The Migraine Postdrome

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **The migraine postdrome is the least studied and least understood phase of migraine. This article covers the salient features of the migraine postdrome and provides insight into the history, clinical symptoms, and future implications of this phase of migraine.**

RECENT FINDINGS: **Prospective electronic diary studies have shown that patients are left disabled with various nonheadache symptoms in the migraine postdrome, and 81% of patients report at least one nonheadache symptom in the postdrome. Hence, it is important to understand this phase better and ensure that more effective treatments become available in the future to lessen the morbidity associated with this phase. Functional imaging shows widespread reduction in brain-blood flow in the postdrome, which explains the multitudes of symptoms experienced by patients.**

SUMMARY: **The disability related to migraine is not exclusive to the headache phase but extends into the postdrome phase and is associated with several nonheadache symptoms that prolong the symptoms experienced by patients with migraine. Further research into the postdrome is crucial to improve our overall understanding of migraine mechanisms. This knowledge may also help to treat the concurrent nonheadache symptoms better in the future. Novel neuroimaging techniques provide a valuable noninvasive tool to push the frontiers in the understanding of migraine pathophysiology. These methods may help shed further light onto the possible links between key brain structures and networks that could be implicated in the pathophysiology of the various migraine phases.**

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Continued on page 1031

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INTRODUCTION

Migraine is a leading cause of disability worldwide,[1] extracting a huge economic burden on global economies.[2,3] Knowing more about the key neural networks and neurotransmitters involved during the various phases of migraine may improve our understanding and management of the condition, which may also open doors to focused therapeutic options. Four main phases of migraine have been described[4]: the migraine aura, premonitory phase, headache phase, and the postdrome. Of these phases, the postdrome is relatively newly described. The postdrome is the period between resolution of the throbbing headache and when the patient feels completely back to normal.[5] During the postdrome phase, patients experience numerous nonheadache symptoms that

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KEY POINTS

- Tiredness, concentration difficulty, and neck stiffness are the most typically reported postdrome symptoms of migraine.
- Postdrome symptoms appear to be common, with 81% to 94% of patients with migraine reporting these symptoms.
- Treatment with triptans does not appear to alter the underlying diencephalic and brainstem mechanisms involved in migraine pathophysiology, and persistent activation of these networks may explain some of the symptoms in the migraine postdrome.
- Comorbidities such as anxiety and depression do not appear to influence the presence or absence of the migraine postdrome.
- Assigning postdrome symptoms into four main groups (neuropsychiatric, sensory, gastrointestinal, and general symptoms) gives clarity in classifying and assessing the symptoms.

can significantly limit the return to normal function in a proportion of patients.[6–8] A prospective daily electronic diary study showed that about 81% of subjects with migraine reported at least one nonheadache symptom in the postdrome (TABLE 3-1).[5] Some data also show the presence of postdrome in a pediatric population.[9] While common and disabling, the postdrome phase is not yet defined in the *International Classification of Headache Disorders, Third Edition (ICHD-3)*.[10] Defining the phase and incorporating it into the headache classification is needed so that vital research can be pursued and standardized.

HISTORY

Research into the postdrome phase is scant. Liveing[11] documented in his 1872 book *Observations on Megrim or Sick-Headache* that sleep resolved migraine attacks. Selby[12] was among the few neurologists who described the postdrome as a characteristic feature of migraine. Selby described the postheadache phase as the anticlimactic act of the migraine drama in which pain and nausea has settled down but patients are left with a difficult to describe prostration and malaise yet typical of migraine. Blau[13] suggested that the postdrome may be due to a slow decline in migraine processes and also hypothesized that it could be the converse process of the premonitory phase.

CLINICAL FEATURES

Patients report various nonheadache symptoms in the postdrome phase (TABLE 3-2). The symptoms can broadly be grouped into neuropsychiatric, sensory, gastrointestinal, and general systemic symptoms.[14,15] Tiredness, concentration difficulty, and neck stiffness are the most typically reported postdrome symptoms.[5] The average duration of the postdrome reported in different studies varies from 18 to 25.2 hours.[6,13]

Postdrome symptoms also appear to be common, with 81% to 94% of patients reporting these symptoms in various studies.[5,7] Although treatment with triptans can be helpful in managing the headache phase, no fundamental alteration appears to occur in the underlying diencephalic and brainstem mechanisms involved in migraine pathophysiology, and this may explain some of the symptoms in the postdrome.[5,16,17] Also, no dominant role appears to exist for comorbidities such as anxiety and depression in the occurrence or absence of the postdrome (CASE 3-1).[6]

In one study involving 40 subjects, patients described 255 nonheadache symptoms in the postdrome.[13] However, several of the symptoms in this cohort were very hard to distinguish between. For example, it is not easy to know the clinical criteria used to distinguish between a subdued mood, depressed mood, bad mood, and introverted mood. Quintela and colleagues[15] strategically addressed this by assigning postdrome symptoms into four main groups: neuropsychiatric, sensory, gastrointestinal (digestive as per the authors of the study), and general symptoms. This gave clarity in classifying and assessing the symptoms. Future research may tell us if it is possible to localize some of these symptoms.

POTENTIAL KEY ANATOMIC STRUCTURES

The key structures involved in the perception of headache include the large intracranial vessels and dura mater[18]; the peripheral terminals of the trigeminovascular system that innervate these structures; the caudal portion of

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Relative Frequency of Postdromal Migraine Symptoms Reported at Baseline and Recorded Prospectively in an Electronic Diary Study[a]

TABLE 3-1

Nonheadache Feature	Percent of Patients Who Recalled Each Postdromal Symptom at Baseline (n = 83)	Percent of Attacks in Which Postdromal Symptoms Were Prospectively Reported During the Electronic Diary Study (n = 425)
Tired/weary	75%	88%
Difficulty with concentration	67%	56%
Stiff neck	16%	42%
Light sensitive	13%	36%
Intolerant/irritable	22%	29%
Dizziness	10%	19%
Yawning	15%	14%
Pale face	18%	21%
Noise sensitive	12%	32%
Hunger/food craving	15%	15%
Thirst	13%	32%
Emotional	13%	24%
Difficulty with thoughts	15%	33%
Constipation	4%	7%
Frequent urination	7%	21%
Nausea/vomiting	6%	15%
Difficulty reading or writing	10%	17%
Difficulty with speech	5%	9%
Other	32%	44%

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the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex); and the pain modulatory systems in the brain that receive input from trigeminal nociceptors.[16]

The first direct clinical evidence that showed involvement of brainstem structures in migraine generation was reported by Raskin and colleagues.[19] Patients (n = 175) underwent implantation of an electric pain stimulation system that was developed for controlling pain (usually intractable low backache). The electrodes were implanted in the somatosensory area of the thalamus or the periaqueductal gray region. Of these 175 patients, 15 who had not typically previously experienced headaches developed headache with what the authors described as "florid migrainous" features. Of these subjects, 13 had electrodes inserted into the periaqueductal gray region, and the headaches persisted following explantation of the electrodes. Subsequently, activation of the ventrolateral periaqueductal gray was shown by positron emission tomography (PET) during a spontaneous migraine attack.[17] Activation of the periaqueductal gray has also been shown using PET imaging in nitroglycerin-triggered migraine attacks.[20]

The dysfunction of neuromodulatory structures in the brainstem is thought to be a core component in the pathophysiology of migraine.[16] As the major noradrenergic nucleus, the locus coeruleus has a vital role in the regulation of cortical function and is known to modulate responses to afferent traffic.[21] This area has been shown to be activated during acute migraine attacks in PET studies[17,22] and could play a dominant role in the postdrome.

Evidence supports the view that the brain in patients with migraine is hyperexcitable to a variety of stimuli. This suggests that neuronal depolarization, which is the presumed initiating event in migraine aura and possibly in migraine without aura, is more easily triggered.[23–25] Because of the hyperexcitability, a lower level of transcranial magnetic stimulation of the occipital cortex is required to produce visual phosphenes in patients with migraine compared with patients without migraine.[26–28] Genetic mutations can increase neuronal excitability through a variety of mechanisms.[29–31] The cortical excitability may indicate the chronicity process in the disease.[32]

TABLE 3-2 **Migraine Postdrome Symptoms**[a]

Category	Symptoms
Neuropsychiatric symptoms	Mood changes, concentration trouble, sleep disturbance (insomnia and hypersomnolence)
Sensory symptoms	Head soreness, photophobia, phonophobia, speech disturbance
Gastrointestinal symptoms	Nausea, flatulence, constipation, vomiting, anorexia, food craving, abdominal pain, diarrhea
General systemic symptoms	Tiredness, urination, fluid retention

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Previous functional imaging studies have shown activations of the posterolateral hypothalamus, midbrain tegmental area, periaqueductal gray, dorsal pons, and various cortical areas such as the frontal, temporal, and occipital regions in the premonitory phase.[20] The symptoms that patients report are broadly similar in the premonitory and postdromal phases.[5,33] Based on the similarity of symptoms, one can hypothesize that a shared neural network may be active in the postdrome and premonitory phases.

Another potential neuroanatomic explanation for postdrome symptoms is diffuse cortical and subcortical involvement given the multitude of symptoms patients describe in the postdrome.[5,6,14,15,34] After evaluating postdrome symptoms within his cohort of subjects, Blau[13] suggested involvement of the whole brain in the pathophysiology of the postdrome but especially the frontal lobes and the hypothalamus as vital structures in this phase. Interestingly, widespread reduction in brain blood flow in the postdrome has been demonstrated in a functional imaging study using arterial spin labeling MRI, which can explain the clinical presentation very well. This study suggests involvement of the various cortical and brainstem areas such as the superior frontal gyrus, medial frontal gyrus, middle frontal gyrus, putamen, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, posterior

CASE 3-1

A 33-year-old woman presented for a consultation regarding her history of episodic migraine. She described getting between one to two headache episodes per month. Her throbbing headaches would respond well to oral sumatriptan, which had been prescribed by her primary care provider. Following the cessation of her throbbing headache, she reported a mixed feeling of relief and mental exhaustion. She felt like her head was "sore and bruised." She also reported tiredness and concentration difficulty. These nonheadache symptoms could last several days and would limit her return to normal function.

The patient was a neurosciences PhD student, and the symptoms were having a profound impact on her ability to write her PhD thesis. Not knowing what these symptoms represented and not being given a diagnosis for these symptoms was making her more anxious. The symptoms were profoundly affecting her quality of life. She had seen several neurologists and had undergone several investigations including several normal brain MRIs. Her neurologic examination was normal.

COMMENT

This case illustrates some of the clinical symptoms patients experience in the postdrome of migraine. This patient had seen various providers who had not given her an explanation for her symptoms, and she ended up having extensive investigations. She was seen eventually in a tertiary headache clinic at the time of her current presentation, following a referral by her primary care provider, and was given the diagnosis of migraine postdrome. Once she was reassured that her symptoms were related to a migraine postdrome, she could better focus on her PhD studies.

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KEY POINTS

- Based on the similarity of symptoms, one can hypothesize that a shared neural network may be active in the postdrome and premonitory phases of migraine.
- Not recognizing the typical postdrome symptoms may lead to patients undergoing unnecessary investigations and hospital visits, and recognition and reassurance regarding postdrome symptoms may alleviate the patient's concerns.
- The role of brainstem noradrenergic mechanisms and cortical spreading depression in the postdrome pathophysiology needs to be explored further. Functional neuroimaging may hold the key.
- The lack of literature surrounding the postdrome phase of migraine and its significant burden for patients in terms of returning to normal function indicate a vital need to understand it better.

cingulate, anterior cingulate, thalamus, hypothalamus, and midbrain in the neurobiology of the postdrome.[35]

PATHOPHYSIOLOGIC MECHANISMS OF THE POSTDROME

The locus coeruleus is a brainstem noradrenergic nucleus located in the dorsal pontine tegmentum. This nucleus provides the major source of norepinephrine to the cerebrum, brainstem, cerebellum, and spinal cord. The existence of reciprocal circuits between this nucleus, the neocortex, diencephalon, limbic system, and spinal cord emphasize its widespread impact within the neuraxis.[36] The locus coeruleus noradrenergic system is one of the first systems that becomes involved during a stressful event. It is involved in a broad range of physiologic and psychological events such as pain processing, behavioral modification, and stress reactivity.[37] Functional imaging studies have shown activation of the dorsal pons in premonitory and migraine headache phases.[17,20,22,38] This activation might include the locus coeruleus,[20] leading to widespread vasoconstriction mediated by an α_2-adrenoceptor mechanism.[39–41] The near global reductions in regional cerebral blood flow seen in the postdrome[35] can potentially be explained by widespread vasoconstriction via α_2-adrenoceptor mechanism through activation of brainstem nuclei. This may serve as a pain modulatory mechanism but, as a consequence, may lead to the protean postdromal symptoms that result from a near global reduction in regional cerebral blood flow.

Another mechanism that can potentially explain the reductions in regional cerebral blood flow in the postdrome is the phenomenon of cortical spreading depression. This bioelectric phenomenon was first described by Leão,[42,43] who demonstrated a wave of spreading suppression of spontaneous EEG activity when electrically stimulating the rabbit cortex. Cortical spreading depression usually silences spontaneous and evoked electric activity for 5 to 15 minutes. However, in certain pathophysiologic states, such as hypoglycemia, hypoxia, and ischemia, cortical spreading depression can occur spontaneously and can be prolonged in nature.[44] Increased susceptibility to cortical spreading depression occurs when astroglial function is hampered.[45] Electrophysiologic studies demonstrate that in patients with migraine a cortical and possibly subcortical dysfunction may explain increased susceptibility to cortical spreading depression.[46,47] Cortical spreading depression is preceded by a fast network of oscillations, suggesting brief hyperexcitability.[43] This is followed by complete suppression of neuronal activity, lasting several minutes, followed by complete recovery.[42] Hadjikhani and colleagues[27] used functional imaging to support cortical spreading depression as the generator of migraine aura. Persistent hypoperfusion following cortical spreading depression has been demonstrated and hence corroborates the notion that the perfusion changes of migraine may be pathophysiologically related to spreading depression.[48]

Functional imaging, including functional MRI (fMRI) and PET, has been increasingly used in migraine and other pain states and has alluded to areas of brain activation that are thought to be key structures in the initiation and propagation of the headache and pain states.[20,49,50] Functional imaging has also helped improve our understanding of the nonpain phases of migraine including the postdrome.[35,51] The paucity of literature surrounding the postdrome phase

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and its significant burden for patients in terms of returning to normal function indicate a vital need to understand it better.

CONCLUSION

The postdrome prolongs the symptoms experienced by patients following migraine headache attacks and is important to clinically recognize. Unraveling what happens to neural activity during this phase may help us improve our understanding of migraine pathophysiology and may also potentially lead to new therapeutic targets and interventions. Functional neuroimaging studies hold the key to unlocking the neural activity in the postdrome phase and identifying therapeutic targets.

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DISCLOSURE

Continued from page 1023

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