is ranked in the highest disability class by the World Health Organization.² The estimated cost of migraine is €27 billion per year in Europe³ and a similar dollar amount in the United States.⁴ The widespread disability produced by migraine is therefore an important target for treatment.⁵ To reduce effectively this burden and optimize migraine treatment, it is important to understand basic migraine mechanisms.

Migraine is divided into 2 major clinical subtypes: migraine without and with aura.⁶ The migraine aura is commonly considered to be a distinct phase of a migraine attack that precedes headache.⁷ There have been remarkably few studies, however, in which the timing of different symptoms of attacks of migraine with aura has been systematically recorded and prospectively studied. A better understanding of the timing of aura relative to other migraine symptoms has the potential to provide insight into fundamental mechanisms of migraine, as well as the most appropriate timing for administration of acute migraine therapies.

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Supplemental data at
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Supplemental Data

CME

As part of a large randomized, placebo-controlled study to examine the efficacy of transcranial magnetic stimulation (TMS) as an acute therapy for patients with migraine with aura, participants recorded their migraine symptoms on an electronic diary.⁸ The results of the study provide an opportunity to examine quantitatively the timing of symptoms during a migraine attack.

The current International Classification of Headache Disorders (ICHD-II) states that migraine headache usually follows the aura symptoms.⁶ Here we have examined an alternative hypothesis, that aura is not consistently a distinct phase of a migraine attack and that it often precedes headache.

METHODS Study methods, and the treatment results of the randomized phase, have previously been reported.⁸ In brief, patients aged 18–70 years and meeting ICHD-II criteria for migraine with aura⁶ were recruited from 16 centers in the United States.

Patients had to have between 1 and 8 migraine episodes per month, with aura preceding migraine for at least 30% of episodes, followed by moderate or severe headache in 90% of attacks.

Key exclusion criteria were aura that lasted more than 60 minutes; presence of metal implants; headaches due to underlying pathology or trauma; and overuse of drugs for headaches or use of drugs that could confound interpretation of study results.

All data were collected prospectively with baseline recordings at the onset of migraine aura. The patients were asked to start recordings of their symptoms on the electronic diary as soon as possible after aura began and always within 1 hour of aura onset. Patients were asked to treat up to 3 attacks. Only attacks starting with a migraine aura were recorded. During phase I, patients activated their diary when they experienced an aura. Patients reported the time elapsed since aura onset (0–15 minutes, 16–30 minutes, or 31–60 minutes) as well as pain intensity and associated symptoms. During phase II, patients reported baseline pain and associated symptoms within 1 hour of onset of aura immediately before treatment; additional data have been previously presented.⁸ In this study we analyzed only 1 data entry per attack, i.e., the entry that was made prior to treatment.

Patients were allowed to continue use of their usual and necessary medical treatments, including stable doses of migraine preventive drugs. The use of analgesics, antiemetics, triptans, ergots, or other drugs that could confound assessment of the efficacy or safety of study treatment within the 12-hour period before treatment were not allowed. Rescue drugs were permitted 2 hours after treatment.

Standard protocol approvals, registrations, and patient consents. All study centers provided institutional review board approval before study initiation, and all participants gave written informed consent. The trial was registered with ClinicalTrials.gov, number NCT00449540.

Headache intensity and migraine definition. Headache intensity was recorded by the diary and graded from 1 to 4: 1 = no headache; 2 = mild headache; 3 = moderate headache; and 4 = severe headache. Patients were asked to rate migraine-associated symptoms, nausea, photophobia, and phonophobia,

using the same scale. The study only included migraine attacks preceded by aura, and we used the patient data to determine if the headache fulfilled the diagnostic criteria for migraine with aura.⁶ It is common for migraine symptoms to develop gradually⁹; during the early stages of an attack these symptoms may not meet criteria for definitive diagnosis of migraine.¹⁰

As the study population reported their migraine early (within 1 hour of onset of aura), we did not expect their headache to have reached peak intensity.

In addition to determining if symptoms fulfilled ICHD-II criteria for migraine with aura, we also applied the following pragmatic definition for the headache to be classified as probable migraine: any headache fulfilling all of the following:

1. The presence of migraine aura
2. The patient reporting headache of any intensity (mild/moderate/severe)
3. Headache associated with at least one of the following: nausea or vomiting, or photophobia and phonophobia

Data analysis and statistics. The primary endpoints of our analysis were the overall incidence of headache and associated symptoms in all attacks at baseline (before treatment) and the number of attacks fulfilling the criteria for migraine with aura at baseline. Additional endpoints were the number of attacks fulfilling the criteria for migraine relative to timing of aura (phase I).

Data from individual attacks in phase I and II were summarized using frequency counts with percentages and descriptive statistics such as means and standard deviation. Internal consistency of reporting of multiple different attacks by individual subjects was measured using Cronbach α analysis. All analyses were performed with SPSS for Windows 17.0 (Chicago, IL).

RESULTS Study population. The mean age at the time of the first migraine headache was 17.8 years (± 9.3); in 70% of patients at least half their migraines were preceded by visual aura. Figure e-1 on the *Neurology*[®] Web site at www.neurology.org shows the progress of individuals through the study. Of patients screened ($n = 276$), 267 patients were enrolled in phase I, trained to use an electronic diary (personal digital assistant), and asked to keep a headache diary for 1 month. A total of 456 attacks were reported during phase I in 201 patients. During this phase 66 dropped out (37 did not treat migraine with aura and 29 deviated from the protocol). The mean number of attacks reported in phase I was 2.3 (± 1.4 ; range 1–9) (figure e-2). Preventive medication was being taken in 76 patients (38%), accounting for 43% of attacks in phase I. In phase II, 201 patients were randomized and allocated to either active treatment or sham stimulation, in a double-blind manner. During this phase, 37 patients did not treat their migraine with aura, and a total of 405 attacks were reported during this phase in 164 patients. The mean number of attacks reported in phase II was 2.5 (± 0.8 ; range 1–3) (figure e-2). Preventive medications were taken by 63 patients (38%) in phase II, accounting for 37% of all migraine attacks. In total, we report data from 861 attacks in 201 patients.

Incidence and severity of headache and associated migraine symptoms. For all 861 attacks, the overall most reported symptom was photophobia ($n = 759$; 88%), followed by phonophobia ($n = 632$; 73%), headache ($n = 628$; 73%), and nausea ($n = 439$; 51%) (figure 1). Headache and other migraine-associated symptoms were frequently present already from the beginning of the attack. For attacks recorded within 15 minutes of aura onset, photophobia was reported in 84%, phonophobia in 67%, headache in 61%, and nausea in 40% of attacks.

The prevalence of the migraine symptoms according to the time elapsed since aura onset can be seen in figure 1. The symptoms graded after severity are presented in figure 2. Only a fraction of patients reported headache and aura without any associated migraine symptoms (0%–3%, data not shown). The internal consistency of the presence of aura, headache, and other migraine-associated symptoms across multiple attacks in each individual subject was high (Cronbach $\alpha = 0.85$).

Incidence of migraine. The percentage of attacks that fulfilled the criteria for migraine as defined either by the ICHD-II⁶ or by our definition of probable migraine was evaluated relative to the timing of aura in phase (figure 3).

Based on ICHD-II criteria, the majority of patients in phase I who recorded data 31–60 minutes after aura onset reported symptoms fulfilling the definition for migraine with aura (56%). Based on our definition of probable migraine that included attacks with mild headache, the majority of attacks recorded within 15 minutes of aura onset reported symptoms fulfilling the definition for migraine (54%), and nearly all of those who recorded data 31–60 minutes after aura onset met criteria for migraine (86%).

DISCUSSION The major finding of the study was that the majority of attacks included headache and other symptoms at baseline when participants first reported aura (figure 1), and 54% of attacks fulfilled the migraine criteria within 0–15 minutes after onset of aura (figure 3). This indicates that migraine headache and associated symptoms are present during the aura phase for the majority of patients in the study.

A small number of previous studies have reported the timing of headache and other migraine symptoms in relation to the aura. Patients filling out a diagnostic aura diary during a migraine attack reported that the interval between the onset of visual disturbance and onset of headache varied between 0 and 120 minutes (median 45 minutes), and only a minority of attacks (13%) had acute onset of visual aura associated with other migraine features.¹¹ Another prospective, but small study ($n = 26$) reported that in half the cases, the aura immediately preceded the headache.¹² In a select group of 362 patients with severe familial migraine with aura, 94% had a headache following the aura with a free interval of less than 1 hour, but only 11% reported headache starting simultaneously with the aura.¹³ A population-based survey found that the headache and aura occurred simultaneously in 4.7% (7 out of 148 patients).¹⁴ By contrast, we report that headache and other migraine symptoms are clearly present early in the attack, during the aura. Previous reports indicate that a typical aura lasts about 30 minutes,^{14,15} which means that our first 2 recordings likely reflect the migraine state at the time of aura.

Our results are not consistent with the current ICHD-II, which states that migraine headache usually follows the aura symptoms,⁶ and these results may therefore have implications for the classification of migraine with aura.

Based on 2 randomized controlled trials, it has been suggested that triptans administered during the aura phase were without effect on both aura and headache.^{16,17} A 4-way crossover, open-label study found,

Figure 1 Proportion of attacks with headache and associated migraine symptoms before treatment

The figure shows the distribution of symptoms during phase I ($n = 456$ attacks) with attacks grouped according to time elapsed since aura onset (0–15 minutes, 16–30 minutes, or 31–60 minutes), and from the randomized phase II ($n = 405$ attacks), within 1 hour of onset of aura.

Figure 2 Migraine symptoms graded after severity

Data from all 861 attacks recorded within 1 hour of aura onset, before any treatment.

however, that oral sumatriptan treatment during the aura produced higher success rates than when treated later.¹⁸ Small studies in select and complicated patient groups also show that triptans do work when taken during the aura phase: in a cohort of familial hemiplegic migraine patients, about half of the patients preferred to use triptans during aura phase of the attacks,¹⁹ with good results, and in a small case series with patients with prolonged aura triptans had excellent effect.²⁰ Timing, rather than the presence of aura, may thus be a determinant of triptan efficacy. Treating the migraine when pain is mild provides statistically significant and clinically relevant enhancements for the patients,²¹⁻²³ and is cost-effective.²⁴ It has been suggested that this advantage could be explained by a lack of central sensitization.²⁵ A small study found similar efficacy of early and late treatment with subcutaneous sumatriptan, suggesting that central sensitization is not important for the response to a triptan.²⁶ Our present results, where a large proportion of patients have prominent migraine features already during the aura, also support the concept that early acute treatments with triptans, TMS,⁸ or others²⁷⁻²⁹ during the aura phase of the attack may result in higher efficacy.

Migraine aura is likely to be the symptom of cortical spreading depression (CSD)³⁰ originally described by

Leão.³¹ In rats, CSD leads to activation of nociceptors that innervate the meninges³² and also activate central trigeminovascular neurons,³³ thereby linking CSD to delayed activation of the trigeminovascular pathway, and potentially to the development of headache.³⁴ We show, however, that in a large percentage of migraine attacks, aura, headache, and other migraine-associated symptoms occur simultaneously. The hemodynamic changes described during migraine aura also do not support the concept of aura as a discrete phase of the migraine attack. Neither aura nor headache is directly correlated with the hypoperfusion followed by hyperperfusion that has been observed with studies of cerebral blood flow during migraine attacks.³⁵ The occurrence of headache at the onset of aura is clearly not consistent with a linear sequence of events in which CSD is needed to activate the trigeminovascular system to cause headache. Our results rather suggest a model with multiple mechanisms involving activation of different brain regions in parallel.³⁶

The very common occurrence of photophobia and phonophobia early in the course of an attack, during the aura phase, indicates that hypersensitivity to sensory stimuli is also an early phenomenon. These data are consistent with the report of photophobia and phonophobia during the premonitory phase when there was no headache at all.³⁷ An increased sensitivity to sensory stimuli can be interpreted as an indication of central sensitization,²⁵ a process that is typically thought of as a secondary event that occurs following onset of headache. The results reported here are more consistent with central sensitization occurring as a primary phenomenon that occurs in conjunction with aura and headache onset.

The study design has certain limitations. Recording of symptoms began with onset of aura symptoms; we therefore do not know the number of cases where aura followed headache. Based on previous reports,^{13,14} however, we expect this number to be small (3%–8%). We also did not record the end of the aura, so we do not know the percentage of patients fulfilling the criteria for migraine prior to the resolution of aura.

The definition of probable migraine that we applied (see Methods) differs slightly from ICHD-II criteria for typical migraine with aura,⁶ but given the limitations of the information recorded, we believe that it is reasonable to conclude that an attack starting with aura and including a headache of any intensity and associated with nausea/vomiting or photo- and phonophobia qualifies as a migraine.

Migraine is a heterogeneous condition that causes symptoms that vary both among individuals and within individuals from attack to attack. The attacks may differ in intensity³⁸ and even headache type³⁹ and we therefore included more attacks per patient. The number of attacks reported per patient varied and some patients therefore contribute more to the data than others.

Figure 3 Percentage of attacks fulfilling the criteria for migraine with aura

Red: probable migraine according to the definition described in Methods. Blue: according to International Classification of Headache Disorders (ICHD-II). In total, 559 attacks (65%) fulfilled the migraine criteria before treatment according to the definition used in the study. Using the ICHD-II, 257 attacks (31%) fulfilled the migraine criteria before treatment.

Only a small number of patients, however, reported more than 3 attacks (figure e-2), and the symptom reports showed good internal consistency. To ensure reliability of the data, we conducted a post hoc analysis including only the first attack for each patient. The results are essentially the same as those for the pooled data which we chose to present because we believe that the higher number of attacks represented by these data are meaningful and important.

The primary strength of the study is the prospective recordings of a large cohort with multiple attacks per patient, with bias reduced by the inability to change data once entered. This type of systematic recording of patient information continues to have potential to provide significant and relevant insight into the clinical manifestations of migraine and how an attack begins, progresses, and resolves.³⁷

These results show that the phases of a migraine attack may not be as discrete as originally believed.

They underscore the fact that migraine is a complex brain disorder in which multiple anatomic and physiologic mechanisms may be occurring simultaneously and in parallel. An increased understanding of the timing and interactions between these mechanisms has the potential to identify new approaches to therapy.

AUTHOR CONTRIBUTIONS

Dr. Jakob, M. Hansen, Dr. Richard B. Lipton, Dr. David W. Dodick, Dr. Stephen D. Silberstein, Dr. Joel R. Saper, Dr. Sheena K. Aurora, Dr. Peter J. Goadsby, and Dr. Andrew Charles have contributed in the analysis or interpretation of data as well as drafting/revising the manuscript for content, including medical writing for content.

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DISCLOSURE

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