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# Review Article

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## Persistent and Repetitive Visual Disturbances in Migraine: A Review

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Visual disturbances in migraineurs, such as visual aura, are typically episodic, that is, associated with the headache attack, and overlaid by head pain and other symptoms that impact the patient. In some patients, however, visual symptoms are dominant due to frequency (migraine aura status), duration (persistent migraine aura and other persistent positive visual phenomena), or complexity (visual snow syndrome). These syndromes are more rare and challenging to classify in clinical practice resulting in a lack of systematic studies on pathophysiology and treatment. We aim at describing clinical features and pathophysiological concepts of typical migraine aura with a focus on cortical spreading depression and differentiation from non-typical migraine aura. Additionally, we discuss nomenclature and the specifics of migraine aura status, persistent migraine aura, persistent positive visual phenomena, visual snow, and other migrainous visual disturbances. The term migraine with prolonged aura might be a useful bridge between typical aura and persistent aura. Further studies would be necessary to assess whether a return of the classification category eventually helps diagnosing or treating patients more effectively. A practical approach is presented to help the treating physician to assign the correct diagnosis and to choose a medication for treatment that has been successful in case reports of these rare but disabling conditions.

**Key words:** migraine aura, migraine aura status, cortical spreading depression, persistent migraine aura, visual snow, prolonged migraine aura

**Abbreviations:** BOLD blood oxygenation level dependent, CSD cortical spreading depression, ICHD International Classification of Headache Disorders, VS visual snow

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### INTRODUCTION

Migraine is characterized by recurrent episodes of headache with specific features.<sup>1</sup> It is well known that migraine is associated with visual symptoms.

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Some of them are useful in making a diagnosis (photophobia), others enable sorting in to subgroups, notably migraine with aura.

The International Classification of Headache Disorders (ICHD) defines aura as reversible, focal neurological symptoms in association (prior or during) with – or even independent from – a migrainous headache that typically lasts less than 60 minutes.<sup>1</sup> In our own clinical experience, most visual symptoms of migraine patients can be dealt with using such a general approach since visual symptoms are short-lasting and overshadowed by the severity of headache and other associated symptoms such as nausea or movement sensitivity. However, a small proportion of patients are predominantly affected by visual symptoms that can be prolonged or even persistent. Recently, several studies have addressed patients with persistent visual symptoms in migraine mainly from a phenotypical or pathophysiological perspective with scarce data on treatment options.<sup>2-7</sup>

Here, we review the current literature on the severe forms of migraine aura<sup>1</sup> – including migraine aura status, prolonged and persistent migraine aura – as well as visual snow,<sup>5</sup> a condition that often occurs with comorbid migraine with aura and consists of a continuous TV-snow like visual disturbance in the entire visual field that comes along with persistent palinopsia, photophobia, impaired night vision as well as excessive floaters, and other entoptic phenomena. First, we discuss the hallmarks of typical migraine aura from a clinical and pathophysiological perspective. Second, we introduce the different temporal courses of visual aura (migraine aura status, prolonged aura, and persistent aura) with clinical data on treatment and prognosis. Third, the phenotype of visual snow syndrome will be described in detail and distinguished from persistent migraine aura. We finally aim at offering a practical approach to the clinician who sees patients with persistent visual problems allowing a correct diagnosis and some first treatment options. However, when not successful, patients should not be dismissed as malingerers but should be sent to headache centers that might offer research options to increase our understanding by offering systematic studies on these rare conditions.

## METHODS

In September 2015, a literature search in PubMed was performed using the key words “migraine aura,” “migraine with aura” combined with “visual” and words indicating information on the temporal course: “duration,” “persistent,” “prolonged,” and “status.” Further key words were “visual snow” and “static.” Further, articles from the reference list of relevant articles were screened, and articles known to be relevant by the authors were considered. For migraine aura status, persistent or prolonged migraine aura and visual snow, case series or smaller studies were selected when describing symptoms, time course, or treatment. For episodic migraine aura, we aimed at describing the typical time course and therefore excluded single case reports or smaller case series. Further, we excluded hemiplegic migraine, migraine with brainstem aura, and retinal migraine.<sup>1</sup>

A limitation of this review is that it presents mainly case series of rare conditions thus not allowing to differentiate between natural course, placebo, and the true efficacy of treatment.

## EPISODIC VISUAL DISTURBANCES IN MIGRAINE

**Typical Migraine Aura.**—Aura derives from the ancient Greek *αἴρα*, meaning “breeze, soft wind.” Traditionally, it has been used for describing a distinct atmosphere or quality associated with something. For migraine, perceptions or symptoms registered in association, typically prior, to the headache itself could be sensed as the “atmosphere” around the most striking symptom. Based on this, it has been recognized for decades that the headache phase divides the entire migraine attack into 3 distinct phases, the most striking headache phase, the preceding prodromal phase, which includes both the premonitory and, in those who get it, the aura phase, and the solely headache-free postdromal phase.<sup>8</sup> When viewed from a distant perspective, the broad Greek meaning of “breeze” summarizes probably all abnormalities realized by patients before the beginning of head pain, although the term has evolved to mean much less. A reasonable division that will be

used in the following paragraphs is the distinction between premonitory symptoms, typical migraine aura and other symptoms.

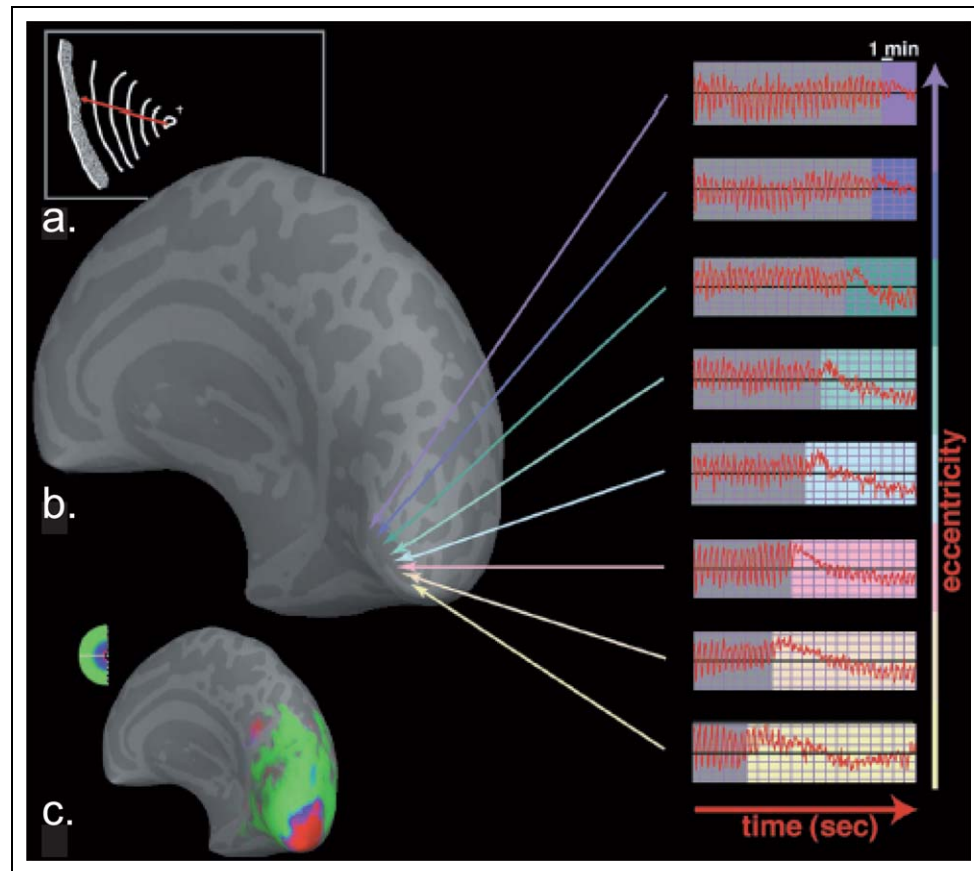
Most patients can predict the onset of their migraine headache.<sup>9</sup> However, it is unlikely that patients therefore suffer from migraine with aura. It is much more likely that patients have some premonitory symptoms, which are present in nearly 80% of patients.<sup>9,10</sup> Despite the recognition of these symptoms over some decades, little is known about the pathophysiology of the earliest phase of the migraine attack. Consistent with the symptoms experienced by patients, such as tiredness, yawning, and thirst, functional neuroimaging has revealed hyperperfusion of the hypothalamus and periaqueductal gray during the premonitory phase suggesting diencephalic and/or mesencephalic origin.<sup>11</sup>

In contrast, typical migraine aura is striking in its clinical presentation and has been subject to continuing efforts in respect of clinical phenotyping and pathophysiological research. The International Classification of Headache Disorders (beta version of the third edition, ICHD-3-beta) summarizes: Typical aura consists of “visual and/or sensory and/or speech/language symptoms . . . and is characterized by gradual development, duration of each symptom no longer than 1 hour, a mix of positive and negative features, and complete reversibility.”<sup>1</sup> In other words, these criteria require highly specific values of the following parameters: (i) neurological symptoms affecting vision, sensory, and/or language, (ii) dynamics involving development (spreading, succession) and duration (5–60 min), (iii) unilaterality, and (iv) association with headache. Importantly, as not all polythetic criteria are required, yet the mention of each one offers its face-valid importance to clinicians and illustrates an important teaching and clinical practice issue of the use of the criteria.

*Typical Migraine Aura and Cortical Spreading Depression.*—One of the main features, which differentiates typical visual aura from other transient neurological conditions such as transient ischemic attack or an epileptic seizure, is the slow progression of symptoms. This character is unique to migraine aura and might be important to

understand the basis of migraine aura pathophysiology. Liveing suggested in 1873 a “nerve storm” was responsible for the symptoms.<sup>12</sup> Lashley was able to map his aura retinotopically and concluded that the symptomatology reflected a cortical process progressing with a speed of 3 mm/minute across the primary visual cortex.<sup>13</sup> In 1944, the Brazilian neurophysiologist Leão identified a wave of inhibition in the electrocorticogram of rabbits spreading at a rate of 2–3 mm/min centrifugally from an electrode of stimulation.<sup>14</sup> He called this phenomenon cortical spreading depression (CSD) and commented on its similarity to migraine aura.<sup>15</sup> Apart from one short note by Milner in 1959 on a possible correlation between the scotomas of migraine aura and CSD of Leão,<sup>16</sup> no attention was given to this observation, likely due to the prevailing hypothesis that migraine aura was caused by a vasospasm and cortical ischemia. In 1981, however, Olesen et al demonstrated a wave of oligemia during clinical aura starting from the occipital area progressing rostrally<sup>17</sup> at a velocity of about 2 mm/min irrespective of arterial territories.<sup>18</sup> This was inconsistent with an ischemic hypothesis and suggested that aura is primarily a neuronal event that is accompanied by vascular changes. In a seminal work, Hadjikhani et al were able to trigger typical visual migraine aura by exercise and demonstrated in functional MRI a change of blood oxygen level dependent (BOLD)-response to checkerboard-pattern stimulation over time consisting of a reduction of amplitude and an initial increase followed by a decrease (depression) of mean BOLD signal.<sup>19</sup> Importantly, when looking at the time course of the migraine aura, this pattern progressed over the occipital cortex from posterior to rostral in congruence with the patient’s experience (from the center of the visual field centrifugally) suggesting a spreading depression of BOLD response (Fig. 1). The velocity of this spread was 3.5 mm/min similar to the CSD from Leão,<sup>14</sup> suggesting that indeed typical migraine aura is a consequence of CSD also in human.

*Typical Migraine Aura and Silent Areas of Cortex.*—Interestingly, the cortical area that first depicted the pattern of depressed BOLD response



**Fig. 1.**—Cortical spreading depression has been first identified in the invasive electrocorticogram of rabbits by Leao.<sup>14</sup> After stimulation, the electrocorticogram flattens. This “depression” moves centrifugally from the stimulation electrode (“spreading”) at a velocity of 2–3 mm/min with subsequent recovery after about 10 min. Such behavior has been associated with typical visual migraine aura in human that starts in the center of the visual field and progresses centrifugally as shown in the insert of the figure (a), modified after Hadjikhani et al.<sup>19</sup> (Copyright (2001) National Academy of Sciences, United States). The authors have used functional MRI assessing the BOLD-response to checkerboard stimulation during typical migraine aura and found a “depression” of the amplitude “spreading” over the occipital cortex (b) in a retinotopic manner (c) suggesting that cortical spreading depression can occur in migraineurs and might be the correlate of migraine aura. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

to checkerboard visual stimulation was outside the striate cortex in area V3a, which belongs to Bordmann area BA19 in respect of microstructure.<sup>19</sup> This suggests a distant origin of CSD that gets symptomatic no earlier than when reaching an eloquent cortical region, such as the primary visual cortex. This is supported by a work from Hansen et al,<sup>20</sup> who analyzed more than 1000 visual auras of an individual patient over almost 18 years. The most frequent time courses of the visual symptoms were consistent with the classic visual aura starting in the center of the visual field and then spreading centrifugally in one hemifield over about 30–60

min.<sup>20</sup> However, a substantial proportion of auras were different, either starting from the periphery or disappearing from the visual field and then reappearing at a distant location.<sup>20</sup> This is important since it suggests that (i) aura can be initiated at different locations in the occipital cortex or even outside the visual cortex and (ii) CSD can “travel” through “silent areas” when symptoms disappear by exiting the visual field and reappear by reentering. Despite these intra-individual variations, this work further underlines that many characteristics of visual auras remain stable and that CSD is an excellent model mechanism of the symptomatology. Another

clinical aspect that could allow us to better understand the different behavior of CSD is the study of the succession of aura symptoms. Two different aura symptoms, such as visual and sensory might reflect the involvement of different brain areas, such as the visual and sensory cortex, which may start sometimes simultaneously and, in other cases, in succession.<sup>21</sup> In the latter case, the textbook explanation is that CSD spreads gradually from visual to sensory areas,<sup>22</sup> whereas in the first case a multifocal CSD might exist or a single CSD originates in a silent area of the brain that later on involves 2 eloquent areas at the same time.

*Typical Migraine Aura Without Headache.*—Not all typical migraine aura episodes are followed by or associated with migraine headache. In a sample of 4000 subjects, Russell and Olesen<sup>23</sup> identified 163 subjects with migraine with aura, of which 62 (38% of migraine with aura) also had typical migraine aura without headache with 7 having exclusively aura without headache (4% of migraine with aura and 0.2% of all). This illustrates the close link between the aura and head pain generation.<sup>24,25</sup> Nevertheless, not all patients with aura developed headache suggesting that both are still separate phenomena. This is strongly supported by the discrepancy of animal studies and clinical studies on migraine prevention: phenytoin,<sup>26</sup> carbamazepine,<sup>27</sup> and ketamine<sup>28</sup> are able to block CSD in animal models without substantial effect on migraine prevention in human.<sup>29,30</sup> Lamotrigine is effective in preventing migraine with aura<sup>31-33</sup> without actually affecting migraine without aura.<sup>33,34</sup> Such differential effect on aura in comparison to migraine, that is, headache, prophylaxis is supported by Bogdanov et al,<sup>35</sup> who demonstrated a marked effect of lamotrigine on CSD, whereas the migraine/headache prophylactic medication valproic acid was clearly less effective on CSD. Lamotrigine thus might be quite specific for aura but not headache prevention.

**Non-Typical Migraine Aura.**—The variability of visual symptoms in migraine is considerable,<sup>23,36-42</sup> and several possible variables could generate these symptoms as a consequence of CSD: Some have been studied, such as different characteristics within

a single visual aura<sup>39,40</sup> or duration and succession of each symptom as described by Hansen et al<sup>20</sup>; others are hypothetical and still need to be assessed systematically, such as color of visual disturbances (for positive phenomena), frequency of flickering (for intermittent phenomena), or shape/location in the visual field. All this variability might be linked to different behavior of CSD or to different location in the (supplementary) visual cortex.

The question remains about the classification of the remaining visual symptoms that might occur prior to, or early on during, migraine attacks but do not reflect premonitory symptoms nor are consistent with clear CSD. Are these CSD in “silent” areas or are these fundamentally different neuronal mechanisms? For instance, it is commonly agreed that a fortification spectrum that may gradually spread right or left in a laterally convex shape is a visual aura. In contrast, not everybody would agree that blurred vision or vision “like looking through heat waves or water” involving the entire visual field is migraine aura in the sense of CSD. Such symptoms have been reported as migraine aura in different studies<sup>38-40</sup> and reports.<sup>43</sup> Moreover “blurred/foggy vision” was considered only when associated with other types of visual illusions, and ended up to be the most common visual symptom.<sup>39</sup>

As a clinician, it might be helpful to identify evidence by accessing information on the symptoms occurring together with the visual symptom in dispute: (i) Does the symptom occur in the same attack with other typical visual aura symptoms or does it occur only independently? (ii) Are the symptoms experienced solely by patients with a typical migraine aura biology? (iii) Does the visual symptom share some properties of typical aura phenomenology, such as spreading, duration, location in the visual hemifield/both eyes or co-occurrence with other, clearer aura symptoms? Although a non-specific symptom, such as visual blurring, may have a different behavior (eg, being more frequently located in the entire visual field without spreading), it cannot be proven that it is not caused by CSD of otherwise “silent” cortical areas, nor can it be established to be due to a CSD-like

phenomenon. This is consistent with a hypothesis by Hansen et al that the transient transformation of visual aura from a curvilinear positive wavefront into a circular scotoma could have been due to a crossing of CSD from V1 to V2.<sup>20</sup> It can be argued that indistinct symptoms are best classified as such; we use the term – Other Visual Disturbance – to invite thought since classifying them all as Typical Aura is both not evidence based and leads to cessation of thinking about their pathophysiology. Assessing such non-classic symptoms using neuroimaging or neurophysiological studies might be necessary to understand whether the pathophysiology behind the variations of visual symptoms in migraines is similar to CSD. Since such studies typically require group-comparisons, exact clinical phenotyping of the individual symptom is necessary in the first place. Second, study groups need to be homogeneous in respect of the symptom without a priori assuming that all visual symptoms are aura and can be interspersed without impact on the study results.

In summary, there are congruent data from clinical and paraclinical findings that typical migraine aura is a result of CSD in the visual cortex. Similar data do not exist for other visual symptoms in migraine. Therefore, clinical practice and especially clinical studies should differentiate between typical migraine aura and other visual symptoms.

## TEMPORAL VARIATIONS OF MIGRAINE VISUAL AURA

According to ICHD-3-beta, typical migraine aura develops gradually over more than 5 min and lasts between 5 and 60 min. Now as polythetic criteria, the criteria do not set absolute limits, but do offer face validity issues. For example, there is current evidence that a substantial proportion of episodes otherwise fulfilling criteria for typical migraine aura deviate in respect of migraine aura duration: Taking into consideration the limitations mentioned above in respect of what should be called typical migraine aura as a consequence of CSD, a prospective study by Russell et al<sup>41</sup> reported that the visual disturbances of typical visual aura had an acute onset in 8 attacks out of 51

(16%). No other prospective studies confirmed this data while retrospective studies reported a rate ranging from 3%<sup>23</sup> to 21%.<sup>39</sup> Little is known on the exact duration of aura symptoms.<sup>44</sup> Viana et al focused on temporal aspects of migraine aura.<sup>21</sup> Results showed that symptoms lasted for more than 1 hour in a substantial proportion of auras (14%–21%). Twenty-six percent of patients had at least one aura (out of 3 recorded) with one symptom lasting longer than 1 hour.<sup>21</sup> Visual auras of duration longer than 1 hour are not uncommon, and the transition to more problematic time courses of migraine aura might be smooth.

ICHD-2<sup>45</sup> dispensed with the ICHD-1<sup>46</sup> term migraine with prolonged aura. Intra-individually, patients typically have auras of duration shorter than 60 min, but can also have longer durations. In one prospective study, 6 patients out of 54 patients with migraine with aura had 3 consecutive auras with at least one symptom lasting for longer than 1 hour, whereas 8 patients experienced aura duration for longer than 1 hour in only 1 attack out of 3.<sup>21</sup> In our opinion the term prolonged aura, while not required in a polythetic system, adds face validity to the classification. Whether a return to this previous term in the classification has clinical utility would be a matter of future research.

**Some Definitions.**—Typical migraine aura is common. In our own clinical experience, patients often present with a long history or even family history and have learned to cope with the occurrence of these visual symptoms, although some are more severely affected with consequences for everyday life, such as driving or career choice. Visual symptoms can further be the main problem (i) in the case of repetitive frequent episodes (migraine aura status), (ii) persistent visual aura, or (iii) persistent other visual symptoms (ie, different from previous visual auras). Such conditions appear to be rare, and only few case reports or case series have been published. Often, they pose substantial challenges to the patient and the treating physician. ICHD-3-beta defines the following temporal variations of migraine aura:

- i. Migraine aura status (ICHD-3-beta code A1.4.5) is listed in the appendix of ICHD-3-beta and

defined as the occurrence of at least 2 aura episodes per day on at least 3 consecutive days. For that, secondary forms have to be excluded, such as reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome and arterial dissection.<sup>1</sup>

- ii. Persistent visual aura without infarction (ICHD-3-beta code 1.4.2) is a visual aura – typical in nature for the patient – that lasts for longer than 1 week. Appropriate tests are able to exclude secondary causes, such as strokes or other structural abnormalities.<sup>1</sup>
- iii. In the current classification, there is no term for persistent visual symptoms in migraineurs that do not resemble the previous auras. Whether such symptoms can be included in (ii) persistent visual aura without infarction is currently unknown. In fact, the literature often does not clearly distinguish between both despite the striking clinical difference. As we will discuss below, we would recommend keeping persistent visual phenomena strictly separated from persistent migraine aura for reporting to appropriately approximate pathophysiology and treatment.

### **MIGRAINE AURA STATUS**

Among 8821 patients with migraine with or without aura, a retrospective study identified only 4 patients with migraine aura status (at least 2 attacks per day for at least 5 days), suggesting that this is a rare condition. All patients were female and had a history of migraine with aura. Mean duration of aura status was 4 weeks, 3 of these 4 patients had further episodes of aura status and 2 responded to treatment with lamotrigine,<sup>47</sup> although separating natural history must be challenging here. A history of migraine with aura seems to be prerequisite for this condition, but it remains unclear why some patients develop aura status when most patients do not. In one study, 2 patients had association with hyperhomocysteinemia and heterozygous mutation of the methylene tetrahydrofolate reductase-encoding gene with improvement after therapy with acetazolamide and folic acid.<sup>48</sup> Haan et al reported 7 patients with migraine aura status, of whom 3 were treated successfully with acetazolamide. Repetitive attempts to reduce medication

failed in the first weeks and migraine aura status recurrence was successfully controlled by restarting acetazolamide. Two patients were finally able to stop medication, suggesting that acetazolamide might suppress the symptoms without actually stopping the underlying pathophysiological process.<sup>49</sup> In the early description by Haas et al,<sup>50</sup> 2 patients were described with repetitive visual phenomena in homonymous visual fields. One patient had a colorful pinwheel-like visual phenomenon lasting several minutes that occurred several times per day over about 5 weeks with a marked decrease during treatment with aspirin and cyproheptadine. The other had a history of typical migraine aura consisting of a flashing C-shaped perception that moved centrifugally over about 20 min. In contrast to this, the patient had “migraine aura status” over about 2 weeks when he experienced concentric grey lines “like ripples in a pond” in the right visual field lasting several seconds and occurring about 100 times per day. Retrospectively, it might be open to discussion whether to call this “migraine aura status” since the events did not resemble previous auras and did not clearly reflect CSD what brings us back to the basic problem of what to call migraine aura as discussed above.

Due to the rarity of the condition, Joao et al have suggested loosening the criteria by requiring only 3 episodes in a maximum of 3 days.<sup>51</sup> In their own series, they identified 8 patients with ICHD-3-beta migraine aura status. By using their own criteria, they confirmed these subjects and 12 in addition, and both groups did not differ substantially from each other except for the female predominance in the non-ICHD-3-beta group. This more liberal approach might allow to study more cases in respect of diagnosis and therapy as concluded by the authors,<sup>51</sup> but it still remains unclear, if both groups actually have a different condition. From a research perspective, it might be best to confine on a few pure cases than on a large number of patients who have a diluted condition.

### **PERSISTENT MIGRAINE AURA WITHOUT INFARCTION AND PROLONGED AURA**

When migraine aura lasts longer than 1 week the term “persistent migraine aura” is applied<sup>1</sup>

provided there is no evidence of infarction in appropriate testing (ICHD-3-beta code 1.4.2). Importantly, there are several aspects that need to be considered: (i) patients have to have a previous history of migraine with aura, (ii) the persistent symptom should be typical for patient's previous auras, and (iii) the criterion of 1 week is based on expert opinion and requires confirmation in the future. Accordingly, patients with a history of migraine or even migraine with aura who have persistent visual phenomena that do *not* correspond to previous auras should *not* be given the diagnosis of persistent migraine aura. The literature has admitted persistent visual aura and what is now widely called visual snow,<sup>5</sup> which we will return to below.

Only case series or small studies have been published suggesting that this is a rare condition. In an early work, Liu et al presented 10 patients with migraine biology and persistent visual phenomena.<sup>52</sup> According to the temporal relation with migraine aura, the authors classified the complaints to being either definitely related to migraine (the persistent visual phenomenon started with migraine aura), probably related to migraine (history of migraine aura and headache during the beginning of the visual phenomenon), or possibly a migraine equivalent (no association with migraine aura or headache). Similar cases have been presented.<sup>53</sup> Wang et al have applied the visual aura rating scale, which assesses similarity to typical migraine aura properties as mentioned above (ie, unilaterality, zig-zag lines, scotoma, gradual involvement, but not duration of 5–60 min since inclusion criterion was persistent migraine aura),<sup>54</sup> on their own patients with persistent visual phenomena and 23 subjects from the literature. They found that the higher the similarity to typical visual aura the higher the likelihood of good outcome.<sup>7</sup> Further, the same group assessed visual cortex hyperexcitability in 6 migraineurs with persistent visual phenomena using visual-evoked magnetic field recording. Comparison to controls with episodic or chronic migraine with or without aura showed that potentiation was highest in patients with persistent visual phenomena. Within this group, potentiation was inversely correlated to disease duration.<sup>3</sup> This

suggests that, similar to the early clinical observation by Liu et al,<sup>52</sup> persistent visual phenomena in migraineurs might (i) differ from other migraine spectrum disorders *and* (ii) might represent different subtypes with different relation to migraine, pathophysiology and prognosis. Further, the reduction of potentiation might indicate that the mechanism of such condition “burns out” over time with albeit persisting symptoms. Belvis et al report a patient with history of migraine with brainstem aura who developed a persistent visual disturbance lasting 9 days. From the description, it remains unclear whether the condition developed from an aura typical for the patient, and the presentation (“white and bright particles falling in both visual fields”) differed substantially from previous auras (“bilateral and total amaurosis plus bilateral paresthesias”) retrospectively doubting the diagnosis of prolonged visual aura<sup>1,55</sup> or “visual snow phenomenon” when applying the appropriate criteria.<sup>5</sup> Bearing these limitations in mind, the authors found signal alterations in the occipital lobe using apparent water diffusion coefficient in the occipital lobe 4 days after the beginning of the symptoms that disappeared 3 days after returning clinically back to normal. Whether this method is useful for studying persistent/prolonged visual phenomena in migraine need to be determined in the future.

Jager et al<sup>4</sup> reported 4 migraineurs with persistent visual symptoms (one with likely visual snow, one seeing “heat waves” in the entire visual field, one having blotches of light in central vision, and one demonstrating an inward shunt of vision). A diagnosis of persistent migraine aura could not be fully established since a direct association with an episode of migraine aura has not been demonstrated for these patients. Patients were extensively studied in MRI using apparent water diffusion coefficient and perfusion studies. In contrast to Belvis,<sup>55</sup> no alterations could be demonstrated. Whether this is due to a difference in disease duration – Jager et al tested patients with symptoms for longer than 3 years<sup>4</sup> whereas Belvis et al tested within 1 week<sup>55</sup> – requires further research. Relja et al reported a patient with persistent visual aura (scintillating scotoma “like a chessboard” in the right visual field)



that occurred after a migraine aura typical for the patient. In SPECT with technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO) there was decreased blood perfusion left fronto-parieto-occipital and right occipital. Similarly, brain perfusion MRI 6 weeks after symptom onset revealed left hypoperfusion that resolved after symptoms improved about 5 months later.<sup>56</sup> Bereczki et al demonstrated a patient with history of visual, sensory, dysphasic, and motor aura who had persistent homonymous hemianopia right. Diffusion weighted imaging revealed purely cortical signal increase, first in the occipital lobe then shifting anteriorly to the temporoparietal cortex and finally disappearing together with a resolution of visual symptoms.<sup>57</sup> Similarly, Kim and Kwon demonstrated cerebral vasogenic edema, cortical hypoperfusion, and hypometabolism in the area corresponding to the symptoms.<sup>58</sup> In summary, electrophysiology, functional brain imaging, and diffusion weighted imaging of patients with persistent visual aura suggest some cortical dysfunction that might represent a correlate of cortical spreading depression, although there still is conflicting data, and the number of patients studied is very limited.

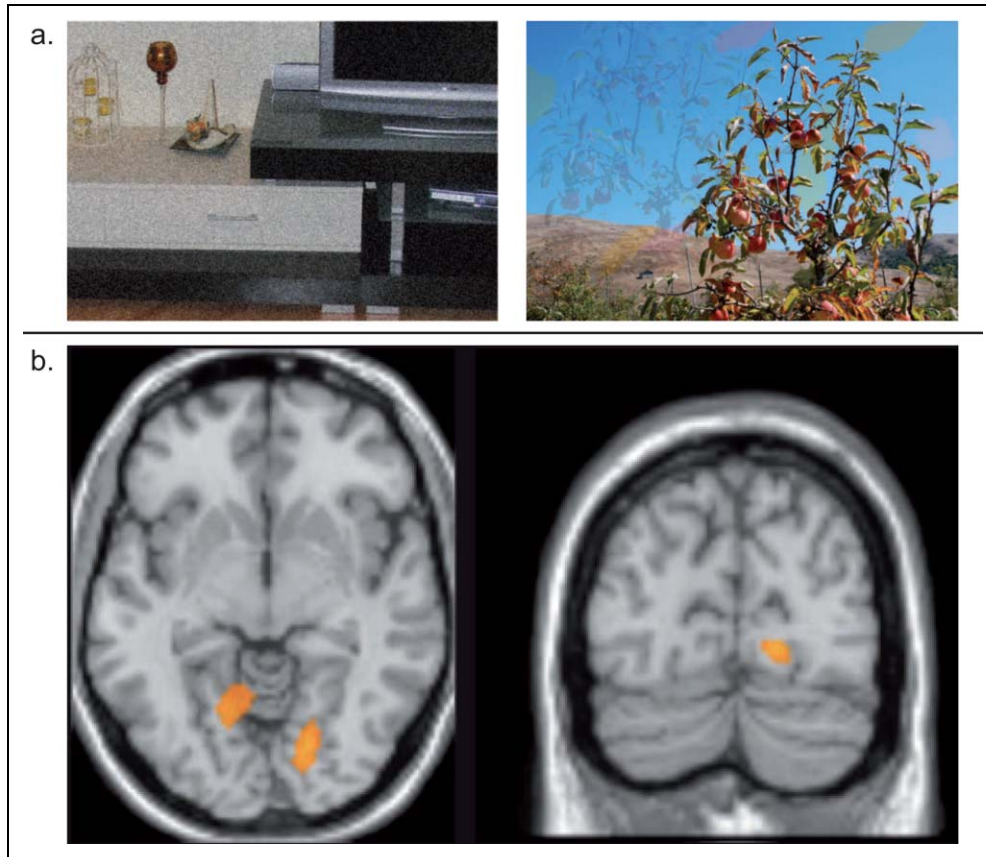
**Treatment Of Persistent Migraine Aura.**—In respect to treatment there are few data available owing to the rarity of the condition. Chen et al reported 2 patients with persistent visual phenomenon. One had coin-sized white spot in the left hemifield after an attack with migraine without aura; the other had stars persistently flickering in the right hemifield moving eccentrically. Both patients had hypoperfusion in technetium Tc99m-hexamethylpropyleneamine oxime (Tc99m-HMPAO) SPECT in the corresponding occipital cortex contralateral to the side of the visual field deficit. Importantly, both patients responded to treatment with lamotrigine.<sup>59</sup> A case series by Rothrock reported 2 patients who had persistent migraine aura for 2 months and 2 years, respectively, starting after aura episodes that were typical for the patient. Treatment with valproic acid 250 mg bid or 500 mg bid completely resolved the symptoms.<sup>60</sup> Two patients reported by Rozen<sup>61</sup> had prolonged visual aura for 7 days and 2 days that

responded to intravenous furosemide. Other patients were successfully treated with prochlorperazine and magnesium.<sup>62</sup> Kaube et al have investigated 25 mg ketamine nasal spray in patients with severe form of prolonged aura in familial hemiplegic migraine and could demonstrate a substantial reduction in duration and severity in 5 of 11 patients.<sup>30</sup> This effect could be only confirmed for a reduction of aura severity but not on aura duration in a study in 18 patients with prolonged aura by Afridi et al, who compared 25 mg intranasal ketamine to 2 mg intranasal midazolam.<sup>63</sup> Limited data therefore would indicate that valproic acid, lamotrigine, furosemide, or ketamine might be useful for the treatment of persistent and prolonged migraine aura.

### VISUAL SNOW (VS)

Patients with VS experience the view of a badly tuned analogue television (“TV-snow”), that is, uncountable tiny dots in the entire visual field flickering typically between black and white (Fig. 2a). Symptoms are continuous and present with eyes open and closed. Liu et al presented 3 patients (patient 6, 7, and 8) in group III (possibly a migraine equivalent) due to comorbid migraine without temporal relationship between the onset and headache or aura.<sup>52</sup> In contrast, Wang et al have ascribed a diagnosis of persistent visual aura to 2 subjects with “TV-snow”-like visual disturbance despite a visual aura rating scale score of 0.<sup>7,54</sup> Similarly, 2 VS patients were commingled with 4 subjects who had different complaints, and all 6 were tested as a group of “persistent visual aura” for visual cortex hyperexcitability by using visual-evoked magnetic field recording.<sup>3</sup> Interestingly, cortical hyperexcitability was inversely correlated with disease duration: patients with VS had symptoms for many years suggesting that VS behaved differently from the other visual disturbances in migraineurs, and thus both groups may not be intermixed for research.

Based on the records of 22 patients seen by one of us (PJG) and the results from an internet survey among patients with self-assessed VS, Schankin et al proposed preliminary criteria that were



**Fig. 2.**—Patients with visual snow syndrome suffer from a continuous TV-static-like visual disturbance in the entire visual field (a. left) and additional visual symptoms, such as palinopsia (a. right).<sup>5</sup> Hypermetabolism of the supplementary visual cortex (lingual gyrus in b.) has been demonstrated in these patients supporting an organic origin of the condition involving processing of visual input.<sup>6</sup> [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

prospectively tested in 142 patients of whom 78 had VS and unremarkable ophthalmological examination. Almost all patients (72% or 92%) had at least 3 of the following additional visual symptoms resulting in the proposal of diagnostic and research criteria (Table 1): palinopsia (trailing and afterimages), exaggerated entoptic phenomena (floaters, blue field entoptic phenomenon, spontaneous photopsia, self-light of the eye), photophobia, and nyctalopia (impaired night vision).

Symptoms were continuous, and 24% of patients reported having the condition as long as they could remember, whereas the remainder had disease onset at around 20 years. The clinical presentation of continuous presence in the entire visual field of visual symptoms without directed movement or zig-zag lines, but with additional visual symptoms, suggests that VS is part of a unique

clinical syndrome that does not resemble typical visual aura. Further, since only 11% of patients had a visual aura around the week of the beginning, VS has to be considered distinct from persistent visual aura. However, 59% of patients had comorbid migraine, and 27% had typical migraine aura suggesting an overlap of pathophysiological mechanisms.<sup>5</sup> In 120 patients with “visual snow syndrome,” comorbid migraine was significantly associated with the additional visual symptoms palinopsia, photopsia, photophobia, and nyctalopia as well as tinnitus.<sup>6</sup> Migraine biology therefore seems to aggravate the clinical syndrome, and VS patients with migraine might therefore volunteer for research more likely than those without. A recruitment bias resulting in a false-high prevalence of migraine in patients with VS is thus possible. A similar problem is unlikely for typical migraine

**Table 1.—Patients With Visual Snow Often Complain of Additional Visual Symptoms, Suggesting the Existence of a Syndrome**


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|    |  |
|----|--|
| A. | Visual snow: dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.   |
| B. | Presence of at least 2 additional visual symptoms of the 4 following categories:<br>i Palinopsia. At least one of the following: after images (different from retinal afterimages) or trailing of moving objects.<br>ii Enhanced entoptic phenomena. <sup>†</sup> At least one of the following: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia.<br>iii Photophobia<br>iv Nyctalopia (impaired night vision) |
| C. | Symptoms are not consistent with typical migraine visual aura ICHD-IIIb. <sup>1</sup>  |
| D. | Symptoms are not better explained by another disorder (especially normal eye exams, no previous intake of illicit drugs).  |

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The table depicts preliminary criteria for such visual snow syndrome, modified from Schankin et al.<sup>5</sup>

<sup>†</sup>Entoptic phenomena are visual symptoms that arise from structures of the visual system. They include photopsia (spontaneous flashes of light), floaters, blue field entoptic phenomenon (uncountable little grey/white/black dots or rings moving in a pulsatile manner over the visual field in both eyes when looking at homogeneous bright surfaces, such as the blue sky), or self-light of the eye (colored waves or clouds when closing the eyes in the dark).

aura, since there was no such association indicating a true pathophysiological overlap.

Functional brain imaging with [<sup>18</sup>F]FDG-PET in patients with VS syndrome (Table 1)<sup>5</sup> showed brain hypermetabolism in the supplementary visual cortex (bilateral lingual gyrus) of Brodmann area 19 (Fig. 2b), but not in the primary visual cortex. Visual snow thus seems to be a disorder of higher visual processing, and not of upstream visual input. This is consistent with patients having normal ophthalmological exam and normal visual evoked potentials.<sup>5</sup>

Importantly, the lingual gyrus might also be important for *adjusting* brightness of light perception. Denuelle et al<sup>64</sup> studied photophobia, which is a clinical hallmark of both migraine and “visual snow syndrome.” The authors identified the primary visual cortex as well as the lingual gyrus being more active when visual stimulation with low levels of light during migraine attacks was compared with identical stimulation in the interictal state.<sup>64</sup> Similarly, migraineurs with interictal photosensitivity have thicker cortex in the right lingual gyrus when compared with patients without such photophobia.<sup>65</sup> When taking into account that photophobia means that light of photon energy typically not able to illicit discomfort or pain is actually painful, the lingual gyrus might be important for *adjusting* brightness of light perception.

“Visual snow syndrome” is characterized by VS plus additional symptoms,<sup>5</sup> such as palinopsia, a failure of suppressing the just-seen,<sup>66</sup> enhanced entoptic phenomena (eg, floaters, blue field entoptic phenomenon) that actually represent visualization of the optic apparatus itself,<sup>67</sup> photophobia and impaired night vision. It is, therefore, conceivable that healthy subjects do not see these manifestations due to an *active suppression system* that might be located in the supplementary visual cortex. This suggests that the lingual gyrus might play an important role in this system.<sup>68</sup> Whether this area is of particular relevance for VS or only for one or more of the additional symptoms such as photophobia needs to be determined. In this respect it is important that [<sup>18</sup>F]FDG incubation occurred in the dark with eyes closed where patients only experienced VS and maybe some self-light of the eye, but not photophobia or palinopsia.<sup>6</sup>

The link between “visual snow syndrome” and the highly comorbid typical migraine aura might be sought in the microstructure of the cortex in the lingual gyrus, which belongs to Brodmann area 19. Hadjikhani et al have identified V3A as the region where earliest functional changes appear during typical migraine aura in functional MRI after visual stimulation,<sup>19</sup> supporting the view that one common pathophysiological concept might cause both conditions. In

the current literature, there are no studies characterizing a pure group of patients with VS on a functional or pharmacological level. One interesting case report by Unal-Chevik and Yildiz found potentiation in repetitive visual evoked potentials in one patient with VS that improved after treatment with lamotrigine in parallel to amelioration of VS.<sup>69</sup> Further, this particular patient depicted occipital bending from left to right. Such bending is not uncommon in subjects without VS,<sup>70</sup> and the unique finding of potentiation with positive response to lamotrigine needs to be prospectively replicated. Our limited understanding of this condition is further reflected in the poor response to treatment by migraine prophylactics or antiepileptic medication<sup>6,71,72</sup> despite the pathophysiological overlap with migraine aura and the evidence of cortical hyperexcitability.<sup>69</sup> Due to the lack of proper studies and only one case report showing some effect by lamotrigine,<sup>69</sup> proper studies of homogeneous patient groups using strict criteria<sup>5</sup> assessing pathophysiology and treatment response will hopefully lead the way to some alleviation of the distressing symptoms of affected individuals.

## **INTEGRATING THE VISUAL SYMPTOMS OF MIGRAINEURS**

Visual symptoms are frequent in migraine patients but often represent a minor problem when compared with the severity of head pain, nausea and movement sensitivity. A small subgroup of patients is predominantly affected by repetitive or persistent visual aura or the migraine-associated phenomenon VS. Approaching a patient with such symptoms in clinical routine is often difficult due to the rarity of the condition and the complexity of patient's history. The following approach has been useful in our clinical practice.

Our view is the patient's history typically reflects their true perception of what they see, and malingering or psychogenic causes are the exception when talking about visual symptoms in migraineurs. The history of "visual snow syndrome," which has often been dismissed as stress-related, attention-seeking, or simply "crazy," taught us that careful history-taking and impartial documentation of symptoms reported by patients over years<sup>2,5</sup> can help to

identify patterns of symptoms that result in the definition of a syndrome<sup>5</sup> and studies demonstrating a possible biological origin.<sup>6</sup> History taking should focus on headache including beginning, frequency and phenotype of current and previous headache attacks to establish (i) diagnosis of episodic or chronic migraine and (ii) the presence or absence of visual or non-visual auras. In this respect, the term "typical migraine aura" should be reserved for symptoms that are consistent with cortical spreading depression irrespective of the occurrence prior, together or independently from headache attacks. This should be demarcated from premonitory symptoms such as neck stiffness, photophobia, or concentration problems. With this preparatory work, establishing a diagnosis of migraine aura status or persistent visual aura seems straightforward.

One approach is to limit the diagnosis of persistent migraine aura to patients whose previous aura symptoms persist,<sup>1</sup> and not to those with an aura typical for the subject followed by completely different visual symptoms that then do not go away. These patients may have a persistent aura, with its typical features, however, one needs to be more careful about secondary causality. For visual symptoms that are neither aura nor visual snow, the term other migrainous visual disturbances seems to state what is known. Visual snow can be identified reliably by asking open questions about the view (i) in the dark with eyes open and on white, but not bright paper (TV-snow-like), (ii) of the blue sky (floaters, blue field entoptic phenomenon), (iii) with eyes closed (lava lamp-like self-light of the eye), (iv) of high contrast objects or moving objects (palinopsia) as well as (v) night vision, and (vii) photophobia. When the diagnosis is established, empiric treatment according to the cases published in the literature (Table 2) would be justified. Verapamil, which is often used in clinical practice to treat migraine with aura<sup>73</sup> and hemiplegic migraine,<sup>74,75</sup> would also be an option when other treatments fail. Table 2 further shows that patients with "visual snow syndrome" often have no response to various treatments, whereas the prognosis of the other forms of persistent visual symptoms in migraine seems to be somewhat better. Early referral to

Table 2.—Overview Over Literature on Persistent Visual Phenomena in Migraine and Migraine Aura Status

| Diagnosis   | Authors, Year                             | Number of Patients <sup>†</sup> | Successful Medication (Daily Dosage)  |
|---|---|---------------------------------|---|
| Migraine aura status  | Beltramone et al, 2014 <sup>47</sup>      | 4                               | Lamotrigine in 2 of 4   |
|   | Cupini et al, 2007 <sup>48</sup>          | 2                               | Acetazolamide in 2 of 2, folic acid in 1 of 2 in addition   |
|   | Haan et al, 2000 <sup>49</sup>            | 7                               | Acetazolamide (500–750 mg/d) in 3 of 3 tried  |
|   | Haas, 1982 <sup>50</sup>                  | 2                               | Aspirin 650 mg/d and cyproheptadine 12 mg in 1 of 2   |
| Persistent migraine aura without infarction                         | Liu et al, 1995 <sup>52</sup>             | 3 (1–3)                         | No response to medication, spontaneous resolution possible  |
|   | San-Juan and Zermeno, 2007 <sup>53</sup>  | 1                               | Possible response to nimodipine   |
|   | Wang et al, 2008 <sup>7</sup>             | 4 (3–6)                         | Propranolol, topiramate, and lamotrigine improved symptoms in 1 reported, lamotrigine, and topiramate improved symptoms in 1 reported |
|   | Relja et al, 2004 <sup>56</sup>           | 1                               | Lamotrigine (75 mg/d) was associated with slow improvement  |
|   | Kim and Kwon, 2015 <sup>58</sup>          | 1                               | Corticosteroids (500 mg/d, tapered)   |
| Persistent migraine aura without infarction and prolonged aura (PA) | Rothrock, 1997 <sup>60</sup>              | 2                               | Valproic acid (500 and 1000 mg/d)   |
|   | Rozen, 2000 <sup>61</sup>                 | 2 (1 PA)                        | Furosemide (20 mg i.v./d) in 2 of 2   |
| Prolonged aura  | Rozen, 2003 <sup>62</sup>                 | 2                               | Prochlorperazine (30 mg/d), magnesium sulfate (2 g/day)   |
|   | Kaube et al, 2000 <sup>30</sup>           | 11                              | Ketamine 25 mg intranasally in 5 of 11  |
|   | Afridi et al, 2013 <sup>63</sup>          | 18                              | Double-blind ketamine 25 mg vs midazolam 2 mg intranasally: reduction of severity in ketamine group, not duration                     |
| Other migrainous visual disturbances                                | Liu et al, 1995 <sup>52</sup>             | 4 (4–5, 9–10)                   | No significant response to medication   |
|   | Belvis et al, 2010 <sup>55</sup>          | 1                               | Spontaneous resolution  |
|   | Jager et al, 2005 <sup>4</sup>            | 3 (2–3)                         | No response to medication in 1 reported.  |
| Visual snow   | Chen et al, 2001 <sup>59</sup>            | 2                               | Lamotrigine (100 mg/d) in 2 of 2  |
|   | Liu et al, 1995 <sup>52</sup>             | 3 (6–8)                         | Nortriptyline and carbamazepine resolved palinopsia in 1 of 3; sertraline reduced symptoms by 50% in 1 of 3                           |
|   | Wang et al, 2008 <sup>7</sup>             | 2 (1–2)                         | No response to medication in 1 reported   |
|   | Jager et al, 2005 <sup>4</sup>            | 1 (1)                           | No response to medication in 1 reported   |
|   | Schankin et al, 2014 <sup>5</sup>         | 78                              | Individual response not listed. No complete resolution listed by any medication   |
|   | Schankin et al, 2014 <sup>6</sup>         | 17                              | Naproxen in 1 reported, no improvement by medication in 9 reported  |
|   | Unal-Cevik and Yildiz, 2015 <sup>69</sup> | 1                               | Lamotrigine (100 mg/d)  |
|   | Beyer and Gaul, 2015 <sup>71</sup>        | 2                               | No response to medication   |
|   | Simpson et al, 2013 <sup>72</sup>         | 1                               | No response to medication   |
|   | Bessero and Plant, 2014 <sup>2</sup>      | 20                              | No response to medication   |

Studies were selected based on the report of a detailed history of the visual disturbance to allow grouping into migraine aura status, persistent migraine aura without infarction or prolonged aura, visual snow, and other migrainous visual disturbances. In the medication column, only successful medication was listed for the purpose of clarity.

<sup>†</sup>Individual patients listed in parentheses.

headache centers where patients could be included in prospective studies would be the next step when such approach fails.

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