Premonitory-like Symptomatology in Migraine

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DOI: https://doi.org/10.17925/ENR.2017.12.01.28

It has been historically accepted that migraine involves symptomatology outside of head pain. These symptoms can be as equally disabling as the pain, and can include tiredness, concentration impairment, memory impairment and mood change. The symptoms may start before the onset of pain and can persist throughout the headache phase, and even after effective headache treatment into the postdrome. Despite knowledge of these symptoms, their neurobiologic basis and relationship to migraine pain is poorly understood. The fact that these symptoms start early, up to hours to days before the onset of headache, and are so symptomatically heterogeneous, suggests that the neurobiology of migraine extends beyond conventionally accepted anatomical pain areas within the brain – what has been known as the pain matrix or network. In a research area where no effective acute abortive drugs have gained a license for migraine since the triptans (serotonin 5-HT1B/1D receptor agonists), in the 1990s, further understanding of such symptomatology will allow therapeutic advances for treatments that may work before the onset of migraine pain and thus prevent it. This review will outline our current understanding about the phenotype and neurobiology of the premonitory (prodromal) symptoms, which for the purpose of this review will be called ‘premonitory-like’, given they can start before or during pain. Symptoms starting after pain resolution (postdromal symptoms) will not be covered here.

Keywords
Migraine, premonitory, prodrome, functional imaging

Disclosure: Nazia Karsan is an Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellow. Peter J Goadsby reports personal fees from Allergan, Amgen, and Eli-Lilly and Company, and personal fees from Abteka Biomedical, Ader Biopharmaceuticals, Autonomic Technologies Inc., Avanir Pharma, Cipla Ltd, Colucid Pharmaceuticals Inc., Dr Reddy’s Laboratories, eTheka, ElectroCore LLC, Navarins, Pfizer Inc., Promius Pharma, Quest Diagnostics, Sioen, Teva Pharmaceuticals, Trigemina Inc., Sicon, and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press; in addition, Peter J Goadsby has a magnetic stimulation for headache patent pending assigned to eTheka. No funding was received for the publication of this article. Peter J Goadsby is a member of the European Neurological Review Editorial Board.

Compliance with Ethics: This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

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Received: 12 March 2017
Accepted: 25 April 2017
Citation: European Neurological Review, 2017;12(1):28-30

Prevalence of premonitory-like symptoms in migraine

The true prevalence of premonitory symptoms among migraineurs is unknown, as most of the studies are retrospective and the numbers reported vary greatly across different studies.1-4 In addition, the majority of the studies performed so far have only looked at symptoms starting before the
onset of headache, the true definition of ‘premonitory symptoms’, rather than looking at the development of such symptoms with or during the onset of pain. Various retrospective studies in the literature have quoted prevalence rates of 9–88%.9–16 See Table 1 for a breakdown of studies to date in the literature looking at premonitory symptom prevalence.

Regardless of the prevalence, Giffin et al.16 showed with an electronic diary study that the experience of these symptoms is highly predictive of impending migraine headache. In this study patients were reliably able to predict the onset of headache 72% of the time, after reporting of impending migraine headache. In this study patients were reliably able to predict the onset of headache 72% of the time, after reporting of impending migraine headache. In this study patients were reliably able to predict the onset of headache 72% of the time, after reporting of impending migraine headache. In this study patients were reliably able to predict the onset of headache 72% of the time, after reporting of impending migraine headache. In this study patients were reliably able to predict the onset of headache 72% of the time, after reporting of impending migraine headache.

Two studies have also shown the existence of such symptoms among children and adolescents, even as young as 18 months.17,18 One of these showed a prevalence of 67% in the cohort of 103 children and adolescents with migraine.17 The other study preselected patients who had reported at least one premonitory symptom.12

These studies highlight consistently the presence of these symptoms among migraineurs and their ability to predict impending headache, as well as their presence or development at any time during a migraine attack. These features suggest that the symptoms may not be directly pain-related or mediated by pain, and are likely mediated by additional brain structures outside of the well-recognised trigeminovascular pain pathway.

**Phenotype of premonitory-like symptoms**

Despite the varying population types used in the studies performed thus far, the phenotype of symptoms reported in adults is largely consistent across these studies (see Table 1).9–16 The most common symptoms seem to be fatigue (see red in Table 1), mood change (see blue in Table 1) and yawning (see green in Table 1). These are consistent across the studies. Other common symptoms are neck stiffness and concentration difficulty.

The most commonly reported symptoms group largely into cognitive- or sleep-related symptoms (mood change, concentration or memory impairment, yawning, sleep disturbance and fatigue), migraine-like symptoms and sensory sensitivities (photophobia, phonophobia, nausea, mild head or eye discomfort and neck stiffness) and other homeostatic symptoms such as frequency of micturition, food cravings and bowel habit change. Paediatric studies have shown that the phenotype in children and adolescents is mostly comparable to that in adults.15–19

**Relationship of symptoms to the neurobiology of migraine**

The role of the brainstem as the driver for migraine attacks has been increasingly accepted.19 Various imaging studies in humans have now shown activity in brainstem structures during acute pain.20,21 Premonitory-like symptomatology clearly involves brain areas outside of pain pathways, given the variable phenotype of symptoms produced. The broad groups of symptoms that most of the symptoms reported by patients fall into could help us understand the biologic basis of the symptoms, by considering involvement of the limbic system (emotional change, tiredness and concentration impairment),22 dopaminergic pathways (yawning),23 the hypothalamus (neck discomfort, sleep disturbance, thirst, cravings, frequency of micturition)22,24 and other brainstem areas (nucleus of tractus solitarius and nucleus).25

Such theories alluding to the wider neurobiology of migraine led to the first functional brain imaging studies during the premonitory stage of migraine.

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**Table 1: A summary of studies performed looking into premonitory symptomatology in migraine**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and recruitment</th>
<th>Patients selected</th>
<th>Most common premonitory symptoms reported</th>
<th>Prevalence if available (of at least one or more symptom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blau et al. (1980)</td>
<td>Retrospective oral questioning (clinic)</td>
<td>50 adults and children (minimum age 12)</td>
<td>Yawning, tiredness, mood change</td>
<td>34%</td>
</tr>
<tr>
<td>Drummond and Lance (1984)</td>
<td>Retrospective oral questioning (clinic)</td>
<td>530 adults</td>
<td>Mood change, appetite change, changes in alertness</td>
<td>30%</td>
</tr>
<tr>
<td>Amery et al. (1986)</td>
<td>Retrospective questionnaire</td>
<td>149 adults</td>
<td>Low energy, pallor, photophobia, phonophobia</td>
<td>Presellected as having premonitory symptoms</td>
</tr>
<tr>
<td>Waelkens (1985)</td>
<td>Prospective questionnaire</td>
<td>49 adults</td>
<td>Irritability, depression, fatigue, hunger, bulimia, yawning</td>
<td>88%</td>
</tr>
<tr>
<td>Russell et al. (1996)</td>
<td>Retrospective face-to-face/telephone interview (clinic)</td>
<td>484 adults</td>
<td>Hyperactivity, depression, fatigue</td>
<td>9%</td>
</tr>
<tr>
<td>Rasmussen et al. (1992)</td>
<td>Retrospective interview and questionnaire (population)</td>
<td>1,000 adults</td>
<td>Depression, tiredness, hyperactivity</td>
<td>14%</td>
</tr>
<tr>
<td>Kelemen (2004)</td>
<td>Retrospective interview (clinic)</td>
<td>893 adults</td>
<td>Tiredness, malaise, fatigue, mood change</td>
<td>30%</td>
</tr>
<tr>
<td>Giffin et al. (2003)</td>
<td>Prospective, electronic diary (clinic)</td>
<td>97 adults</td>
<td>Tiredness, concentration difficulty, stiff neck</td>
<td>Preselected as having premonitory symptoms</td>
</tr>
<tr>
<td>Schoonman et al. (2006)</td>
<td>Retrospective questionnaire (clinic)</td>
<td>461 adults</td>
<td>Fatigue, phonophobia, yawning</td>
<td>87%</td>
</tr>
<tr>
<td>Quintela et al. (2006)</td>
<td>Retrospective questionnaire (GP surgery)</td>
<td>100 adults</td>
<td>Anxiety, phonophobia, irritability, low mood, yawning</td>
<td>84%</td>
</tr>
<tr>
<td>Cuvelier et al. (2009)</td>
<td>Retrospective questionnaire (clinic)</td>
<td>103 children and adolescents</td>
<td>Face change, fatigue, irritability</td>
<td>67%</td>
</tr>
<tr>
<td>Karsan et al. (2016)</td>
<td>Retrospective, analysis of clinic letters (clinic)</td>
<td>100 children and adolescents</td>
<td>Fatigue, mood change, neck stiffness, yawning</td>
<td>Presellected as having premonitory symptoms</td>
</tr>
</tbody>
</table>

The most common premonitory symptoms are colour-coded: fatigue (red), mood change (blue) and yawning (green).
in 2014. These provided supportive evidence for the early involvement of the dorsal pons, hypothalamus and various cortical areas in migraine attack, and interestingly revealed early involvement of the brainstem before the onset of pain. These findings confirmed the suspected brain regions hypothesised as being involved in mediating some of the symptoms reported by patients, including an area in the brainstem which seemed likely to be the nucleus of the tractus solitarius mediating nausea.19

The occurrence of premonitory symptoms, their ability to predict an impending headache and the anatomical structures alluded to in imaging studies during premonitory symptoms, suggest that they could provide vital neurobiologic information about the basis of a migraine attack, and important clues about therapeutic development in the future. If we can understand the neurotransmitter systems at play early before the onset of pain, we may be able to understand how to develop targeted therapies that work on these systems and may be able to prevent pain onset at all.

Small studies of this type have been performed using dopomperidone, taken during premonitory symptoms, acting on the dopamine pathway.20,21 and have shown promising results, but larger randomised placebo-controlled trials are warranted.

In addition, triggering studies as a way of modelling human migraine have also increased knowledge in this area. Nitroglycerin (NTG) and pituitary adenylate-cyclase activating protein (PACAP) have been shown to be able to trigger premonitory symptoms in migraineurs, similar to those experienced with spontaneous attacks.22,23 NTG is a well-established migraine-triggering model in the literature,24 but it has not been used extensively yet to study premonitory-like symptomatology. PACAP is newer in migraine research25 and its ability to trigger migraine26 has led to interest in agents targeted against the PAC1 receptor as a possible treatment for migraine.27 In a similar way, the human triggering models may, in the future, allow us to explore new effective triggering compounds and thereby further study antagonising the exogenous trigger molecules, in the hope of being able to prevent premonitory symptoms and pain onset.

Conclusions

Migraine is a disorder of more than head pain, and comprises heterogeneous non-painful symptomatology that can be equally debilitating, and contribute to the morbidity of the attack. These non-painful symptoms may start hours to days before the onset of pain, or start alongside the pain, and may persist after headache resolution. It is likely from observation of our patients in the clinic that these symptoms are probably under-reported. This is partly due to failure of patient recognition unless asked, and due to physicians not asking about specific symptoms that patients may not themselves have associated with a headache attack, or may have associated with trigger factors rather than premonitory-like symptoms. Recognition of the presence of these symptoms, particularly before the onset of headache, and differentiation of them from true migraine triggers, can help patients understand the wider impact of the attack, and reliably predict the onset of impending headache, as well as allow early and effective headache management.

Education about these symptoms, and helping patients understand that these are explained as being part of the migraine attack, can increase understanding of the symptoms, and limit unnecessary misinterpretation of some of these symptoms as migraine triggers and therefore limit unhelpful lifestyle modifications. In addition, in the paediatric population, education about the recognition of these symptoms among parents, teachers and carers, can allow prompt treatment in this population who may not always be able to display or vocalise pain. From a research perspective further understanding of the neurobiologic basis of these symptoms, through functional imaging and through pre-clinical models, will help us understand the regions of the brain likely to be involved, and thereby help with planning future therapeutic clinical trials.

In addition, increasingly studying the symptoms in humans through triggering models, imaging studies and treatment in randomised-controlled trials may help us identify future therapeutic targets. Identification of specific neurotransmitter systems in certain brain regions could help development of targeted migraine therapies, in an exciting era when migraine therapeutics has evolved greatly, but there will always be a need for more targeted acute and preventive therapies to help those affected by this disabling disorder with greater efficacy and limited side-effects profile. Future clinical trials should assess efficacy of the drugs in question in treating association-specific headache symptomatology in migraine, as well as headache, as this can be equally debilitating and impair the quality of life of those affected.

References