Prodromes and the early phase of the migraine attack: therapeutic relevance

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Summary

A migraine attack is a multiphasic event. In some patients the initial phase of the attack is characterized by the presence of “prodromes” or “premonitory symptoms” which are not recognized by the patient as part of the attack. Premonitory symptoms are defined as “symptoms preceding and forewarning of a migraine attack by 2-48 hours, occurring before the aura in migraine with aura and before the onset of pain in migraine without aura”. Migraine premonitory symptoms should be differentiated from aura and symptoms of premenstrual syndrome. This differentiation, which is crucial to correct diagnosis, is based on two principal aspects, namely, the timing of these premonitory symptoms prior to the headache pain and their clinical characteristics. The neurotransmitters dopamine and serotonin are possibly involved in the development of premonitory symptoms, as demonstrated by experimental models and by the efficacy of migraine aborting and preventive treatments. Accurate recording of premonitory symptoms may contribute to efforts to design the best therapeutic approach in migraine patients.

KEY WORDS: experimental model, migraine pathogenesis, premonitory symptoms, treatment.

Assessing the presence of premonitory symptoms

“Probably the most neglected aspect of migraine, both by clinicians and by researchers, was the occurrence, in a substantial fraction of migraineurs, of early, subtle premonitory phenomena. This part of the migraine attack, which is sometimes better known by patients than by their doctors, deserves much more attention” (1). A migraine attack is a multiphasic event. In some patients the initial phase of the attack is characterized by

the presence of “prodromes” or "premonitory symptoms (PS)”, which are not recognized by the patient as part of the attack. Prodromes as well as "postdromes", or resolution symptoms, are not included in the IHS classification as major criteria. In the past, prodromes and "aura" have often been defined, indifferently, as the premonitory phase of a migraine attack. However, the distinction between aura and prodromes has been clarified over the years – the former being defined as a focal neurological deficit (visual or sensory, etc.) –, therefore allowing the diagnosis of migraine with aura.

In the first edition of the IHS classification (2) (Introduction to diagnostic criteria for migraine without aura), the distinction between aura and prodromes has been clarified over the years – the former being defined as a focal neurological deficit (visual or sensory, etc.) –, therefore allowing the diagnosis of migraine with aura. The authors specify that “some patients can experience a “premonitory phase” occurring hours or days before the headache. Premonitory symptoms include hyperactivity, hypoactivity, depression, craving for particular food, repetitive yawning and other less typical symptoms reported by some patients”. The aim of this definition was to better differentiate PS from aura. Fifteen years after its publication, however, it had become clear that it was inadequate. Hence, the revised IHS classification (ICHD-II, 2004) (3) provided further notes to better clarify the distinction. In the "definition of terms" section, PS are defined as “symptoms preceding and forewarning of a migraine attack by 2-48 hours, occurring before the aura in migraine with aura and before the onset of pain in migraine without aura”. Among PS, the most common are: fatigue, elation, depression, unusual hunger, and craving for certain foods. Osmophobia, one of the accompanying symptoms or PS of migraine attacks, has also been included as an adjuvant – although not mandatory – criterion in “A1. Migraine”, the part of the appendix that codes additional clinical features for this headache type. According to the IHS guidelines, PS are clearly distinct from the focal neurological signs of the aura phase. The revised classification rejects the terms “prodrome” and “warning symptoms” and strongly recommends that those symptoms preceding the migraine (with or without aura) pain by up to 48 hours, and including various combinations of “fatigue, difficulty in concentrating, neck stiffness, sensitivity to light or sound, blurred vision, yawning and pallor” should be defined as PS.

The first detailed description of migrainous PS was given by Blau in 1980 (4). Changes in mood, energy level, and appetite were reported, as were food cravings, nausea, altered sense of hearing or of smell, swelling or fluid retention, excessive yawning, muscle pain or tenderness, irritability, confusion, extreme sleepiness, and impaired speech or impaired memory.

The distinction between aura and migraine PS is based on two main aspects, namely the timing of the occurrence of these symptoms prior to the headache pain, and their clinical characteristics. Both PS and aura develop
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gradually. However, by definition, an aura does not last more than 60 minutes, it is always related to focal cortical activity, and cortical spreading depression might represent its underlying pathophysiological mechanism (5). On the contrary, PS are more likely to derive from different areas of the central nervous system (CNS) and they are characterized by general/behavioural features. Premonitory symptoms have a longer duration and they may not resolve prior to pain onset. Some of them may well be part of the symptoms that accompany the pain phase: PS can precede attacks of pure menstrual migraine without aura and/or menstrually-related migraine without aura, two new entities included in the appendix of the revised IHS classification and coded, respectively, as A 1.1.1 and A 1.1.2. These two types are characterized by a wide range of psychological and physical symptoms, often grouped under the definition premenstrual syndrome (PMS), usually beginning 2-3 days before menses and including lower abdominal pain, breast tenderness, asthenia, depression and irritability as the main symptoms (6). To accurately distinguish PS from PMS, detailed recording of clinical features by the patient is necessary. A prospective clinical diary of migraine attacks related and not related to menses is useful for this purpose. To date, no clinical studies have been performed to address this issue. Recently, Granella et al. (7), without looking specifically for PS, evaluated the differences emerging between migraine attacks related and unrelated to menses in a clinical sample.

The timing of occurrence of PMS symptoms largely coincides with that of true PS of migraine without aura not related to menses. Furthermore, drugs such as magnesium, bromocriptine and lisuride (dopaminergic agonists) are effective on PMS and related headache as well as on PS in migraine not related to menses (8). The prevalence of PS among migraineurs, as reported in studies performed before and after publication of the first edition of the IHS classification, ranges from 7% to 88% (9).

Recently, a Japanese epidemiological study showed that the most frequent PS in headache patients were fatigue and loss of vigour and a higher prevalence of PS was found in migraine patients (in particular, migraine with aura patients) compared to tension-type headache patients, particularly loss of vigour (10).

Migraine premonitory symptoms: pathogenesis and clinical experimental models

The timing of PS suggests that CNS changes start up to three days before the headache; this suggestion is supported by evidence of electrophysiological changes occurring within the 24 hours before the headache. Many studies favour an increasing abnormality of cortical excitability interictally reflecting a higher susceptibility of the migrainous brain to precipitating factors (11). Also, the quality of PS suggests a major involvement of dopaminergic and serotonergic systems in their pathogenetic mechanisms. Improved knowledge of the neurochemical systems involved in the early phase of a migraine attack could further efforts to define the correct treatment strategy for PS. The most common PS reported in clinical studies are: yawning, sleepiness and dysphoria. These symptoms are probably related to dopamine (DA) involvement since several studies have demonstrated the existence of a central hypersensitivity to dopaminergic stimulation in migraineurs (12,13). There is an increased sensitivity to apomorphine in migraine patients and yawning can be elicited by relatively low doses of D2 receptor agonists in these patients, an effect that cannot be blocked by peripheral D2 antagonists such as domperidone (13). High doses of dopaminergic agonists induce hyperactivity and irritability in both human and animal models. The above findings are all consistent with the hypothesis of an activation of dopaminergic neurotransmission in migraine disorders (12).

Furthermore, the DA antagonist domperidone may prevent an attack when given during the prodromal phase of migraine (14-16), although the drug penetrates the blood-brain barrier poorly and its effect seems to indicate a peripheral D1 receptor action. Other experimental data suggest that symptoms occurring before migraine pain are probably related to an activation of peripheral DA receptors. Taken together, these observations suggest that dopaminergic mechanisms may play a role in the premonitory phase of a migraine attack and support the hypothesis that a chronic decrease of DA synthesis and release could provoke a post-synaptic DA receptor hypersensitivity, both in central and peripheral pathway receptors. Supporting this hypothesis, other experimental data, such as the measurement of DA levels during menses in female migraineurs (based on the demonstration that falling oestrogen levels produce DA receptor hypersensitivity) or during migraine attack (17), and the measurement of tyrosine and 3,4-dihydroxyphenylacetic acid (DOPAC) levels in cerebrospinal fluid during the attack (18), support the notion of a central dopaminergic involvement. Dopamine does not seem to be directly involved in inducing migraine attacks, as demonstrated in a clinical study (13) on 35 migraine patients who received increasing dosages of apomorphine (up to 10 mg/kg s.c.), ruling out the hypothesis of DA as a "migraine unmasker". Symptoms associated with migraine attacks, such as yawning, drowsiness, dizziness, vomiting, nausea and sweating induced by apomorphine, did not resemble those symptoms accompanying or preceding spontaneous migraine attacks. Pre-treatment with domperidone significantly reduced the incidence of nausea, vomiting and dizziness, but not yawning and drowsiness. Therefore, the test is not useful as a clinical experimental model of the full-blown migraine attack. Interestingly, apomorphine-induced vasodilatation does not provoke pain, thus ruling out vascular events as primary mechanisms in migraine attack pathophysiology. Conversely, yawning, combining the highest frequency in the premonitory phase with the best attack predictability ratio, was recently found to be the most reliable clinical marker for future studies on PS (19). Also, spontaneous-like yawning and other common PS may be specifically and consistently reproduced using NO donors in migraine patients (20).

Gene studies reported an increased density of DA, D3, D4 (21) and D5 (22,23) receptors in peripheral blood lymphocytes (PBD) from migraine patients compared with controls. The increased density of these DA receptors in PBD may reflect the dopaminergic hypersensitivity observed in migraine patients, supporting the hypo-
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The presence of mood disorders, including depression, irritability and fatigue, among PS suggests the involvement in NO donor-induced migraine attacks (28). The presence of mood disorders, including depression, irritability and fatigue, among PS suggests the involvement in NO donor-induced migraine attacks (28).

Indirect support for 5-HT involvement in migraine PS is provided by the observation that 5-HT reuptake inhibitors are the treatment of choice for PMS, namely for the dysmenorrheic disorders that commonly precede a menstrual migraine attack (30). The NO-donor glyceryl trinitrate (GNT), given at the dose of 0.5 mg/kg/min, was used to induce migraine attacks to explore their clinical features (20). A study conducted by Jenzer and Bremgartner (34) in a clinical trial of migraine showed that 72% of migraine attacks were associated with PS that had occurred within the 72 hours prior to the headache (19). The high prevalence of PS allowed the authors to conclude that PS should be taken into consideration when scoring a patient’s impairment of quality of life due to migraine disability. Only a few non-randomized trials have been performed to assess the efficacy of molecules in migraine PS. The available trials concern DA agonists, antagonists, and natriuretic peptides (26). In contrast with these data, PET studies have failed to demonstrate hypothalamic activation in NO donor-induced migraine attacks (28).

The diary correlation was 100% between prodrome and predictable PS followed by headache. The presence of PS may, therefore, eventually help to establish whether DA has a role in PS occurrence, and the treatment of PS or aura with dihydroergotamine nasal spray was effective in 36% of migraine patients compared to 26% following administration of placebo (33), while a larger number of patients (86%) with no pain or with pain relief after domperidone administration was reported by Jenzer and Bremgartner (34) in a clinical study of 143 migraine patients.

No clinical trials in which DA agonists/antagonists (such as flunixin, pizotifen, bromocriptine, lisuride, dihydroergocriptine, apomorphine) are used as preventive drugs have been designed to explore effects on PS. The treatment of PS or aura with dihydroergotamine nasal spray was effective in 36% of migraine patients compared to 26% following administration of placebo (33), while a larger number of patients (86%) with no pain or with pain relief after domperidone administration was reported by Jenzer and Bremgartner (34) in a clinical study of 143 migraine patients.

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Domperidone (8 mg i.v.), a peripheral DA antagonist, was effective in aborting nausea and vomiting during migraine attacks in 18 out of 23 patients (32). When domperidone was given during PS, it showed a dose-related efficacy to prevent imminent attacks (from 30% with 20 mg to 63% with 40 mg) (16). Compared to placebo, 30 mg of domperidone is useful to prevent imminent attacks of classic migraine (pre-IHS classification) in 66% of patients compared to 5% of patients receiving placebo, when administered hours before the predicted onset of headache (14,15).

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onset of migraine. The drug was effective in 60% of cases in preventing headache when administered during PS. In 69% of patients the effect of naratriptan was consistent across all treated PS. Headache occurred in spite of treatment during PS. However, the pain was less severe than that typically experienced in the past and 44% of the ensuing headaches were reported as mild. Naratriptan was less effective on pain when taken too close to its onset (i.e., less than 2 hours beforehand).

How these medications may act during PS to prevent or modify subsequent headache is not fully understood. Placebo-controlled, randomized trials, should be conducted to assess whether treatment during the premonitory phase would prevent migraine. Treatment during PS will revolve around an accurate assessment of a prodromal threshold (“point of no return” or “inevitability”) that would reliably predict headache.

In conclusion, in order to improve diagnostic and treatment criteria we need clinical trials based upon: a) accurate recording of PS and of their timing, matching interview/diary data with neurophysiological data; b) accurate recording of pre-menstrual symptoms (especially where menstrually-related migraine is not present); c) appropriate choice of drug on the basis both of the drug’s half-life and of PS timing; d) adequate early treatment (acute or short prophylaxis) for any migraine attack in the same patient.

References

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