Cortical spreading depression: origins and paths as inferred from the sequence of events during migraine aura

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Summary

Patients with migraine with aura often experience a variety of visual and somatosensory phenomena and disturbances of higher cortical functions. Analysis of these alterations may provide important information about the involvement of different cortical regions in cortical spreading depression (CSD).
We report five cases of migraineurs who experience unusually abundant clinical phenomena during auras. These patients were selected from a cohort of migraine with aura patients who were interviewed, using a specially designed questionnaire, to evaluate the presence of higher cortical dysfunctions. On the basis of the aura symptoms they reported, we attempted to infer the origin and the possible paths of CSD in each patient. According to their reported symptoms, CSD could begin in the primary visual cortex, in the primary somatosensory cortex or simultaneously in both, and propagate to the posterior parietal cortex, the temporal lobe and Broca's area. We believe that clinical descriptions of aura could play an important role in further investigations of the pathophysiology of migraine.

KEY WORDS: cortical mapping, cortical spreading depression, higher cortical dysfunction, migraine with aura.

Introduction

Migraine is a chronic primary brain disorder with episodic clinical manifestations. It affects about 11% of the adult population and shows a clear female predominance (Lipton et al., 2002; Bigal and Lipton, 2009). Up to one third of migraineurs experience aura with visual, somatosensory, dysphasic and, rarely, motor phenomena. The exact pathophysiology of migraine aura is still unknown, although altered cortical excitability has been proposed as an important factor in spontaneous cortical spreading depression (CSD) (Welch et al., 1990).
The occipital cortex is considered to be the area where most migraine-related CSD starts (Hadjikhani et al., 2001). CSD is a dynamic process that progresses through contiguous areas of the cortex and it has been suggested that the clinical manifestations of auras might reflect the involvement of other cortical areas beyond the occipital region (Vincent and Hadjikhani, 2007). Migraine aura descriptions differ from patient to patient and can include different visual, somatosensory, motor and language disturbances (Russell and Olesen, 1996; Vincent and Hadjikhani, 2007). This variety of disturbances suggests that other areas, besides the primary visual cortex, can be affected, including the cortical areas outside the occipital lobes. This, in turn, supports the hypothesis that the process causing the aura can engulf the entire post-central cortex in its course, in the manner of a CSD wave observed in animal experiments (Dahlem and Hadjikhani, 2009).
Disorders of higher cortical functions (HCFs) are more frequent than previously thought (Vincent and Hadjikhani, 2007; Petrusic et al., 2013). Specifically, migraine patients have reported symptoms related to color naming disorders, prosopagnosia, retrograde amnesia, the déjà vu phenomenon, dysnomia, dyslexia, manual dyspraxia and spatial disorientation (Vincent and Hadjikhani, 2007; Petrusic et al., 2013). We demonstrated HCF disorders in 65% of patients during visual and/or somatosensory aura, with the duration of aura found to influence the type and frequency of these disorders (Petrusic et al., 2013).

Case reports

Five patients from a cohort of 66 patients diagnosed with migraine with visual and/or somatosensory aura (Petrusic et al., 2013) are here described: four females and one male, each fulfilling the relevant International Headache Society (IHS) criteria (Headache Classification Subcommittee of the IHS, 2004) and presenting abundant clinical phenomena. A specially designed questionnaire was used for data collection.

Written consent was obtained from all the patients. In each case, the sequence of aura events was noted in order to establish the presumed path of CSD.

Patient 1

A 37-year-old right-handed man presented with a 20-year history of migraine with aura occurring once a month.
This patient's aura begins with homonymous hemianopsia lasting for one hour. Fifteen minutes after the visual phenomena start, the patient experiences numbness on the ipsilateral half of the body starting with the leg and spreading upwards. Simultaneously with the numbness, he experiences difficulty finding words, an inability to properly name familiar people and objects, the déjà vu phenomenon, difficulties with writing, reading and calculating, and an inability to understand other people's speech. During some attacks, he is unable to recognize objects by touch and to coordinate precise hand movements.
In this patient, headache starts immediately after the resolution of the aura symptoms. Pain of moderate to severe intensity is located mainly in the forehead, accompanied by photophobia and phonophobia, and lasts up to 24 hours. Chocolate, strong smells, physical activity, and elevated ambient temperature are triggers of these migraine attacks. He is a smoker, consuming 10 cigarettes per day. The patient's personal history is unremarkable. His paternal grandmother had migraines. Neurological examination, brain magnetic resonance imaging (MRI), electroencephalography (EEG), and cranial artery ultrasound gave unremarkable results. Echocardiography showed minor mitral and tricuspid valve prolapses without significant regurgitation.
A diagram of the presumed path of CSD was drawn, based on the patient's description of the aura symptoms (Fig. 1).

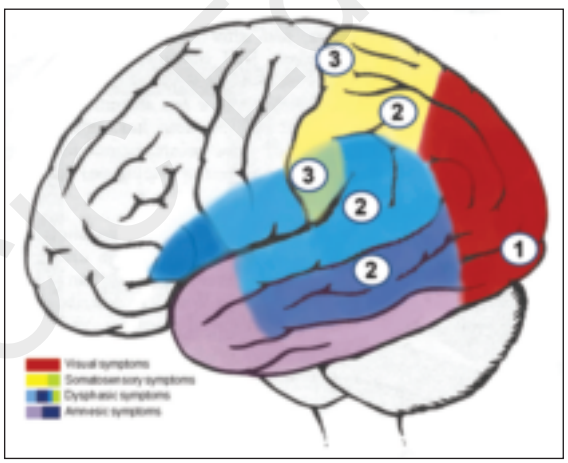

Figure 1 - Presumed path of cortical spreading depression in patient 1.
Comment: The fact that aura begins with visual symptoms points to the primary visual cortex as the site of origin of CSD, which radiates simultaneously to the parietal lobe (involving the primary somatosensory cortex) and the temporal lobe.

Patient 2

A 51-year-old woman presented with a 22-year history of migraine with aura occurring once a month.
This patient's aura starts with flickering and glittering in the visual field lasting 45 to 60 minutes. The visual aura is followed by speaking difficulties, anomia, retrograde and anterograde amnesia, the déjà vu phenomenon, dysarthria, difficulties with reading and calculating, manual imprecision and right-left disorientation.
Diffuse, pulsating pain accompanied by nausea follows the aura and lasts up to 24 hours. Combined analgesics such as caffetin® (paracetamol 250 mg, propyphenazone 210 mg, codeine phosphate 10 mg and caffeine 50 mg) or aspirin are usually efficacious for the headache. The patient's medical history revealed occasional tension-type headaches and hyperthyroidism treated during the previous three years.
Due to the atypical description of aura symptoms, the patient was referred to our Headache Center. The results of general and neurological examinations, EEG and head MRI, and hematological and biochemical tests, including antinuclear antibodies, were unremarkable. As the patient reported that she dreaded her aura symptoms, propranolol and amitriptyline were recommended as prophylactics regardless of the low migraine frequency.
Again, a diagram of the presumed path of CSD was drawn on the basis of the patient's report of the aura symptoms (Fig. 2).

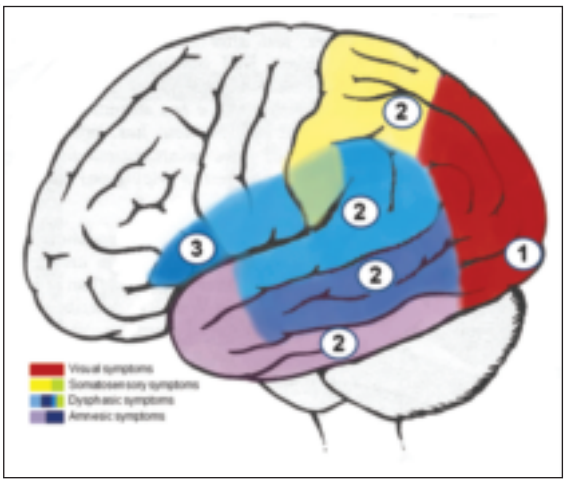

Figure 2 - Presumed path of cortical spreading depression in patient 2.
Comment: The fact that aura begins with visual symptoms points to the primary visual cortex as the origin of CSD, which radiates simultaneously to the posterior parietal cortex, temporal lobe and Broca's area.

Patient 3

A 42-year-old right-handed woman presented in 2007 with a six-year history of migraine with aura occurring two to three times a year.
This patient's aura starts with flickering, glittering, blurry vision and narrowing of one visual field lasting

20-30 minutes. At almost the same time, she experiences numbness and coldness of one hand and of the ipsilateral half of the face together with speech difficulties. She cannot understand the speech of others, find and pronounce certain words, or recognize familiar faces or sounds from her surroundings (e.g. bird twitters, automobile horns). Symptoms of the aura persist during the first 10 minutes of headache.
The headaches are severe and last several hours. The patient's medical history revealed occasional tension-type headaches, hypothyroidism successfully treated with levothyroxine, and polycystic ovary syndrome. Her mother has migraines without aura.
Whereas neurological examination, EEG, CT brain scan, and ultrasound examination of the neck arteries gave normal results, a transcranial Doppler (TCD) bubble test was positive and a transesophageal echocardiogram confirmed patent foramen ovale.
Figure 3 shows the presumed origins and sequences of cortical activation in this patient, based on her description of the aura symptoms.

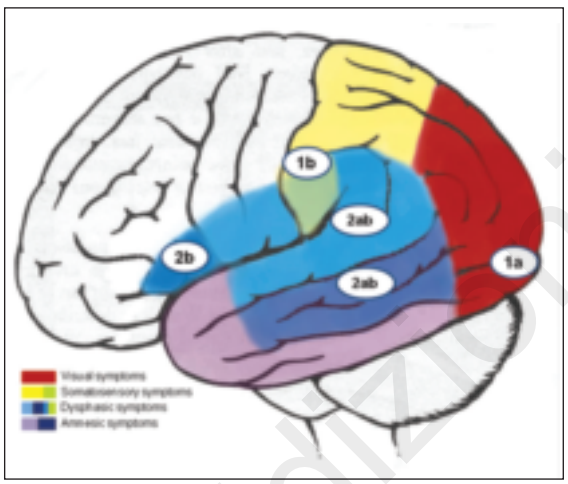

Figure 3 - Presumed path of cortical spreading depression in patient 3.
Comment: The almost simultaneous appearance of visual and somatosensory symptoms raises the possibility that CSD starts in two sites, i.e. in the primary visual and somatosensory cortices, and then radiates to the parietal and temporal lobes involving speech regions.

Patient 4

A 31-year-old right-handed woman presented in 2011 with an 11-year history of migraine with aura.
This patient's attacks always begin with glittering, which lasts for 10 minutes. Occasionally (in every fourth attack), visual symptoms are associated with numbness of both hands radiating toward the face and tongue, these symptoms lasting for 20-30 minutes. In attacks with numbness, the patient also experiences difficulty finding words, and cannot read, write or calculate; she is also unable to recognize sounds from her surroundings, coordinate precise hand movements, and recall past events. All the reported symptoms of higher cortical dysfunction persist for 20 minutes and gradually resolve.
The patient reports a free period lasting about 30 minutes between the aura and a one-sided headache. The quality of the pain is dull, occasionally pulsating; it is mild to moderate in intensity and accompanied by nausea. She also suffers from migraine without aura. Because of increased headache frequency and overuse of simple and combined analgesics, she was admitted to hospital and successfully treated.
During that hospitalization, she was thoroughly investigated. Head MRI, blood tests, echocardiography and TCD findings were normal, as were the findings of standardized EEG and EEG after sleep deprivation. The patient's medical history revealed surgery due to a polycystic thyroid gland without thyroid dysfunction, dysmenorrhea and gastritis. Her father also had migraine with aura.
Figure 4 shows the presumed origins and sequences of cortical activation based on the aura events described by this patient.

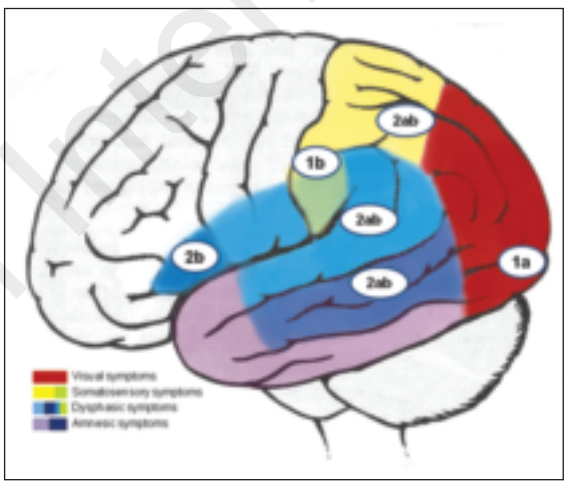

Figure 4 - Presumed path of cortical spreading depression in patient 4.
Comment: The patient's symptoms suggest that CSD has two sites of origin, i.e. in the primary visual and somatosensory cortices, and radiates to the parietal lobe, temporal lobe and Broca's area. Given the bilateral numbness, both the left and right primary somatosensory cortices could be involved.

Patient 5

A 50-year-old right-handed woman presented in early 2009 with a 25-year history of migraine with aura occurring 10-15 times per year.
This patient's attacks start with numbness of the fourth and fifth fingers of the left hand and the tongue starting 70 minutes before the onset of the headache and persisting during the headache. After 10 minutes, these features are followed by flickering, glittering and a narrowing of half of the visual field, which last until the headache begins. Speech difficulties appear in about half of the auras, in the form of difficulty finding words, beginning 40 minutes after the visual phenomena and lasting 10 minutes. Sometimes, these speech difficulties are accompanied by additional phenomena: inability to name familiar persons or objects,

understand written text, coordinate precise hand movements, or recall past events.
The headache is unilateral, intense, non-pulsating, and associated with osmophobia, photophobia and phonophobia, and nausea and vomiting; it lasts six to seven hours with a modest response to analgesics. In addition to her attacks of migraine with aura, the patient also has twice-monthly episodes of unilateral headache of moderate intensity and without associated symptoms. Otherwise, the patient's medical history was unremarkable. Her sister has similar migraine symptoms.
Neurological examination, laboratory tests, including anti-nuclear antibodies, CT brain scan, head MRI and MR angiography, as well as ultrasound examination of the arteries of the neck and head, gave normal findings. The TCD bubble test was positive and echocardiography revealed a septal interatrial aneurysm.
The sequence of this patient's reported aura symptoms is presented in figure 5.

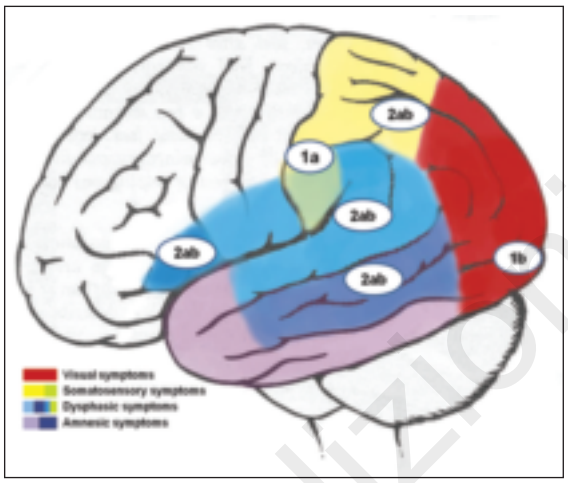

Figure 5 - Presumed path of cortical spreading depression in patient 5.
Comment: The onset of aura with somatosensory symptoms points to the primary somatosensory cortex as the first site of origin of CSD, which radiates to the posterior parietal cortex, temporal lobe and Broca's area. The origin site could be the primary visual cortex, located in the occipital lobe, from where CSD spreads to the parietal and temporal lobes, and then, possibly, to Broca's area.

Discussion

We have here described the aura symptoms experienced by five migraine patients and hypothesized the origin sites and paths of CSD in these patients, on the basis of the events they reported (Fig.s 1-5).
Patients 1 and 2 described similar sequences of events with simple visual phenomena at the beginning of aura followed by phenomena indicating the simultaneous involvement of the primary somatosensory cortex, the temporal cortex and the perisylvian cortical region. In these two patients, a spread of the cortical depolarization from the primary visual area, localized in the occipital lobe, to contiguous parietal and temporal cortices was hypothesized. The presumed sites of origin and paths in patients 1 and 2 are in line with current MRI findings demonstrating that CSD originates in the occipital region and moves rostrally (Rogawski, 2008; Durham and Garrett, 2009).
The sequences of events described by patients 3 and 4 indicated simultaneous onset of aura in the occipital and parietal cortices. Instead, the description given by patient 5 suggests that her aura begins in the parietal cortex and then spreads to the occipital and posterior parietal cortices. These descriptions suggest that CSD can begin outside the occipital cortex. Research papers (Hadjikhani et al., 2001; Kunkler and Kraig, 2003) have hypothesized that CSD could originate in the hippocampal and somatosensory cortex. In patient 5, according to the information provided, somatosensory phenomena appear before other symptoms and have the longest duration; this raises the possibility that CSD originates in the primary somatosensory cortex and spreads radially through the brain network. Cortical dysplasia in these regions has been suggested (DaSilva et al., 2007; Hadjikhani, 2008), although it was not detected by conventional brain MRI in our patients. Furthermore, it can be assumed that CSD originates from multiple cortical regions simultaneously.
Higher order sensory processing of visual, auditory, and tactile information is generally thought to be organized according to a general subdivision into a ventral stream and a dorsal stream (Frasnelli et al., 2012). The dorsal stream, extending from the visual cortex to the posterior parietal cortex, has a role in spatial perception, whereas the ventral stream, extending from the visual cortex to the temporal cortex, processes object perception. This model of separate processing according to stimulus characteristics has been confirmed in the human visual (Haxby et al., 1991), auditory (Rauschecker and Tian, 2000) and somatosensory (Reed et al., 2005) systems, as well as in multisensory integration processes (Renier et al., 2009).
With regard to the primary visual cortex as the site of origin of visual auras, other authors have observed that visual auras could arise not only from the primary visual cortex, but also from other extrastriate areas (e.g., V2, V3yVP, V3A, and V4v) (Hadjikhani et al., 2001). In all our patients, the occipital lobe was an origin site of CSD, which thereafter spread via the ventral and dorsal visual streams into the parietal and temporal lobes. The ventral stream is associated with object recognition and form representation, which could explain the difficulties recognizing familiar faces reported by patient 3. Indeed, other studies show that the most specific forms of prosopagnosia are due to lesions of the right posterior network including the occipital face area and the fusiform face area (Gainotti and Marra, 2011). The face identification defects observed in patients with left temporal-occipital lesions seem to be due to a semantic defect impeding access to person-specific semantic information from the visual modality (Gainotti and Marra, 2011). Four of our patients reported disorders of HCFs linked to the superior parietal lobule: difficulties with coordinating

precise hand movements, inability to recognize objects by touch, and right-left disorientation, which is associated with CSD through the visual or sensory dorsal stream. Many symptoms, such as difficulties with writing, reading and calculating, indicate propagation of CSD into the inferior parietal lobule.

The spread of induced CSD is usually confined to the hemisphere in which it was initiated (Hadjikhani et al., 2001). Although a precise match in terms of speed has been observed between aura symptoms mapped onto the cortical surface and CSD, their spatiotemporal patterns usually show size and shape differences (Dahlem and Hadjikhani, 2009). In three of our patients, the somatosensory cortex could, on the basis of the time of onset of somatosensory symptoms, be presumed to be the site of origin of CSD, which is in line with the findings of functional MRI studies (Hadjikhani et al., 2001). It has previously been demonstrated that the cerebral architecture is characterized by a subdivision into two parallel sensory processing pathways linking modality-specific primary regions with modal processing regions. The dorsal pathway runs through the posterior parietal cortex and the ventral pathway through the temporal and inferior parietal regions to the frontal cortex, where both pathways terminate (Reed et al., 2005). Areas of the secondary sensory cortex in the left and right hemispheres are densely interconnected, and stimulation on one side of the body will activate secondary sensory areas in both hemispheres (Clarey et al., 1996; Iwamura et al., 2001; Ragert et al., 2011). This may be a plausible explanation for the simultaneous numbness of both hands reported by patient 4.

The dual-stream model of speech processing outlined by Hickok and Poeppel (2007) suggests that the temporoparietal junction is important for translating the auditory code into the articulatory code. Dhanjal and colleagues (2008) further refined this hypothesis and suggested that this area is important for polysensory integration during speech processing. Aphasia has many patterns and levels of severity (Hoffmann and Chen, 2013). In clinical practice, some patients complain of speech and memory difficulties during auras (Manzoni et al., 1985; Eriksen et al., 2006). Our patients, in addition to speech difficulties during their auras, also had difficulties naming familiar persons and recalling information from the past. Speech difficulties were pronounced in all five patients and one of them reported aura lasting 70 minutes. In a previous study we demonstrated that aura lasted longer in patients with dysphasia (Petrusic et al., 2013).

Two of our five patients could not understand other people's speech during auras, an impairment that could be linked to cortical depression in Wernicke's area. Receptive or sensory aphasia is commonly associated with Wernicke's area lesions (Robson et al., 2012). All our patients reported word-finding difficulties, dyslexia and difficulties in writing and interpreting writing, which could be linked to the angular gyrus, Broca's region, or middle temporal gyrus. Interactions between these distant regions are enabled by the arcuate and superior longitudinal fascicle fibers (Schmahmann et al., 2007; Frey et al., 2008). Three of the presented patients were unable to name familiar persons or objects during migraine aura, which suggests that CSD could pass through the left temporal medial gyrus and/or inferior parietal lobule (Baldo et al., 2010; Fridriksson et al., 2010; Suchan and Karnath, 2011). This presumed path could also explain the retrograde amnesia reported by three of our patients (Ota et al., 2007). The prefrontal cortex, particularly the left hemisphere, is involved in episodic memory encoding and the déjà vu phenomenon (Spatt, 2002; Maril et al., 2003), which were also reported by our patients.

According to the International Classification of Headache Disorders: 2nd edition, aura lasts between five and 60 minutes (IHS, 2004). In recent studies (Viana et al., 2013), including one by our group (Petrusic et al., 2013), it has been shown that aura may last longer than one hour in a significant proportion of migraineurs. The symptoms in aura may arise gradually and alternate between visual, somatosensory and dysphasic phenomena, lasting up to 60 minutes total, as in four our patients. Also, a single aura symptom may last more than 60 minutes, as in our patient 5. Visual symptoms often last up to 20 minutes, corresponding to the distance for CSD propagation which is approximately 60 mm, the length of the visual areas located along the calcarine sulcus (Dahlem and Hadjikhani, 2009). The reported duration of visual symptoms in three of our patients was longer, i.e. 30 to 60 minutes. Prolonged aura duration is mostly seen with somatosensory and dysphasic aura (Viana et al., 2013). We can only suggest that the duration of the aura may depend on the site in which the CSD originates and the adaptive capacity of the regions that are affected by the phenomenon.

The concomitance of HCFs during aura could represent an excellent opportunity to study brain connections (Rorden and Karnath, 2004; Rorden et al., 2009). Although the validity of the data here presented could be questioned due to the possibility that some data are distorted by patients' recollections, as well as the unequal eloquence of different cortical regions, we strongly believe that clinical descriptions of aura could play an important role in further investigations of the pathophysiology of migraine.

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