



# Circadian rhythms and migraine

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■ To determine whether migraine exhibits a circadian rhythm or occurs randomly throughout the day, we analyzed the time of migraine onset in 15 migraine sufferers (migraineurs) over 20 weeks. The patients suffered 211 migraine attacks over 20 weeks (range 3 to 30, median 13). Twelve of the 15 migraineurs had 50% or more of headache onsets during a 4-hour block of time. As a group, the migraineurs showed a circadian variation in migraine onset, with a marked increase in attacks between 6 AM and 8 AM, peak frequency of migraine onset between 8 AM and 10 AM, and a dramatic decrease in frequency between 8 PM and 4 AM. The circadian rhythm of migraine onset parallels that of myocardial infarction, platelet aggregability, plasma cortisol, and plasma catecholamines. These associations suggest that alteration of vasomotor tone may be involved in the initiation of migraine attacks.

□ INDEX TERMS: MIGRAINE; CIRCADIAN RHYTHM □ CLEVE CLIN J MED 1992; 59:326-329

**A**lthough migraine is among the most common maladies of mankind, little is understood about the mechanisms that trigger migraine attack. Circulating hormones,<sup>1</sup> platelet aggregability,<sup>2</sup> pericranial musculature pain sensitivity,<sup>3</sup> and vasospastic events<sup>4</sup> all follow circadian rhythms that may affect migraine.

It was recently shown that nonfatal myocardial infarction<sup>4</sup> and sudden cardiac death<sup>5</sup> are more likely to occur between 6 AM and noon than during other times of the day. Platelet aggregability also increases during the period from 6 AM to 9 AM.<sup>2</sup> Nonfatal myocardial infarction and sudden cardiac death are vascular events that share some similarities with migraine: they are associated with ischemia, platelet hyperaggregability, and changes in vasomotor tone.<sup>2,6</sup>

Knowledge of migraine rhythms may lead to an understanding of the pathogenesis of migraine and may improve our ability to treat migraine. To determine whether migraine exhibits a circadian rhythm or occurs randomly during the day, we analyzed the time of migraine onset over several months for a group of migraine sufferers (migraineurs).

## METHODS

The study was conducted in 15 patients with a history of migraine with or without aura for at least 1 year who were participating in a blinded, placebo-controlled trial of a nonsteroidal anti-inflammatory drug (NSAID). Headache diagnoses were made using International Headache Society<sup>7</sup> criteria. Patients with cluster headache or frequent tension headaches were excluded. All patients were healthy except for their migraines and were on no daily medications other than the nonsteroidal medication or placebo. Patients were instructed to compile a headache diary, noting the

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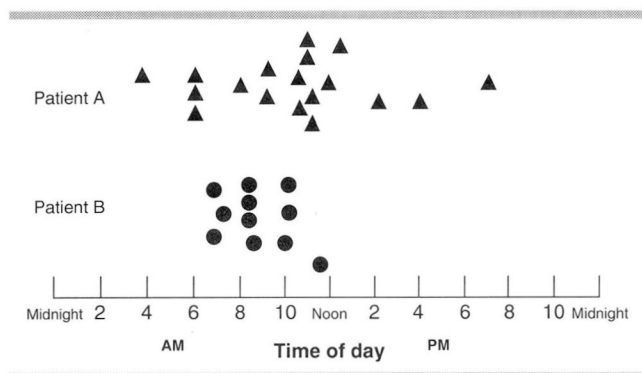


FIGURE 1. Data for two migraine patients showing time of onset for each attack.

time of onset of migraine attacks along with other data. The diary was reviewed monthly. The study was approved by the institutional review board. Informed consent was obtained from the subjects after the nature of the study had been explained.

Each patient completed the diary for 20 consecutive weeks between December 1989 and August 1990. The data were analyzed by plotting the hour migraine onset for individual patients and for the entire group.

## RESULTS

The 15 subjects recorded 214 migraine attacks during the study period. No time of onset was noted for 3 attacks, so these were omitted from the analysis, leaving 211 analyzable migraine attacks. The number of migraine attacks over the 20-week period ranged from 3 to 30, with a median of 13 attacks per patient.

Analysis of the individual patient data showed that for 12 of 15 patients (80%), more than 50% of their migraine attacks began within a 4-hour period. In 9 of these 12 patients (75%), the 4-hour period was between 6 AM and noon (Figure 1). In 2 patients (17%), the majority of migraine attacks began between 2 PM and 8 PM, while in 1 patient, more than 50% of migraine attacks began between 4 AM and 8 AM.

As a group, the migraineurs showed a marked increase in attack onsets between 6 AM and 8 AM, a peak frequency of migraine onset between 8 AM and 10 AM, and a dramatic decrease in frequency between 8 PM and 4 AM (Figure 2). Of 211 migraine attacks, 111 (52.6%) occurred between 6 AM and noon, 59 occurred between noon and 6 PM, 21 occurred between 6 PM and midnight, and 20 occurred between midnight and 6 AM. The incidence of migraine onset during the

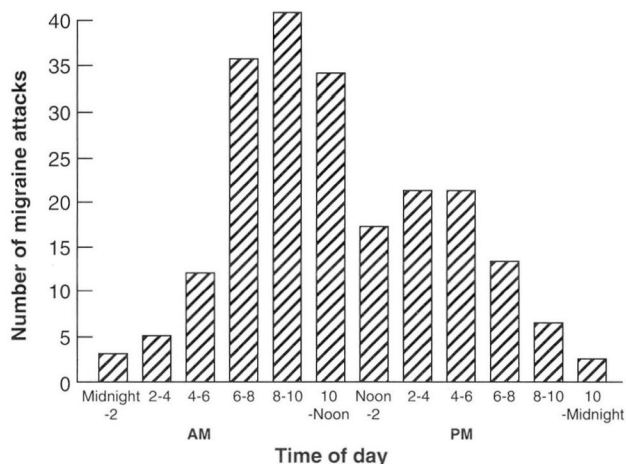


FIGURE 2. Number of migraine onsets per 2-hour time period for 15 migraine patients.

period from 6 AM to noon was 3.3 times greater than the average incidence during the other three 6-hour time periods ( $P < 0.05$ ) (Figure 3).

## DISCUSSION

The data obtained in this study demonstrate a prominent circadian rhythm in the time of migraine onset. This rhythm is marked by a low frequency during the night and a peak occurrence between 6 AM and noon. This pattern is noted both for the group and for individual patients.

A similar circadian rhythm has been demonstrated for nonfatal myocardial infarction<sup>4</sup> and for sudden cardiac death,<sup>5</sup> which are more likely to occur between 6 AM and noon than during other times of the day. Platelet aggregability also increases during the period 6 AM to 9 AM.<sup>2</sup>

Nonfatal myocardial infarction and sudden cardiac death share other similarities with migraine: both the cardiac events and migraine are associated with changes in vasomotor tone and ischemia, and platelet hyperaggregability has been associated with both conditions.<sup>2,6</sup>

Myocardial infarction and migraine may also share a similar pathogenesis. Tofler and colleagues<sup>2</sup> reported that platelet aggregability has a circadian variability that parallels non-fatal myocardial infarction and sudden cardiac death. The present report suggests that the circadian variability of platelet aggregability also parallels that of migraine.



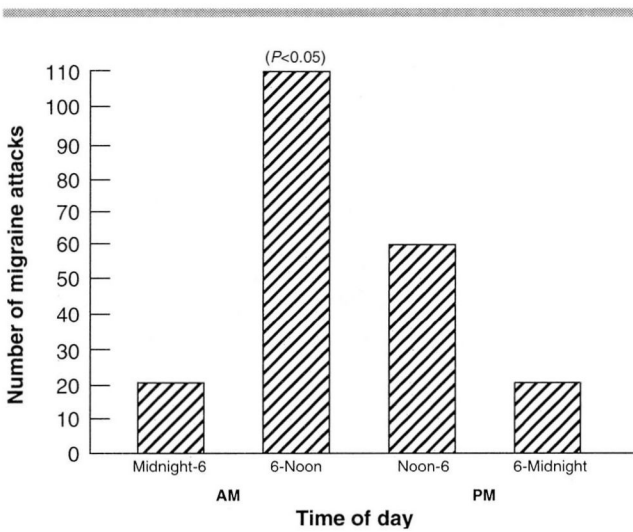


FIGURE 3. Number of migraine onsets per 6-hour time period for 15 migraine patients.

Platelet hyperaggregability may lead to the release of chemical mediators such as serotonin, which may induce vasospasm. Increased sympathetic nervous system activity may also play a role in both cardiac events and migraine. Plasma catecholamine levels rise during the period 6 AM to noon<sup>1</sup> and could also induce vasospasm. Vasospasm may initiate migraine by inducing reactive vasodilation or cerebral hypoxia.

The similarities in time pattern of these phenomena suggest that migraine is related to other vascular events. Both migraine and coronary artery disease are more common in patients with hypertension,<sup>8,9</sup> and both conditions are amenable to prophylactic therapy with aspirin,<sup>10</sup> beta blockers (without intrinsic sympathomimetic activity),<sup>11</sup> or calcium-channel blockers.<sup>12</sup>

The circadian pattern observed in migraine may also be related to changes in the firing rate of serotonergic neurons in the dorsal raphe nucleus. Raskin<sup>13</sup> has proposed that the core abnormality of migraine is unstable serotonergic neurotransmission leading to increased raphe neuronal firing rates. Dorsal raphe units maintain a slow, regular firing pattern as long as there is no change in arousal level. They be-

come totally silent during rapid eye movement sleep. The serotonergic neurons increase their firing rate in response to visual, auditory, or somatosensory stimuli.<sup>14</sup> It is possible that early morning arousal and the marked increase in sensory stimuli may trigger increased dorsal raphe nucleus firing rates, causing the increased frequency of morning migraines via serotonergic effects on platelets and vascular tone.

Cerebral infarction has a circadian pattern similar to migraine, with an increased frequency in the late morning hours.<sup>15,16</sup> This is in contrast to subarachnoid hemorrhage, which has been reported to peak between 6 PM and midnight.<sup>17</sup>

Waking from sleep with a headache is considered a common mode of onset for migraine, and previous reports suggested a temporal relationship between migraine and sleep.<sup>18,19</sup> Dexter<sup>19</sup> reported that two subjects who routinely awakened with migraine awoke within 10 minutes of the end of a rapid eye movement period of sleep. However, our data suggest that migraine more commonly occurs after a period of wakefulness than immediately upon awakening.

Determining the rhythm of migraine onset may be difficult, due to the influence of chronic medications and trigger factors such as diet and sleep changes. Beta blockers can alter the circadian rhythm of myocardial infarction, and might also effect the rhythm of migraine. For this reason, patients taking beta blockers were excluded from this study. The patient population was limited to healthy subjects with long-standing migraine headache without tension-type headaches. While this limited the number of subjects, it prevented the introduction of confounding variables into the data. To minimize the influence of specific trigger factors on migraine onset, and to limit the effects of seasonal variation, patients were studied for 20 consecutive weeks in the period from December through August.

Prophylactic medications for migraine—beta blockers, calcium-channel blockers, NSAIDs, and methysergide—are often administered in the morning, and it is probable that plasma levels of many of these drugs are at their nadir at the time when migraine is most likely to occur. Reviewing a patient's circadian pattern may permit the time of drug administration to be adjusted so that peak plasma levels occur when the patient is most at risk for migraine.

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