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Migraine biochemistry and visual snow

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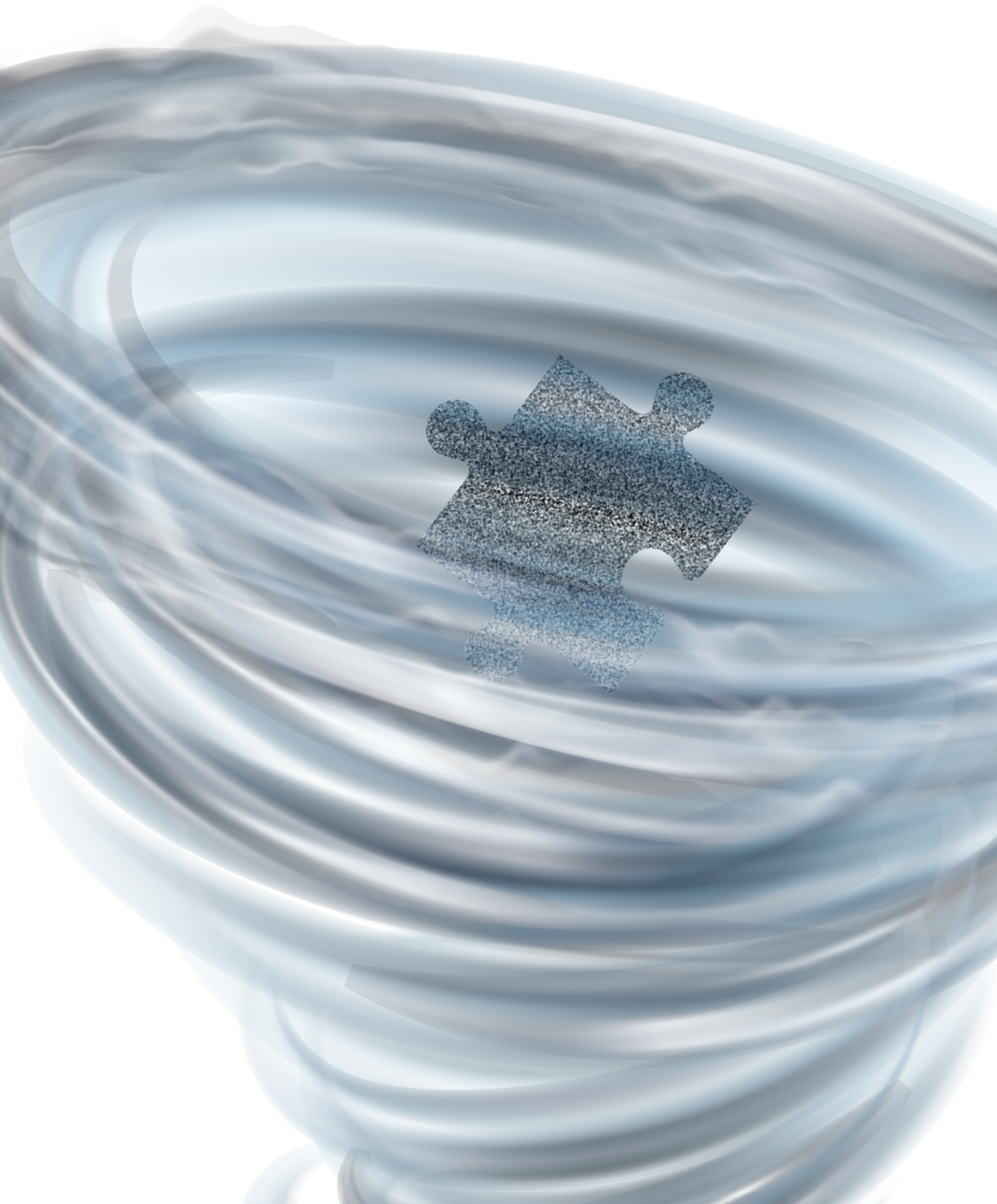
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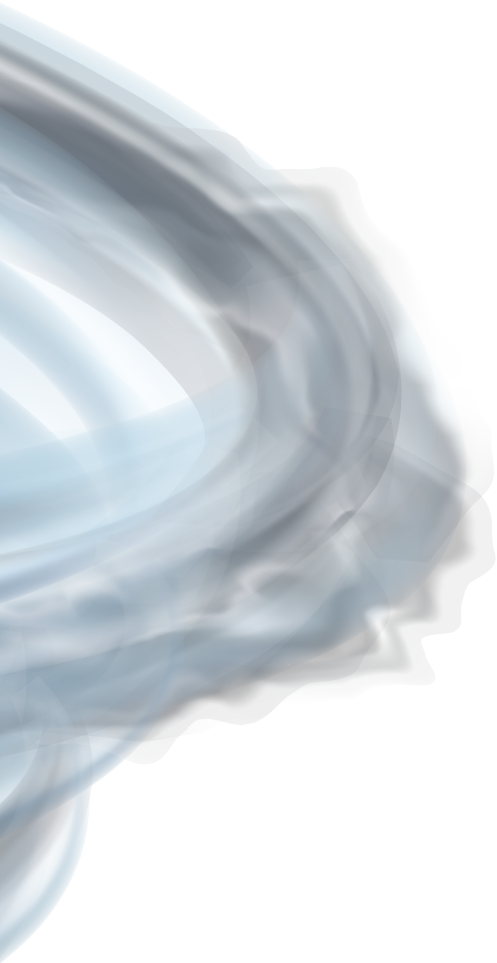
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PART II

Migraine and visual snow





5

Symptoms related to the visual system in migraine

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Abstract

Migraine is a common headache disorder characterized by often-severe headaches that may be preceded or accompanied by a variety of visual symptoms. Although a typical migraine aura is not difficult to diagnose, patients with migraine may report several other visual symptoms, such as prolonged or otherwise-atypical auras, “visual blurring”, “retinal migraine”, “ophthalmoplegic migraine”, photophobia, palinopsia, and “visual snow”. Here, we provide a short overview of these symptoms and what is known about the relationship with migraine pathophysiology. For some symptoms, the association with migraine is still debated; for other symptoms, recent studies indicate that migraine mechanisms play a role.

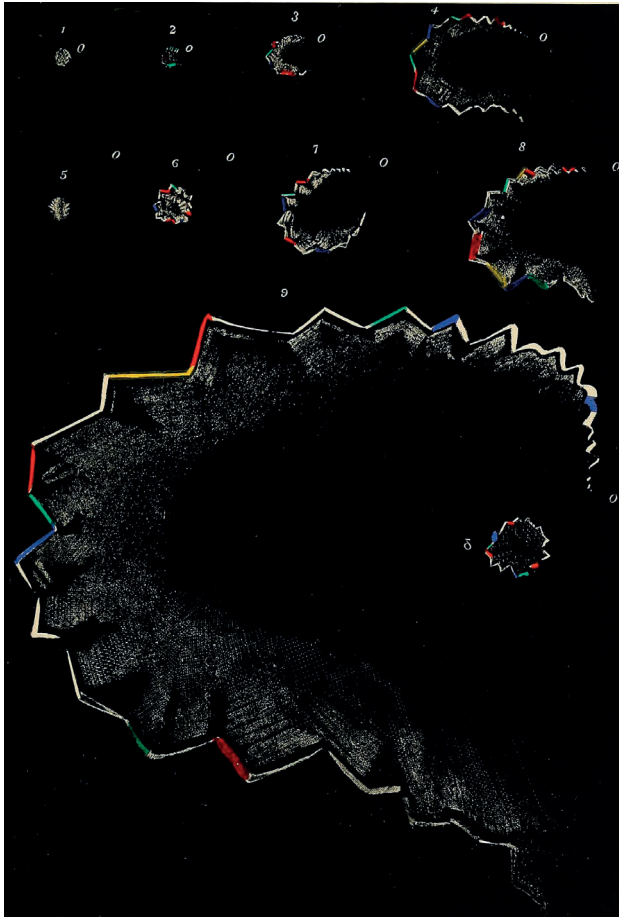
Introduction

Symptoms related to the visual system are common in migraine, a neurovascular brain disorder characterized by episodes of often-severe headache lasting between 4 hours and 3 days.¹ In almost one third of patients with migraine, the headache is preceded by a visual aura² but there are several other visual symptoms related to migraine. The purpose of this narrative review is to provide a brief overview of these visual symptoms. Because migraine prevalence is high—lifetime prevalences are 33% in women and 13% in men²—many physicians, especially general practitioners, neurologists, and ophthalmologists, will see patients with migraine. First, as background, the typical migraine aura is discussed, followed by the differential diagnosis of atypical auras. Next, visual symptoms other than migraine aura are reviewed: photophobia, palinopsia, and visual snow.

Typical visual migraine aura

In its most typical form, a visual aura begins with a “scintillating scotoma”, a small blind spot with a flickering, brightly colored, and typically jagged front—the so-called fortification spectrum—that generally expands in a C-shape to one side of the visual field (Figure 1).^{1,3} The expansion is gradual and lasts between 5 and 60 minutes.¹ These visual symptoms are fully reversible and should not be accounted for by another disorder, according to the third edition of the International Classification of Headache Disorders.¹ The positive symptoms often take shapes other than a classic fortification spectrum. Patients commonly report that the aura starts with light flashes or balls of light that gradually expand across the visual field.^{4,5} Furthermore, positive symptoms do not have to occur; patients can also report that the scotoma (that is, the blind spot or the hole in the visual field) has no colors or jagged lines. When patients close their eyes, the positive features of an aura remain visible. Besides having visual symptoms, patients may experience sensory symptoms, speech problems, and sometimes motor symptoms during their auras.¹ If a person has had two attacks fulfilling criteria for migraine with aura, he or she is classified as a migraine-with-aura patient.¹ If a person has only attacks without aura, he or she is classified as migraine-without-aura. Migraine-with-aura patients can still have attacks without aura. In a general-population study, median attack frequency was 12 attacks per year and 25% of patients with migraine had at least two attacks per month.²

Figure 1. Example of a migraine aura



Legend: This picture illustrates the typical gradual expansion of a migraine aura along with the characteristic fortification spectrum.

Gradual expansion is considered the most typical feature of a migraine aura.¹ This corresponds with the suspected underlying pathophysiological mechanism called “cortical spreading depolarization” (CSD): a wave of intense neuronal and glial depolarization that is followed by neuronal depression. Preclinical and clinical studies suggest that the velocity of CSD through the occipital cortex is in line with the velocity of the visual spread observed by patients.^{6–8} Patients can report a classic cascade in aura symptoms: the aura starts with visual symptoms and is followed by sensory symptoms, aphasia, and sometimes motor problems.⁹ It is believed that in these cases the CSD expands from the occipital cortex to the motor cortex.¹⁰ However, a prospective diary study showed that in 34% of patients the aura symptoms start simultaneously, suggesting that CSD may also start in a non-symptomatic brain area and reach two cortical areas at

about the same time.⁵⁻¹¹ Sometimes patients report complex visual phenomena during their auras, such as distortions of observed body parts (for example, disproportionately large ears, sometimes referred to as the Alice in Wonderland syndrome) or visual splitting (one half of the observed face shifts upwards or downwards).^{3,12,13} This suggests that more complex processes of visual perception, involving orientation and size, can also be altered during migraine attacks. Additionally, patients often report that during migraine auras their vision is “blurred” or “foggy” or that they see “heat waves”. In the diary study, this was registered in 33% of auras.⁵ However, information on gradual expansion was not collected. Furthermore, these symptoms have not been prospectively studied in migraine-without-aura patients. Therefore, there is still discussion about whether these symptoms are part of the aura spectrum.

In most patients, the aura is followed by a migraine headache. Typically, the headache starts after the aura has ended, although the headache can also start during or—in rare cases—before the aur.^{5-9,14} In a minority of attacks, the aura is not followed by headache^{4,9} and this classically occurs in elderly patients and is often referred to as “late-life migraine accompaniments”.¹⁵

Current acute migraine medication is able to treat the headache only and has no effect on the auras. Preventive drugs such as beta-blockers, candesartan, topiramate, valproate, and amitriptyline and nortriptyline are generally considered when patients have an average of more than two attacks per month. When successful, the auras can also be prevented. For patients with frequent auras, lamotrigine can also be tried.¹⁶

Atypical visual migraine auras

Atypical auras are important to identify because of the differential diagnosis with other diseases. First, migraine auras can mimic stroke because of the homonymous visual field defects or additional focal symptoms.¹⁷ However, in migraine aura, symptoms gradually develop whereas in stroke they are often maximal from the start. Furthermore, classic aura features (colors and zig-zag lines) are generally not present in stroke.¹⁸ Nonetheless, it can be hard to discriminate between the two diagnoses and other clinical factors such as age and cardiovascular risk factors should be taken into account. When the aforementioned “late-life migraine accompaniments” in an elderly patient are considered, secondary causes such as cerebral amyloid angiopathy should also be excluded. Amyloid spells (that is, transient focal neurological episodes caused by superficial cortical siderosis) can mimic migraine auras.¹⁹

Second, occipital epilepsy can also present with visual symptoms followed by headache but without the characteristic motor seizures. Classically, patients describe these symptoms as colored phosphenes³, although phosphenes can also be reported as aura

symptoms by patients with migraine.²⁰ However, visual symptoms in epilepsy generally last shorter than 5 minutes and often start in the periphery of one temporal visual field whereas in migraine the auras generally start more to the center and expand to the periphery.²⁰ These criteria are not specific and sometimes electro-encephalography recordings could help in diagnosing occipital seizures. The following entities have been described as variants of migraine aura, although the actual relationship with migraine has been criticized for some of them.

Prolonged and persistent aura

In migraine, visual auras can last longer than the classic 60 minutes that is defined by the International Classification of Headache Disorders.^{21, 22} In one diary study, 26.4% of patients had a visual aura, a sensory aura, or speech problems that lasted longer than 60 minutes.²² This is often referred to as “prolonged aura”. However, visual auras lasting longer than 2 hours are considered rare and require additional investigation since they can be associated with cerebral infarction. The term “migrainous infarction” is used for these cases, but only if the aura is typical of previous auras, there are imaging signs of ischemic infarction in the relevant area and other causes of stroke are ruled out.¹ Most cases of migrainous infarction are of cortical origin, suggesting that CSD could play a role; however, this could be confounding by indication since cortical infarcts are more likely to be classified as migrainous whereas subcortical infarcts may be attributed to a different cause.²³⁻²⁵ There is still debate on whether increased prevalence of patent foramen ovale in patients with migraine could play a role as well.^{23, 26}

If infarction and other causes of binocular visual disturbances are excluded and aura symptoms last longer than 1 week, the term “persistent aura without infarction” is used.¹ This is very rare. Symptoms can last months to years. Evidence on treatment is limited, lamotrigine is recommended on the basis of case series²⁷, and in one randomized controlled trial intranasal use of ketamine in patients with prolonged auras limited the aura severity but not the duration.²⁸

Migraine aura status

Some patients with migraine with aura may experience a sudden and large increase in the frequency of their auras, typically without headache. If at least three auras occur over a period of 3 days, the term “migraine aura status” is used.¹ However, this diagnosis requires that secondary causes, including occipital infarction, arterial dissection, reversible cerebral vasoconstriction syndrome, and posterior reversible encephalopathy syndrome, be excluded.^{1, 29} Retrospective studies indicate that a migraine aura status is rare.^{30, 31} Aura frequency can spontaneously normalize within a few weeks, but acetazolamide³² or valproate³¹ could aid in this process and prevent new episodes, although evidence is limited to case reports.

Retinal migraine

The relevance of “retinal migraine” is still debated and unfortunately the term has been misused to describe visual auras, although these are binocular and homonymous and therefore of cortical origin. The term “retinal migraine” is reserved for monocular, fully reversible visual symptoms with at least two of the following criteria: the visual symptoms spread gradually during at least 5 minutes, last between 5 and 60 minutes, and are accompanied or followed within 60 minutes by headache.¹ Importantly, secondary causes of monocular visual disturbances should be excluded. Critics of retinal migraine argue that symptoms are not monocular in patients with this diagnosis but binocular and that patients were not properly instructed to discriminate between monocular and binocular symptoms.³³ Nonetheless, cases have been reported of recurrent, transient monocular visual disturbances followed by migraine headache in patients who were clearly instructed.³³ Proponents additionally argue that CSD can occur in the retina, although these studies are still limited to *in vitro* models.³⁴

Ophthalmoplegic migraine

Some patients with migraine—in particular, children with migraine—reported transient double vision after a migraine attack. This ophthalmoplegia involved mostly the third cranial nerve. Therefore, the term “ophthalmoplegic migraine” was introduced. A prerequisite is that the ophthalmoplegia is preceded by a “migraine-like” headache in the prior four days. However, a literature review of published cases showed that one third of cases did not have a headache fulfilling migraine criteria.³⁵ Furthermore, the time between the headache and the ophthalmoplegia could be as long as 14 days and there was often focal enhancement of the third cranial nerve on magnetic resonance imaging. It was therefore re-classified as “recurrent painful ophthalmoplegic neuropathy”, and demyelination was suggested to play a role.^{1,35}

Photophobia

One of the main discriminating symptoms between migraine headache and other headache disorders is photophobia accompanying the headache, often occurring simultaneously with phonophobia.¹ Patients often report that the migraine headache is worsened by the presence of light and that they have to lie in the dark. Therefore, photophobia is classically viewed as an ictal symptom. However, studies focusing on the premonitory phase—most often defined as the 48 hours before the migraine attack starts—found that up to 49% of patients already experienced photophobia before the headache developed.³⁶ Furthermore, patients report that they have light aversion on days not preceding or following a migraine attack.³⁸ There is increasing evidence for this hypersensitivity to light. Interictally, patients with migraine have a lower light discomfort threshold than controls.³⁹ Additionally, many of them find patterns with high contrast more discomforting to look at.^{38, 39} This is supported by visual hyperexcitability studies using visual adaptation

techniques⁴⁰, visual evoked potentials⁴¹, and positron emission tomography (PET) brain imaging⁴² in patients with interictal migraine. Interestingly, migraine-with-aura patients reported more discomfort than migraine-without-aura patients, suggesting that visual hyperexcitability could play a more prominent role in the former.³⁹ This is in line with the hypothesis that migraine-with-aura patients have a lower threshold to experience a CSD. Although light stimulates nociceptive trigeminal neurons⁴³, it is thought that central processes involving thalamus and visual cortex have a more important role.⁴⁴ There is also recent evidence from longitudinal studies that visual sensitivity already increases in the days preceding a migraine attack.^{45,46} Although these discoveries are promising, they have not led to therapeutic options for photophobia.

Palinopsia

Palinopsia is derived from the Greek words *palin* (again) and *opsis* (vision) and is used to describe perseveration of visual images. This can be experienced as seeing an afterimage of an object (after staring at an object and looking away) or as a series of images when an object is moving (Figure 2).⁴⁷ Especially the former can be a normal physiological phenomenon when the stimulus was bright or there was a high contrast, and it results mostly in a negative afterimage: the afterimage is in complementary color. A positive afterimage, which has colors similar to those of the original image, is generally not considered physiological, although there is no strict cutoff in terms of frequency, duration, or other characteristics.⁴⁷ There is evidence that patients with migraine are more prone to palinopsia, although the number of studies is limited and methods differ^{45, 48, 49}, complicating estimates on the prevalence of this symptom. In palinopsia, as in photophobia, it is thought that a central origin in the lateral geniculate nucleus of the posterior thalamus or visual cortex plays a role. Possibly altered sensory processing leading to palinopsia occurs primarily in the days preceding a migraine attack.⁴⁵

Figure 2. Example of palinopsia



Legend: An example of a moving object (the hand is moving from left to right) with perseverance of multiple images is shown.

Visual snow

Visual snow is characterized by the continuous presence of countless small dots in the entire visual field (Figure 3).⁵⁰ Patients often describe it as “TV static from a detuned analogue television” since the dots are flickering on and off.⁵⁰ Although the severity of the snow can vary during the day, symptoms are never fully absent. Visual snow was not considered a separate entity until 2014.⁵⁰ Earlier reports often referred to the snow as a form of “persistent migraine aura”, possibly because many patients have a history of migraine with aura.^{27, 51-55} However, in visual snow, the classic migraine features such as scintillating scotomas and fortification spectra are absent.^{1, 50, 54} Furthermore, persistent migraine auras often start unilaterally and expand whereas patients with visual snow generally report that it started in the entire visual field and there was no spatial expansion.⁵⁰

Little is known about the epidemiology of visual snow.^{50, 56} Age of onset is often in the early twenties. In visual snow, in contrast to migraine, current data do not show an increased prevalence in females. Visual snow seems to be related to migraine: two case series found that between 47% and 59% had a history of migraine and that the prevalence of migraine with aura was relatively high compared with that of migraine without aura.^{50, 56} Furthermore, patients with migraine sometimes also report seeing visual snow, albeit transient and not continuous. In a prospective diary study, 8% of patients with migraine reported visual snow during their visual aura but not outside the aura.⁵

Figure 3. Example of visual snow



Legend: Patients with visual snow observe tiny dots in the entire visual field. The dots often resemble the “static” from a detuned analogue television because the dots “flicker on and off”. Classically, the dots are black/gray on a white background and white on a black background, but colors may vary.

A diagnosis of visual snow is made after exclusion of secondary causes of pan-field visual disturbances, such as lesions in the visual pathways and retina. Nevertheless, ophthalmic and neurological examinations in patients with visual snow are generally normal.⁵⁰ Most patients report additional visual symptoms: palinopsia, enhanced entopic phenomena (excessive floaters or blue field entoptic phenomena and spontaneous photopsia), photophobia, and nyctalopia. Therefore, it was proposed that visual snow is part of a clinical syndrome.⁵⁰ The syndrome criteria were proposed for research purposes and have no current clinical consequence for diagnosis or prognosis. Visual snow has also been reported as a persistent visual effect after intake of illicit hallucinogenic drugs such as LSD and ecstasy.⁵⁷ However, since there are patients with visual snow who never used hallucinogenic drugs⁵⁰ and since visual snow is also reported in children⁵⁸, it seems that hallucinogenic drug use is not the only potential risk factor.

It is hypothesized that cortical hyperexcitability plays a role in visual snow as well. Theoretically, the visual disturbances can also be localized to bilateral retinal pathology; however, this seems unlikely since ophthalmological examinations and electroretinograms are generally normal in patients with visual snow.⁵⁰ Therefore, visual snow is generally considered a cortical problem. Indeed, there is some evidence that cortical excitability parameters are increased in patients with visual snow and without comorbid migraine. This has been tested by using visual tasks⁵⁹ and visual-evoked potentials⁶⁰, but findings still have to be replicated in larger studies. One study using [¹⁸F]-2-fluoro-2-deoxy-D-glucose PET showed hypermetabolism in the lingual gyrus, an area that modulates visual processing, in visual snow patients compared with healthy controls.⁶¹ The same area was shown to be involved in previous migraine studies on photophobia.^{42, 62} However, because 14 out of 17 patients with visual snow also had comorbid migraine, it remains unknown whether this hypermetabolism is specific for visual snow.⁶¹ Treatment of visual snow is limited to case reports and expert opinion. Lamotrigine may sometimes help.^{63, 64}

Conclusions

The visual aura is the most typical form of visual disturbances in migraine but there are several other visual symptoms that people with migraine report. In this review, we have given a short clinical overview of these symptoms and what is known about the relationship with migraine pathophysiology. Although there are currently no specific therapeutic options focusing on visual symptoms, recent studies have begun to unravel some of the mechanisms that are involved.

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