Prodromes and predictors of migraine attack

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Summary

Premonitory symptoms of migraine include a wide and heterogeneous collection of cognitive, psychic and physical changes preceding and forewarning of an attack by a few hours to 2-3 days. To date, premonitory symptoms have received little attention in the literature, being treated more as a curiosity than as a primary feature of migraine. This paper provides an extensive critical review of this neglected area of migraine research in the light of the recent advances in our understanding of the pathogenetic mechanisms of migraine. Epidemiological and clinical studies that have investigated the premonitory symptoms of migraine lack scientific rigour, producing conflicting results, whilst genetic and pathophysiological investigations are still in their very early stages. There is evidence supporting the idea that premonitory symptoms could be used as a phenotypical marker to identify subgroups of migraineurs which could show correlations with specific clinical expressions of the disease, genotypes, or responses to treatments. Future studies are needed to clarify the clinical, pathophysiological and therapeutic significance of premonitory symptoms.

KEY WORDS: epidemiology, migraine, pathogenesis, premonitory symptoms.

Introduction

Although it has been recognized for centuries that non-headache symptoms may warn of an impending migraine attack (1,2), the first detailed studies of this phenomenon did not appear until the 1980s, when the “clinical-descriptive approach” to migraine research, culminating in the publication of the first edition of the International Headache Society (IHS) diagnostic criteria (3), was at its height. The first to deal with this topic was Blau, who coined the term “complete migraine” in reference to attacks preceded by changes in mood, alertness, appetite and fluid balance (4). Lance described these same clinical phenomena as “premonitory migraine” in 1982 (5). Over the next few years Waelkens et al. extended these preliminary observations, referring to “warning symptoms” (6,7) and performing the first feasibility studies of a “last moment” preventive therapy of migraine, administering a dopamine agonist (domperidone) during the early “warning symptoms” (8,9). The great merit of these early studies on premonitory symptoms (PS) was that they recognized migraine as a complex, primary neurological process of which headache is just one phenotypical characteristic and the sole therapeutic target. In spite of this, PS continued to receive little attention. Indeed, it was not until 2003 that there appeared the first prospective study of non-headache PS of migraine, which also assessed their predictive value (10). This was followed in 2004 by the first demonstration that PS can be reproduced in an experimental human model of migraine (11). However, the terminology regarding PS is confusing, with many authors still using ambiguous terms such as prodromes, warning symptoms, precephalgic and pericephalgic aura (12).

Thus, to date, there has been no rigorous scientific study of PS, which are treated more as a curiosity than as a primary feature of migraine. The time is thus ripe to review this neglected area of migraine research in the light of the recent advances in our understanding of the pathogenetic mechanisms of migraine.

How common are premonitory symptoms?

Studies investigating the prevalence of PS of migraine pose a number of methodological problems. The main obstacle is the absence of a strict, generally accepted, operational clinical definition of PS. In the first edition of the IHS Classification and Diagnostic Criteria for Headache Disorders (ICHD-I), PS are defined as those symptoms occurring “hours to a day or two before a migraine attack (with or without aura)” (3). They usually consist of hyperactivity, depression, craving for special foods, repetitive yawning and similar atypical symptoms. The aim of the IHS Committee was to establish a clear distinction between aura and premonitory symptoms, and to introduce standardized terminology, excluding ambiguous terms such as migraine “prodromes” or “warning symptoms”. Unfortunately, this definition, failing to furnish criteria either on the temporal profile of PS or on their ability to predict an impending migraine attack, proved inadequate for epidemiological studies.
Furthermore, due to the low number of high-quality studies on this subject, these limitations are only partially overcome in the recently published 2nd edition of the IHS classification (ICHD-II) (12). 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 the common PS are fatigue, elation, depression, unusual hunger, craving for certain foods”.

In the absence of biological markers, the above may serve as a transitory standard for a phenomenological definition of PS; prospective field-testing, clinical experience and increased knowledge of migraine mechanisms will determine how well it works and identify new ways of improving it.

In addition to the lack of a common case definition, there are other methodological factors that affect the accuracy of prevalence estimations of PS. Most of the available studies were conducted either before the publication of the IHS criteria for migraine, or in clinical populations (which could present a selection bias). Another major problem that may affect the reliability of data on the frequency of PS is the procedure used to investigate their presence. Estimates based on data collected by direct questioning may differ from estimates based on the general eliciting of responses. In fact, PS are often so vague that patients will identify them only when specifically questioned by the physician. In many cases, family members were often able to report PS of which the patient himself was unaware (7). It is thus difficult to reflect this clinical phenomenon in a questionnaire or an interview. For instance, if patients are simply asked whether they are able to predict a migraine attack or whether they experience symptoms before the painful phase, they are unable to distinguish between precipitating factors, or their clinical correlates, and PS. There is thus a risk of overestimating the prevalence of PS in epidemiological studies. Most of the studies investigating PS prevalence did not include adequate control populations and did not consider the role of potential confounding factors, such as psychiatric comorbidity and premenstrual syndrome. Finally, the retrospective data collection strategy is flawed by the occurrence of recall bias.

Therefore, it is not surprising that, in the different series reported to date, the prevalence of PS has ranged greatly, from 7 to 85% (4,6,7,13-20). Even when considering only post-IHS diagnostic criteria, population-based studies, very marked differences still emerge. Indeed, only about 7-16% of subjects with migraine studied in two Danish studies (15,16), versus as many as 61-70% of those studied in a Swedish (17) and in an American study (19), reported the occurrence of PS.

No significant difference was found between gender and migraine subtypes in two studies (15,16), whereas no study has investigated the potential influence of other socio-demographic and clinical variables on prevalence rates for PS.

To summarize, studies of PS prevalence in migraineurs lack scientific rigour and produce conflicting results. In concrete terms, it might be said that when accurately investigated (general population sample, physician-conducted interview, precise case definition), PS are relatively uncommon.

What clinical features are present during the premonitory phase of a migraine attack? What is their relative frequency and their relationship with the headache phase?

The PS of a migraine attack include a wide and heterogeneous collection of clinical manifestations: psychic, cognitive and physical changes (Table I). Many PS are vague, poorly stereotyped and slowly developing, making their clinical recognition and differentiation difficult. Each patient may experience more than one PS, the average number of reported symptoms ranging from three to twelve (4,7). No study has looked for preferential associations among the different symptoms. There is general agreement that the intra-individual consistency of PS is high, as is their inter-individual variability (6,7,13,18). Data on the relative frequency of PS are conflicting and inconclusive, due to the methodological difficulties discussed earlier. Early studies on PS emphasized mood and behavioural changes as the most typical and frequent non-headache symptoms predicting an impending migraine attack (4,6,7,21). This point of view, despite being based on few studies lacking scientific rigour, was reflected in the IHS definitions of PS (3,12) and inspired subsequent research into PS, leading to an overestimation of symptoms like elation, hyperactivity and depressive feelings, whereas other symptoms have probably been overlooked (10). It is worth noting that, in the only available prospective study, the role of mood swings as a PS was drastically downgraded (10). On the contrary, tiredness, fatigue and drowsiness, as well as irritability, have been reported among the most common PS in both prospective and retrospective studies (6,7,10,15,20,21), regardless of the data collection strategy used. Nevertheless, the high prevalence of tiredness might reflect the high background prevalence of this symptom in migraineurs as well as in the general population (10).

The most commonly reported neurological complaints were intellectual disturbances (7,11). Interestingly, the majority of symptoms labelled as neurological complaints (sensory intolerance, nausea, vomiting, neck stiffness, head pain, allodynic symptoms) are known to accompany the full-blown migraine attack and continue through the postdrome phase (10). Some of them are key elements of the IHS definition of acute migraine (3,12).

Waelkens defined most of them as “evolutive warning symptoms” because they appear between a few minutes and a few hours before the onset of the headache, they soon become troublesome, they rapidly increase in intensity, and they inevitably lead to the typical migraine headache (6). This distinction between evolutive PS and non-evolutive PS (the latter being symptoms that precede the attack by one or two days, that are neither striking nor troublesome, and that show no tendency to worsen as the attack approaches), albeit substantiated by therapeutic trials with dopamine agonists (8,9), remains largely speculative. In fact, it derives from retrospective studies that almost exclusively investigate selected populations of migraineurs with aura in which no clear distinction is drawn between aura and PS (6). In addition, it has been demonstrated that symptoms like nausea or light and sound intolerance may be experienced up to two days before the attack and, when prospectively evaluated, the predictive value of Waelkens’ evolutive PS
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Table I - Clinical classification and relative frequency of premonitory symptoms and their relationship with the headache phase.

<table>
<thead>
<tr>
<th>Premonitory symptoms</th>
<th>Frequency</th>
<th>Headache phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood and behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness, behavioural sluggishness, sleepiness, fatigue</td>
<td>Very common</td>
<td>+</td>
</tr>
<tr>
<td>Intolerance, irritability, hostility</td>
<td>Common</td>
<td>+</td>
</tr>
<tr>
<td>Emotionality</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Restlessness, hyperactivity</td>
<td>Uncommon*</td>
<td>–</td>
</tr>
<tr>
<td>Depression, apathy, passivity</td>
<td>Uncommon*</td>
<td></td>
</tr>
<tr>
<td><strong>Neurological complaints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory hypersensitivity (including pain)</td>
<td>Common</td>
<td>++</td>
</tr>
<tr>
<td>Head and neck pain or discomfort (tension-type quality)</td>
<td>Uncommon</td>
<td>++</td>
</tr>
<tr>
<td>Cephalic and extracephalic allodynia (sensitivity to touch, cutaneous/muscle tenderness, etc.)</td>
<td>Very common</td>
<td>++</td>
</tr>
<tr>
<td>Photophobia</td>
<td>Common</td>
<td>++</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>Uncommon*</td>
<td></td>
</tr>
<tr>
<td>Hyperosmia, osmophobia, smell and taste distortion</td>
<td>Uncommon*</td>
<td></td>
</tr>
<tr>
<td>Kinesiophobia</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Hyperesthesia, Haptophobia</td>
<td>Uncommon*</td>
<td></td>
</tr>
<tr>
<td>Ear symptoms, tinnitus</td>
<td>Uncommon</td>
<td>+</td>
</tr>
<tr>
<td>Throbbing blood vessels in the head</td>
<td>Uncommon*</td>
<td></td>
</tr>
<tr>
<td><strong>Impaired language and cognition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor concentration</td>
<td>Very common</td>
<td>++</td>
</tr>
<tr>
<td>Slow thinking</td>
<td>Common</td>
<td>++</td>
</tr>
<tr>
<td>Difficulty with reading or writing</td>
<td>Common</td>
<td>++</td>
</tr>
<tr>
<td>Difficulty with speech, dysphasia</td>
<td>Uncommon</td>
<td>++</td>
</tr>
<tr>
<td><strong>Dysmodulation of pain-related motor and autonomic, brainstem integrated reflexes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>Very common</td>
<td>+</td>
</tr>
<tr>
<td>Nausea/vomiting, slow digestion</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Accommodation disturbances, blurred vision</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Conjunctival injection, lacrimation, rhinorrhea, nasal congestion, ptosis</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Jaw tightness</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Sialorrhoea, dry mouth</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Balance, coordination and motor symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Common</td>
<td>+</td>
</tr>
<tr>
<td>Clumsiness, tendency to fall</td>
<td>Uncommon</td>
<td></td>
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<tr>
<td>Tremor</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yawning</td>
<td>Common</td>
<td>–</td>
</tr>
<tr>
<td><strong>General complaints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic disturbances (dysmodulation of supratentorial integrated coordinated autonomic function)</td>
<td>Common</td>
<td>+</td>
</tr>
<tr>
<td>Thirst</td>
<td>Uncommon*</td>
<td>–</td>
</tr>
<tr>
<td>Increased appetite, craving for certain foods</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Frequent urination</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Constipation, abdominal bloating, diarrhoea</td>
<td>Uncommon</td>
<td>=</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized weakness or muscular ache</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td><strong>Cutaneous, vascular and other signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema (including diffuse or localized skin reddening)</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Dermatographism/urticaria</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Seborrhoea</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Pale face, lustreless eyes, ring around the eyes</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Shivering, cold feelings, flu</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Swollen veins (temple, face, extracephalic areas)</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

* Symptoms rated as common or very common in retrospective series; ? undetermined; = equally reported in the headache phase and the premonitory phase; + more common in the headache phase than in the premonitory phase; ++ much more common in the headache phase than in the premonitory phase; – less common in the headache phase than in the premonitory phase.
was not found to be higher than that of non-evolutive PS (10).

Most of the PS classified as general complaints possibly represent the clinical counterparts of hypothalamic dysfunctions (6-9,18,20). As for mood swings, their role as a PS has been probably overestimated (10). On the contrary, other general complaints have been investigated only rarely in studies on PS, being regarded more as a curiosity than as an issue for scientific consideration (22).

With few exceptions (yawning, hunger and food craving, increased energy), the majority of PS become more common in the headache phase suggesting that headache is only one feature of the migraine attack (10). From a pathophysiological perspective, the main findings regarding the clinical features of PS may be summarized as follows: a) PS are heterogeneous and often mutually unrelated; b) the intra-individual variability of PS is lower than their inter-individual variability; c) the majority of PS may be explained as the clinical expression of central nervous system changes starting up to three days before the headache and persisting through the painful phase and into the postdrome (in other words, migraine is a complex neurological process in which headache is just one of the potential symptoms of the attack); d) many neurological symptoms experienced during the premonitory phase develop into symptoms typically associated with migraine headache, that is to say, headache evolves from the premonitory phase over a variable period of time.

What is the predictive value of premonitory symptoms?

The predictive value of PS was recently investigated by Giffin et al. (10) in a multicentre, prospective study using a hand-held electronic diary system. The authors included only subjects who reported non-headache symptoms (in at least two out of three attacks) that they believed predicted headache. When present, PS were followed by a migraine attack within 72 hours on 72% of occasions and in 82% of patients PS were followed by a migraine attack more than 50% of the time. Patients were asked to predict the probability of an attack each time they experienced PS. The results showed that the more certain patients were of their prediction, the greater was their probability of having an attack. It is noteworthy that patients who rated their level of functioning as poor or very poor in the premonitory phase were more likely to predict migraine than those functioning well or normally. These data indicate that PS may contribute to migraine-related disability. Symptoms varied in their ability to predict a migraine attack (10). The highest predictability ratio (percentage of sessions with PS followed by correct prediction of migraine headache/percentage of sessions with PS followed by incorrect prediction of migraine headache) were obtained for difficulty with speech (4.9), difficulty with reading or writing (3.49), yawning (2.07), increased emotionality (2.04), photophobia (1.83), and slow thinking (1.74). The most common symptoms (tiredness, difficulty concentrating, and stiff neck) were less commonly followed by migraine, suggesting that these symptoms may be either incorrect predictors of migraine or, alternatively, the beginning of abortive migraine attacks. Yawning was the symptom that, by combining the highest frequency in the premonitory phase with the best predictability ratio, emerged as the most reliable clinical marker for future studies on PS.

A positive sensitivity of PS (PS preceding migraine attack in more than 2/3 of events) in 46% of 460 migraine patients attending an outpatient clinic has been recently reported (23); in this subgroup a positive predictive value (defined as PS followed by an attack in more than 2/3 of attacks) was observed in 68% or more of the subjects, which is consistent with previous findings. Details about the methods used in this study are not yet available.

Recently, it has been demonstrated that in migraine patients spontaneously experiencing PS, such as yawning, tiredness, and neck stiffness, these symptoms may be specifically and consistently reproduced in an experimental model of glyceryl trinitrate (GTN)-triggered migraine (11).

Taken together, these data suggest that selected populations of migraineurs who report PS can accurately predict the full-blown migraine and that PS are heterogeneous with regard to their predictive value.

These findings also argue for a biological dysfunction underlying the premonitory phase that can be operative up to three days before headache and triggered by nitric oxide donors. The incomplete evolution of PS into a migraine attack supports the notion of an adaptive, homeostasis-restoring role for these symptoms.
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formation processing, PS and migraine pathogenesis remains undetermined. From a practical point of view, scientists engaged in the field of migraine research must take into account the duration of time that has elapsed since the last attack and consider as interictal only those phenomena occurring within the 72 hours either side of a migraine attack.

To summarize, PS that warn of an impending migraine attack may occur up to three days before the headache phase and most of them are experienced in the 48 hours preceding the attack. On this basis, the time-window used by the IHS committee to define PS (see below) allows a good, but probably incomplete representation of this phenomenon.

Can we consider premonitory symptoms as specific for migraine?

Early studies suggest that PS are specific for migraine attacks and that their presence should help in differentiating migraine from other headaches (6). More recently, PS have been reported to occur in all the primary headaches, such as tension-type headache (TTH) and cluster headache (CH), as well as in migraine.

Rasmussen et al. (15,29) reported that PS such as “low spirits, tiredness and elation” occurred with similar frequency in migraine with aura (16%), migraine without aura (12%), and TTH (9%). In three recent, retrospective, population-based studies from non-western countries, premonitory mood and behavioural complaints were reported in a significantly higher proportion of migraineurs (21%-38%) when compared with TTH (5.9%-25%) and other headache patients (7.5%) (30-32). These discrepancies in the literature may be partially explained by methodological differences in PS definition and data collection. It is noteworthy that patients identified as PS only aspecific mood and behavioural complaints, whereas more stereotyped symptoms, such as yawning or neck stiffness, whose predictive value has been confirmed in prospective series, were never reported. The finding raises the issue of a potential artifact due to methodological bias (33). In addition to epidemiological studies, the relationships of PS with subsequent headache-associated symptoms, and a higher occurrence of postdromes (20).

Can we consider patients experiencing premonitory symptoms as a distinct clinical subgroup?

Migraine is characterized by a great variability of phenotypical expressions. The clinical heterogeneity of migraine involves both the attacks and the disease and appears to be the result of complex genotype-environment interactions. Epidemiological studies on PS, though inconclusive, have revealed that PS are consistently experienced by only a limited number of migraineurs (6,10,18). This finding raises the question of whether PS could be used as phenotypical markers to identify subgroups of migraineurs in whom correlations can be sought with specific clinical expressions of the disease, genotypes, or responses to therapeutic agents.

Several authors have investigated whether there is a correlation between specific patient and attack characteristics and the presence of PS. Amery et al. (7), in a pre-IHS, retrospective study on a selected population of migraineurs with and without aura, reported a significant positive correlation between the number of reported prodromes, patient characteristics (female sex, age, duration of disease, duration of migraine attacks, presence of other headache type), and attack characteristics (number of trigger and aggravating factors, number of symptoms accompanying the headache phase). In another retrospective, post-IHS study, migraineurs without aura experiencing PS had a significantly higher positive familiarity for migraine, a lower mean age at onset and a higher number of trigger factors when compared to other patients (14).

More recently, Kelman retrospectively investigated 893 migraineurs with PS; these subjects differed from patients without PS in many clinical variables, such as a higher number of triggers, a longer duration of aura, a longer time to peak of headache, a longer maximum duration of headache, a longer time to respond to a triptan, more headache-associated symptoms, and a higher occurrence of postdromes (20).

These clinical studies suggest that patients experiencing PS might have a stronger constitutional migraine trait and present a more full-blown migraine. Unfortunately, these clinical studies present numerous imperfections. Apart from the methodological limitations discussed earlier and the lack of correction for possible confounding factors, they tend – inaccurately and inappropriately – to consider PS as a unitary phenomenon. More interestingly, an association between the dopamine D2 receptor genes and migraine without aura has been found in a subgroup of “dopaminergic migraineurs” (i.e., patients experiencing dopamine-mediated symptoms such as repetitive yawning) from Sardinian families (36). Thus, there is some evidence that some PS might represent the clinical expression of a different pathophysiological mechanism (i.e., dopaminergic hypersensitivity) or genetic background, but these observations need to be validated in further studies investigating the familial recurrence of PS and their association with migraine comorbid disorders.
What is the pathophysiology of premonitory symptoms?

The pathophysiological mechanisms underlying PS remain largely speculative due to the lack of scientific studies specifically investigating this phenomenon. Possible explanations for PS can be based both on recent advances in our understanding of migraine pathogenesis and on clinical data. Any approach to the pathophysiology of PS should be based on the following evidence:

a) PS are clinically heterogeneous suggesting the contribution of multiple pathogenetic mechanisms;
b) the headache phase is not completely distinguished from the pre-headache phase, suggesting that the two may share common pathophysiological mechanisms;
c) migraine is a chronic disorder whose basic mechanism is supposed to be a genetic susceptibility to a lower response threshold of the central nervous system to specific migraine trigger factors when compared to healthy subjects (37). The inability to handle migraine triggers results in a primary central nervous system dysfunction that secondarily activates headache pain. The basic neural biological mechanism is supposed to be an instability of the brainstem or diencephalic nuclei involved in pain and sensory modulation control (37, 38). Cortical spreading depression could be an alternative or complementary central nervous system dysfunction responsible for initiation of migraine with aura attacks (37-39);
d) the key anatomo-functional structure involved in migraine pathogenesis is the pain modulation network. This is a complex network of supraspinal structures which act, through direct and indirect facilitatory and inhibitory pathways, on spinal cord and trigeminal nociceptive afferents (40). Brainstem nuclei, such as the periacqueductal grey (PAG), are located in a strategic convergent position and represent the main output channel of this highly integrated system. Due to the reciprocal interconnections between the PAG and other supratentorial and brainstem nuclei that are part of this network, PAG activation may be the result of facilitatory influences arising from supratentorial or other brainstem centres. This functional organization explains how a migraine attack may arise, for instance, from hypothalamic or cortical activation, and how some symptoms, typically expressed during the headache phase (nausea, vomiting, photophobia, phonophobia) might be experienced before and beyond the painful phase; e) migraine pain is mediated by the activation of visceral nociceptive afferents. Visceral pain is characterized by a prompt and intense activation of motor and autonomic adaptive responses (41). The neck stiffness or discomfort experienced by some migraineurs before their migraine attacks may reflect the activation of a trigemino-cervical motor reflex aimed at reducing aggravation of pain by head movements.

From the above, a conceptual framework emerges of the pathogenetic mechanisms potentially involved in the genesis of PS (Fig. 1). In summary, some PS may indeed represent trigger factors or their clinical counterparts (Fig. 1 A). Alternatively, PS may arise from diffuse supratentorial brain activity, involving multiple neurotransmitter systems (19) (Fig. 1 B). These symptoms indicating a change in cortical excitability and arousal (imbalance of excitatory/inhibitory processes) might represent the clinical expression of the neurophysiological changes observed before the migraine attack, and suggest an increased susceptibility of the migrainous brain to precipitating factors (24, 27). Other PS may reflect changes in the hypothalamic region, or in cortico-limbic structures participating in the pain network system, that may in turn disinhibit brainstem structures, thus leading...
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to the emergence of full-blown migraine (19) (Fig. 1 C). Most of these symptoms reflect a dopaminergic hyper-sensitivity and some of them are mediated by nitric oxide pathways (11).

Finally, many PS reflect the same biological mechanism underlying the headache phase (disinhibition of brainstem nuclei regulating the amount of pain and other sensor- input activities, Fig. 1 D), with the full-blown migraine headache finally developing when a critical physiological threshold is reached (10). From a practical point of view, each mechanism could be targeted by individualized non-pharmacological and/or pharmacological approaches.

References