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# Functional Prodrome in Migraines

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## Abstract

**Purpose of review:** Migraine attacks often follow prodrome symptoms. Prodrome symptoms are inconsistently and incompletely defined in literature. Here we define the functionality of the common prodrome symptoms and introduce additional ones that have so far eluded investigators. Prodrome types are not just symptoms but represent physiological changes that signal why a migraine may occur.

**Recent findings:** Migraine associated prodrome types are considered as symptoms and precursors to an oncoming migraine with or without pain.

**Summary:** The understanding of the function of each prodrome may help in understanding migraine, how and what needs to be treated. By understanding the function of prodrome, migraines may be averted with success.

**Keywords:** Migraine; Prodrome; Sensory connections

## Introduction

Migraine is considered to be a neurological disorder [1-10] although some facets of migraine may contain a cardiovascular connection [11,12]. Prodrome, symptoms, and migraine triggers are confused in literature [3,13-19]. A study that associated prodrome with premonitory symptoms (PS) studying 2223 migraineurs found that the large majority of migraineurs had PS and the more severe the ensuing migraine, the more sensitivity to PS [20]. This study is an important marker to evaluate the function of prodrome, showing that the severity and type of prodrome are indications of migraine strength and likely migraine type. For example aura indicates aura migraine whereas partial paralysis of the body is indicative of a hemiplegic migraine. However, while aura is defined as prodrome, it is also defined as symptom, and part of an ongoing migraine event as well [18] but not so in the case of other migraine types. Aura migraine is also indicative of the type and location of the migraine: complex or aura migraine [21] located in the occipital cortex. Other migraine types may also be specific to anatomical locations and may have different prodrome. Research on migraine subjects is very specific to the understanding of pain symptoms as opposed to triggers and prodrome that are assumed to be necessary but inconsequential precursors, with respect to the why and how of migraines. Without investigation of prior events leading to triggers that culminate in prodrome and end up in migraine pain, prevention and successful treatment of migraine is not possible. Such prior events may include alternate treatments such as acupuncture that have found mixed results in helping migraine pain in academic research [22,23] but which may modify test results.

While research classifies migraines into types like classic, aura, hemiplegic, trigeminal, etc., these classifications are merely anatomical representation of where the region of brain is suffering cortical depression (CD) and where the cortical spreading depression (CSD) is started and through what regions of the brain it travels [24-32]. Most research is focused on CSD in aura migraine because it is identifiable by the subject and is also visible in the scanner [1,31-33]. Some research associate CDS only with aura type migraines [34]. However, while CSD may not be visible by the migraineur in the case of a non-aura migraine, it is there and is detectable in other types of migraines as well [26,28,29,35,36].

Triggers, prodrome, symptoms, and their function as they relate to and indicate the particular migraine type are vaguely defined and without logical order. This makes it very difficult to conduct research where researchers can ask relevant questions. Prodrome is defined as a set of possible conditions that appears suddenly and precedes a migraine but no suitable explanation is yet provided why they happen. Perhaps the most comprehensive explanation of prodrome and how they relate to migraine is defined by Burstein, Noseda, and Borsook [1]. But even in their strong explanation we miss the full understanding of the implication and meaning of what a prodrome, a symptom, or a trigger represents in terms of migraine anatomy, let alone the possibility of using information from the type of prodrome for prevention of a type of migraine.

## Prodrome Functionality

While we did not conduct a clinical trial, we did conduct research in a specific migraine group on Facebook (FB). To date, over 4000 migraineurs or family members taking care of migraineurs (such as children or migraineurs too sick to participate) joined and participated in our evaluation. We wanted to understand migraine types, symptoms, prodrome and triggers of a wide population that is international, multi-cultural and contains both sexes in various ages. We understand the weakness of group selection as we are dealing only with migraineurs who joined the group. However, we specifically wanted to understand only migraineurs and with the limitation of FB we could evaluate only those who joined voluntarily. Because some of our findings may also be valid for non-migraineurs, we concentrate

here on those findings that are not known to appear in non-migraineurs.

Our research yielded amazing results about migraine cause and treatment [37]. Here we focus on the definition and the meaning of prodrome. We rename prodrome to functional prodrome (FP) to emphasize that prodromes have very specific functions relative to migraines and each prodrome type has a specific role, signaling critical information about the upcoming migraine. This is not utilized in current migraine prevention or treatment. We also show that once prodrome is noticed, migraine is already under way only the CSD has not yet been initiated. For brevity we only analyze the most well understood prodrome types: sensitivity to bright light, loud noise, strong scent, yawning, anxiety, GI symptoms such as IBS, vomiting, and food craving. We also add a few types of prodrome that have not been noted in literature and encourage further research in these areas.

CD is a brain region with lack of electrical activity and CSD is the brain's attempt at shocking non-functioning brain regions by voltage into functioning again [1,37-39]. Prodromes such as fatigue, food cravings, and difficulty concentrating are associated with brain regions about to become low in voltage energy as the brain is starting to experience CD. Other prodrome types, such as sensitivity to bright light, sound, scent, and touch are signs of CD in brain regions with these associated brain functions. The actual migraine pain is created by the CSD at it reaches pain sensing receptors of the meninges [32]. It is understood that migraineurs possess a unique brain architecture by having multisensory integration of sensory organ neurons [40] and that these neurons have more sensory connections with each other than what we find in the brain of a non-migraineur [9,39,41,42]. It is also understood that a migraine brain uses more voltage simply by having multiple sensory receptor connections [42,43] which are in need of more voltage energy [41,44]. The amount of energy a migraine-brain uses differs from the energy use of a non-migraine brain [45]. These findings point to the importance of noting that migraineurs have different brains from non-migraineurs and that the various migraine types may refer to the anatomical differences among brains. Since prodrome is present prior to most migraine attacks, its relevance needs to be examined more closely to discover its functions.

## Functional Prodrome Signaling

Anxiety is the main and first FP that migraineurs experience prior to a migraine attack. Our hypothesis takes us to a genetic evolutionary brain modification that is connected to the hyper sensitivity of migraineurs' sensory organs [40]. We suggest that migraineurs' hyper sensitivity allows them to pick out changes in the environment with great accuracy and speed. While a migraineur may have poor vision, she will see peripheral changes better and faster than non-migraineurs. Based on our experience in the FB migraine group, migraineurs sense changes in the environment rather than judge them troublesome in their totality. Thus a peripheral move of a single leaf is a cause for action to a migraineur with her hyper sensory organs tailored specifically to discern such minor inputs. Similarly to sight, migraineurs possess special hearing that detects unusual sounds. They have the ability to sense sounds from far away that are not within the white noise of their environment. Similarly, sensitivity to strong scents is really sensitivity to scents that are above and beyond scents in their regular environment. This implies that while walking in a rose garden full of rose scent may not trigger a migraine, a heavy odor of perfume, gas leak, bacterial infection, home scenting, etc., in an everyday setting, does trigger migraine because it is different from the norm.

All of these environmental differences sensed by a migraineur initiate a fight-or-flight response; an evolutionary response to the stress of real danger, a response that in our modern world is perceived danger. When a migraineur senses a perceived danger, it is not any different in her brain's reaction to that of a danger from a real predator lurking nearby in ancient times. Given the very large percent of the population with migraines [46], the evolutionary nature of this special brain is very likely the genetic foundation of migraines. Anxiety caused by such irritants in all migraineurs starts the process of multiple physiological changes in the body: non-essential functions stop such as digestion, leading to irritable bowel syndrome (IBS), vomiting, and nausea [47]. The body releases adrenaline to increase breathing and heartbeat, to get more oxygen to the blood, enhancing running speed and allowing for fast decisions. Since a migraineur does not run off the excess adrenaline, it leads to restless legs syndrome (RLS), dizziness, and irritability. Migraineurs also yawn to get more air. Yawning potentially has one additional role. If we look at today's primates, yawning is a threat response to the stress of challenge. It is possibly also a signal of danger or dominance causing stress. Thus all of the listed prodromes here fit within the expression of anxiety alone. Therefore anxiety is not a prodrome but a biological reaction of precisely choreographed chain of events with the functional goal of "get away". Since anxiety is present in migraineurs prior to receiving any medication, some are medicated against anxiety with various success depending on the medicines they receive [48-51].

Food craving is another classic functional prodrome example. Most migraineurs we interviewed crave sugar or sweets before migraine pain. The brain loves to use glucose for energy. Obviously its first instruction to the individual (in the form of cravings) is to get more glucose; some of the brain regions are not functioning and the brain needs energy. Instead of glucose, the brain actually needs proper balance of potassium and sodium to initiate voltage and resupply energy needed [52,53]. Studies point to the importance of magnesium which is also a critical element to provide energy for all cells, including neurons [54-55]. Interestingly a study as early as 1951 showed that migraineurs had "busy brains" and excreted 50% more sodium in their urine than non-migraineurs did [56]. Putting this together with the heightened sensory organ sensitivity of migraineurs [40], it becomes clear that food craving is a signal that certain brain regions are not functioning and energy needs to be supplied. Since the brain seeks energy, the message received by the migraineurs is "eat sweets." Eating sweets further depletes sodium from the cells, reducing energy reserves even further [57]. This shows that food craving is a function of an ongoing CD. The CD is not felt by the migraineurs but a migraine is already underway. Thus food craving is a FP.

Sensitivity to bright light has a very important functional role. This particular prodrome is well known to precede and accompany migraines plus it may be a permanent condition even when it does not initiate migraines [58]. Migraineurs appear to have better night vision but are bothered by strong light most likely because their pupils do not close tight enough in bright light but are able to open wider in the dark than the pupils of non-migraineurs. Experimental direct evidence to pupil abnormality is weak in humans [59-62] but direct evidence is shown in animal studies [63].

## Other Undescribed FP

### Glucose sensitivity as a FP: carbohydrate consumption induces migraines

In our research with the FB migraine group we found additional migraine associated prodromes that have strong functions and which we did not find noted anywhere in literature. One of the most prominent FP is oedema and its associated urine color and frequency. These are possible markers of metabolic disorder that is very often mentioned to be correlated with migraineurs but with the caveat that the relationship is not well understood [25,64-72]. We found that as a result of glucose removing water and sodium from intracellular space [57], carbohydrates seem to cause oedema for migraineurs. While the amount of carbohydrates varies, based on our non-clinical evaluation - using the USDA database for precise measurement of serving size and associated carbohydrate levels - we found that migraineurs' carbohydrate tolerance level is between 5 gr and 20 gr carbohydrates maximum per meal. We established the tolerance level by measuring migraineurs' physiological response to eating a known carbohydrate amount fruit (blueberries) on empty stomach. The amount selected (2 cups) has too little potassium (228 mg), magnesium (18 mg), sodium (3 mg), and calcium (18 mg) to affect electrolyte in ways other than the changes caused by carbohydrates (35.79 gr net carbs with 29.45 gr free sugar). We asked for tests of several different quantities (from two to one to half cup) to measure the response until we reached the threshold at which level glucose in the fruit did not cause oedema. We timed when they felt thirsty, when first urination appeared, and urine color after the various carbohydrate levels of consumption. When migraineurs had no thirst and no change in urinary pattern within 30 minutes after consumption, we assumed the carbs threshold was not passed.

Because of the very low carbohydrate threshold of most migraineurs we tested, the metabolic syndrome connection may be found in their glucose sensitivity. Once migraineurs reduce carbs servings to below their threshold level, migraines do not follow. The moment they pass their carbohydrate threshold, migraines do follow. Re-establishment of sodium, potassium and water balance eliminates the migraine, supporting the direct connection between glucose sensitivity and migraines. Further research needs to evaluate the particular carbohydrate threshold levels and the genetic connection to such sensitivity by clinical trials.

### Oedema- Functional prodrome signifying glucose sensitivity

We searched literature for the connection of oedema and migraine and only found reference to vasodilation and inflammation within the brain [11,12,73] but none that suggested visible oedema as a migraine prodrome or symptom in any way. We found that as a result of the glucose sensitivity, when glucose sends intracellular water to extracellular space and also removes sodium via the influx of potassium [57], the extracellular water collection visibly causes oedema. Migraineurs report such oedema as swollen eye lids, swollen puffy under-eyes, tightening of rings, shoes, oedema mark upon pressing into the ankle, etc. Since oedema is a permanent feature of migraine but it is so overlooked, we hypothesized that it was not observed because as long as the migraine body is always in some state of oedema, a little extra oedema some carbs cause may not be visible while carbs are consumed in larger amount continuously. Upon proving to migraineurs of the FB group that sugar and other high simple carbohydrates induce their migraines, the majority has stopped consuming any form of sweeteners. Once the general oedema caused by permanent high levels of glucose in the body was eliminated and the associated weight gain disappeared, oedema became visible at every level from the smallest levels of carbohydrates consumed. We found that this type of oedema can easily be compensated by the consumption of salt, resupplying the sodium content of cells. The cells then are able to collect and hold onto water from intracellular space, removing much of the oedema. Migraine ceases as soon as electrolyte homeostasis is achieved by the application of salt and sometimes of potassium, depending on the extent of the oedema.

### Sleep disturbance: Migraine brain oversensitivity induces migraines

Sleep deprivation is a known migraine cause [74-76]. Sleep has additional functions beyond waking with a rested mind, like repairing damaged brain cells and cleaning debris caused by fragments left behind from its daytime busy life [77-79]. In particular, sleep is necessary to reset glucose homeostasis [80]. Because the migraine brain is so active and is enhanced with more alertness by the multiple connections of the sensory organs, most migraineurs experience sleep disturbance and deprivation. Since glucose homeostasis is not achieved in a restless sleep, this may explain the glucose sensitivity of migraineurs and also the connection to metabolic disorders. Further research is necessary to evaluate this theory.

### Variability of a single eye's size- a critical prodrome

In the extensive literature examining prodrome types we found nothing about the sudden change of eye size, usually the eye opposite to the side of pain. In the FB migraine group, members have posted their photos of such eye size changes and although not all of the migraineurs noticed this particular prodrome, we feel this is important to mention because it is so prevalent. Further research could identify its exact relation to migraines. Nevertheless, we can categorically state that upon noticing the change in eye size, taking immediate action by supplementing the brain with minerals to support voltage, resets the size of the eye and migraine is averted within 20 minutes.

## Conclusion

We discussed the importance of prodrome as function of migraine attacks rather than symptoms. As functions, they are often suggestive of the location and the cause of migraine and provide ample time for migraine attack prevention by immediately supplying voltage enhancing minerals. Clinical studies are highly recommended in the working relationship between CD and CSD by applying voltage nourishment of sodium and/or potassium and water to the migraine brain upon the discovery of CD to find the underlying mechanism by which CSD and its associated migraine pain is averted. We also recommend that migraineurs be warned about their possible glucose sensitivities and its likely connection to the metabolic syndrome that is associated with migraines.

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