Features of migraine aura as "Holy Grail" for studying pathophysiology of migraine with aura

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Received: August 18, 2015
Published online: September 02, 2015

First experience of complex migraine aura symptoms can be challenging for physicians to diagnose on a basis of patients report. Also, great variety and abundance of symptoms during migraine aura represent a great model for investigation of brain networks and pathophysiology of higher cortical functions. Moreover, knowledge about pathophysiology of the migraine with aura is still not entirely understood. We strongly believe that clinical descriptions accompanied with contemporary neuroimaging continuous to play an important role in investigations of the migraine aura. Herewith, we will try to highlight findings in our previous studies with the addition of reference to allodynia in migraineurs.

**Keywords:** Migraine aura; Higher cortical dysfunction; Cutaneous allodynia


According to the Global Burden of Disease study 2013 (GBD2013), migraine is the sixth highest specific cause of adult disability worldwide \[1\]. Knowing that every fourth migraineurs has an aura \[2\] and a pathophysiology of the aura is not entirely understood \[3\], the importance of comprehension of their origin and mechanisms urge neuroscientists' widely attention. That said, we strongly believe that clinical descriptions of aura in combination with contemporary neuroimaging could play an important role in further investigations of the pathophysiology of migraine aura.

Migraine aura is commonly considered to be a distinct phase of a migraine attack that mainly precedes the headache \[2\]. Widely accepted hypothesis about the pathophysiology of the migraine aura is centered toward a primary brain phenomenon called the spreading cortical depression, which may account for the clinical symptoms of migraine with aura \[4\]. It is found that cerebral blood flow reduction appears to move across the cortex at a rate of 3-6 mm/min and is preceded by a phase of hyperperfusion (spreading cortical depolarization - CSD) consistent with that seen in spreading cortical depression \[5\]. Besides spreading cortical depression, other important players in the pathogenesis of migraine aura were investigated: channelopathies, neuronal-glial gap-junction communications and microembolisation \[6, 7\].

Visual aura is most common, followed by somatosensory, and then dysphasic aura \[8\]. Recent studies \[9, 10\], suggest that higher cortical dysfunctions (HCD) during the aura are more often reported by patients who suffer from migraine with aura. Hereafter, we will try to highlight findings in those research papers \[9, 10\] with the addition of reference to allodynia in migraineurs.
What can we conclude from the reports of our patients? Alongside that in migraineurs the most common manifestation and most investigated [11, 12, 13] is visual phenomenon; somatosensory and language impairment, as well as other HCD, during aura reported by patients suggest involvement of other cortical areas beyond the occipital region in majority of patients [10]. Moreover, patients with visual and somatosensory aura mainly reported 5 to 10 minutes delay of the beginning of somatosensory symptoms after the beginning of visual aura, but also in some patient’s somatosensory aura onset occurred at the same time or before visual aura. These findings could indicate that origin of CSD is not necessary occipital lobe, as well as that CSD could origin from different cortical regions possibly even simultaneously [14].

Worth mentioning, some patients had memory disturbances during the aura, such as difficulties in remembering the events or more frequently in recalling past events [9, 10]. Also, patients reported difficulties in calculating, naming, performing precise movements with hands, spatial orientation, recognizing objects by touch, as well as neglect phenomena. The occurrence and sequence of different HCD in the same patient point out the variety of different possible paths of CSD propagation through the cortex [15]. The somatosensory cortex plays major importance in multisensory integration processes [16, 17]. We can assume that magnitude of CSD affection of somatosensory cortex, especially secondary somatosensory regions, is linked to the number and types of HCD. Eventually, it could be speculated that the presence of multiple symptoms during migraine aura is due to independent islands of cortical hyperactivity, rather than to spread of hyperactivity over long distances [18].

Also, origins and paths of CSD in complex aura symptoms may be best explained by illustration (Figure. 1) in our previous paper [19].

Unlike to the aura that usually precedes headache, allodynia mainly occurs during painful phase of migraine. These both fascinating phenomena, although not entirely understood yet, have their origins in brain cortex. Migraine patients often report on aversion to various sensory stimuli during an acute migraine attack, particularly cutaneous [20]. Cutaneous allodynia is defined as the perception of pain when a non-noxious stimulus is applied to normal skin [21]. It’s actually an important feature of migraine that reveals more about what happens in the brain of migraineurs.

**Figure 1. Presumed path of CSD in migraineurs with visual, somatosensory and dysphasic auras.** Comment: The beginning with somatosensory symptoms indicates the primary somatosensory cortex as the first origin of CSD, radiating to the posterior parietal cortex, temporal lobe, and Broca’s area. The second CSD origin could be the primary visual cortex, localized in the occipital lobe and spreading to the parietal and temporal lobes, and then, possibly, to Broca’s area. Reprinted with permission [19].
Patients may describe pain to touch, such as with resting one’s head on a pillow, lightly brushing one’s hair or with wearing a contact lenses [22]. Subjective feeling of cutaneous allodynia may be best illustrated by drawn of our patient (Figure 2).

Frequent severe attacks of migraine with aura can lead to an increased tendency for central sensitization [22]. Central sensitization arises sequentially from first-order neurons that innervate the meninges to second-order neurons in the trigeminal nucleus caudalis [23, 24], and possibly involves cortical neuronal dysfunction as well [20]. Witting et al, in a PET study have shown that brush evoked allodynia activated the posterior parietal cortex, suggesting the involvement of distinct cortical areas in the processing of allodynia [25]. We would like to stress these finding as important for understanding emphasized allodynia in migraineurs during the migraine aura. Also, sensitization of third-order trigeminovascular neurons during headache can explain how migraine induces cutaneous alldynia outside the referred pain area [26].

To summarize, findings of the high incidence of HCD symptoms during the migraine aura are important information for physicians to have in mind when facing new cases of migraine with unusual aura. The concomitance of HCDs during aura could represent an excellent opportunity to study brain connections. Migraine with allodynia results from the process of central sensitization, characterized by over excitability of pain nerve cells. Overall, we strongly believe that clinical descriptions of migraine beyond the pain could play an important role in further investigations of an obviously multilayered pathophysiology of the migraine aura.

References


