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REVIEW

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Aura phenomenon: a proposal for an etiology-based clinical classification

Umberto Pensato[1,2], Andrew M. Demchuk[3], Jens P. Dreier[4], Kevin C. Brennan[5], Simona Sacco[6*] and Michele Romoli[7]

Abstract

Background The term "aura" refers to a well-defined pattern of usually positive, progressive, and reversible neurological symptoms, with spreading depolarization as the underlying mechanism. While commonly associated with migraine, aura can also occur in other neurological disorders (i.e., cerebrovascular disorders). However, current terminology inadequately describes its different underlying clinical etiologies.

Main body We propose the following terminology and etiology-based clinical classification for the aura phenomenon: (i) *Migrainous Aura* (when the etiology is migraine), *(ii) Non-migrainous Aura* (when there is an alternative etiology), *(iii) Aura of uncertain clinical etiology* (when etiology is unclear), *and (iv) Migrainous Infarction* (a typical migrainous aura in a patient with migraine with aura associated with an infarction in a corresponding anatomical brain region).

Conclusion This nuanced classification aims to aid in the diagnostic evaluation and phenotyping of aura phenomenon, ultimately improving the diagnosis and management of the different associated neurological conditions. Moreover, it could promote effective communication and translational mechanistic research.

Keywords Migraine with aura, Migrainous infarction, Migrainous aura, Stroke, Cortical spreading depression

Background

Aura is a complex neurological phenomenon that may precede or accompany migraine headaches, presenting in approximately one-third of individuals with migraine [1–4]. The presence of aura in individuals with migraine reflects distinctive pathophysiological mechanisms and is associated with characteristic clinical manifestations and potential management implications. Accordingly, migraine is subclassified based on the presence or absence of aura, delineating two main subtypes: *migraine with aura* and *migraine without aura* [5, 6]. The aura phenomenon in migraine may present with a diverse spectrum of clinical characteristics, frequencies, and durations [7–9]. Positive visual symptoms are present in approximately 90% of individuals, yet somatosensory, language, or motor manifestations can also occur [7, 8, 10, 11]. Migraine headache attacks accompanied by

*Correspondence:
Simona Sacco
simona.sacco@univaq.it
[1]Department of Biomedical Sciences, Humanitas University, via Rita Levi Montalcini 4, Pieve Emanuele, Milan 20072, Italy
[2]IRCCS Humanitas Research Hospital, via Manzoni 56, Rozzano, Milan 20089, Italy
[3]Calgary Stroke Program, Depts of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada
[4]Center for Stroke Research, Charité University Medicine Berlin, Campus Charité Mitte, Charitéplatz 1, 10117 Berlin, Germany
[5]Department of Neurology, University of Utah, 383 Colorow Drive, Salt Lake City, UT 84108, USA
[6]Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy
[7]Department of Neuroscience, Bufalini Hospital, AUSL Romagna, Cesena, Italy

aura are typically less responsive to acute therapies [12]. Additionally, the presence of aura plays a significant role in guiding the decision-making of preventive medications and hormonal therapies in migraine individuals [6]. Compelling experimental evidence suggests that cortical spreading depolarization (SD) is the central pathogenic mechanism underlying the aura phenomenon [13–15]. SD is characterized by a slow, progressive depolarization across the contiguous brain cortex, culminating in a massive release of neurotransmitters and a transient hyperemia, followed by a mild, sustained hypoperfusion [15]. The resulting changes in brain activity are thought to account for the clinical manifestations of aura [16]. Additionally, some lines of experimental and clinical evidence support SD's putative role also in the genesis of migraine headaches themselves. Yet, the aura phenomenon can manifest concomitantly with a headache or even independently, further complicating its relationship with migraine [5, 7]. A critical aspect of migraine with aura lies in its association with an increased risk of ischemic stroke, particularly at a young age [17, 18]. The underlying mechanisms of this association remain incompletely understood [17]. Ischemic and hemorrhagic strokes are the two neurological disorders most strongly associated with SDs and SDs can be detected electrocorticographically in up to 70–90% of these patients in neurocritical care units [19, 20], arguably suggesting a potential pathophysiological connection.

The International Classification of Headache Disorders (ICHD) is the reference for diagnosing and classifying headache disorders. It has evolved over the years and continues to be updated as our understanding of headache disorders advances [21, 22]. The ICHD-3 provides clear criteria for diagnosing *migraine with aura* [5]. However, there is a lack of well-defined terminology and criteria to define and describe the aura phenomenon itself and auras that occur in clinical contexts beyond migraine. SD and aura-like symptoms have been consistently documented in various brain injuries, mainly cerebrovascular disorders [19].

Hereby, we advocate for a more nuanced terminology and propose an etiology-based clinical classification system for the aura phenomenon, as outlined in Table 1; Fig. 1, to highlight that not all aura phenomena are linked to migraine. We argue for a distinction between the clinical etiology (migraine vs. non-migraine) rather than the pathophysiological etiology (that is SD) of the aura phenomenon. Indeed, different clinical conditions might converge on the common pathway of SD, though, whether SD mechanisms are uniform or diverse across these conditions remains uncertain and is beyond the scope of this article. Furthermore, we draw parallels with the terminology used in epilepsy to strengthen our clinical reasoning, as detailed in Table 2. Finally, we provide exemplary case studies that highlight the improved clarity and communicative efficacy of adopting this novel terminological framework (Supplementary Materials).

Table 1 Glossary of revised aura terminology

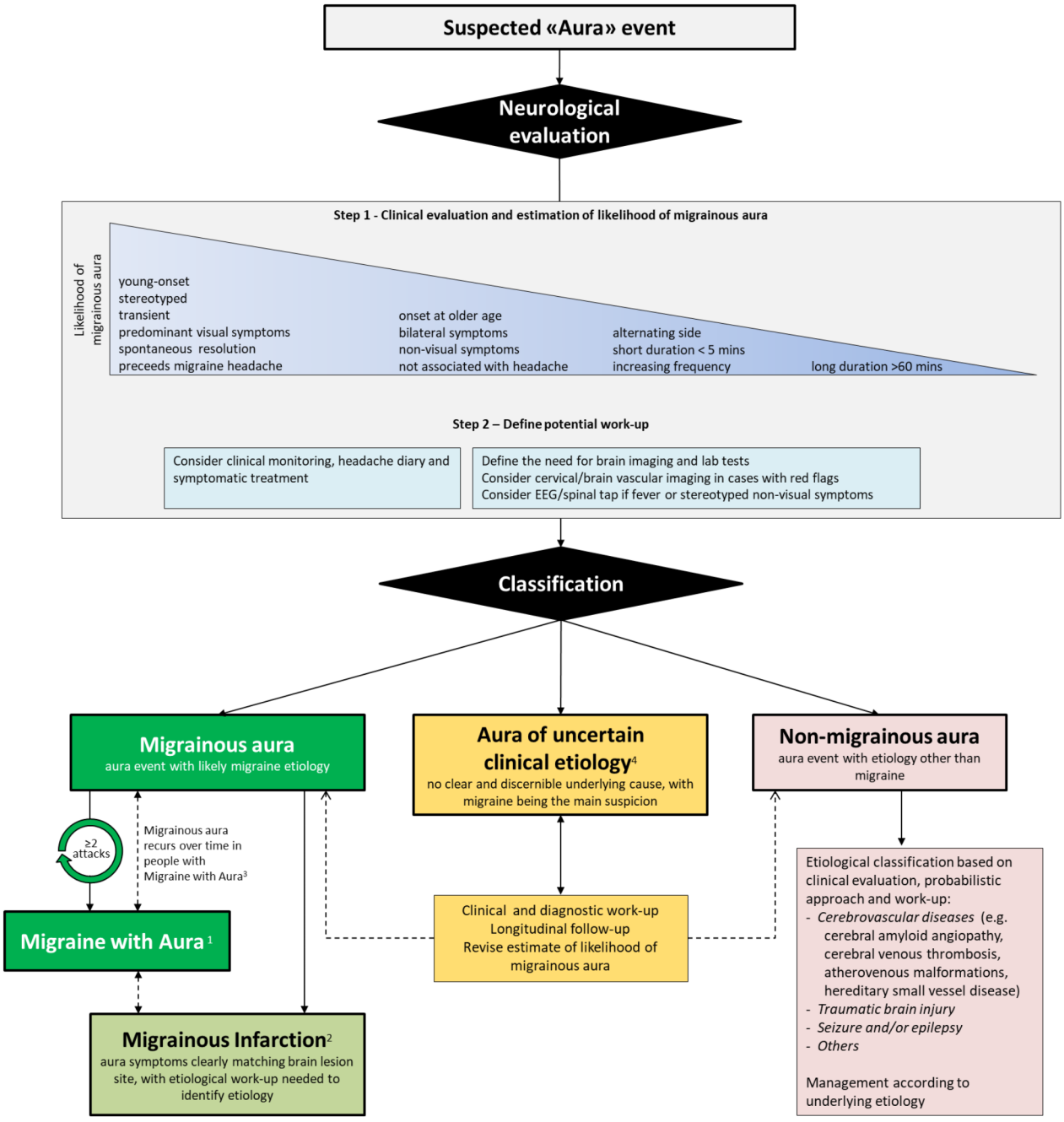
Migraine with Aura refers to the clinical condition characterized by repetitive migraine aura attacks as reported in the ICHD-3 diagnostic criteria[5].
Migraine with Aura attack refers to the multifaceted clinical attack of migraine with aura patients characterized by headache, migrainous aura, and other symptoms.
Aura refers to an episode characterized by the typical clinical features of the aura phenomenon.
Migrainous Aura defines an aura phenomenon whose underlying etiology is migraine
Non-migrainous aura defines an alternative etiology of aura. For instance "non-migrainous aura related to cerebral amyloid angiopathy".
Aura of uncertain etiology refers to an aura whose underlying etiology is still unclear.
Migrainous Infarction refers to a typical migrainous aura in a patient with migraine with aura associated with an infarction in a corresponding anatomical brain region, as defined in the ICHD-3rd edition[5].
Non-migrainous Infarction refers to ischemic stroke that presents with atypical or no aura in a subject with history of migraine

Search strategy and selection criteria

We reviewed the literature with a structured search strategy. We used the following terms with no language restrictions to search PubMed from starting date to December 31st, 2023, and we reviewed all titles: ((migraine with aura [MeSH] OR migrain* OR hemicrani* OR migraine with aura) AND aura [Tit/ab])) OR [aura [Tit/ab] AND (brain diseases [MeSH]). We then identified and screened 5960 titles. We used tags to identify relevant papers, including "Aura phenotype", "Aura risk factors", "Migrainous aura" and "non-migrainous aura", "systematic review", "aura burden", "brain infarction". We prioritized papers in the last ten years for this review article.

Migrainous aura

The current terminology surrounding migraine with aura is often ambiguous, making it difficult to clearly distinguish between (i) the aura phenomenon itself, (ii) the multifaceted migraine with aura attack – characterized by aura, headache, and other symptoms –, (iii) and the broader clinical disorder that predisposes to these attacks—"*migraine with aura*" [13]. Moreover, a substantial proportion of migraine patients may experience migraine headache with aura attacks, migraine headache without aura attacks, and aura without headache, leading to a notable dissociation between the frequency of headache attacks and aura episodes. As a result, it becomes challenging to describe with current terminology whether the aura phenomenon, the headache, or both are chronic/episodic or responsive/refractory to treatment.



1. According to ICHD-3 classification criteria: A. At least two attacks fulfilling criteria B and C; B. One or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal; C. At least three of the following six characteristics: at least one aura symptom spreads gradually over ≥5 minutes, two or more aura symptoms occur in succession, each individual aura symptom lasts 5-60 minutes, at least one aura symptom is unilateral, at least one aura symptom is positive, the aura is accompanied, or followed within 60 minutes, by headache.
2. According to ICHD-3 classification criteria: A migraine attack occurring in a patient with *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes; Neuroimaging demonstrates ischaemic infarction in a relevant area, matching symptoms.
3. In people with Migraine with Aura, events of aura can recur, and according to clinical evaluation can be defined as Migrainous Aura. Whenever atypical features occur, clinician may consider Non-migrainous aura diagnosis and etiological work-up
4. Aura of uncertain etiology can be suspected in the presence of red flags for the event of aura (see table 3), and/or in case of aura events not fulfilling ICHD-3 criteria for migraine with aura, including isolated aura («aura sine emicrania»).

Fig. 1 Diagnostic algorithm for the clinical etiological classification of aura

Table 2 Terminology parallelism between seizure and aura

Clinical manifestation	Seizure	Aura phenomenon
Pathogenetic mechanisms	Abnormal/excessive or synchronous neuronal activity in the brain with secondary transient impairing of neuronal function	Spreading depolarization-induced brief burst of epileptoid activity followed by spreading depression
First differential in work-up	Non-provoked vs. provoked seizure	Migrainous vs. non-migrainous aura
Predisposing conditions	Epilepsy syndrome vs. acquired epilepsy	Migraine with aura and genetic aura syndromes vs. other neurological conditions
Repeating episodes	Epileptic seizures, and epilepsy diagnosis (according to ILAE guidelines)	Migrainous aura, and Migraine with Aura diagnosis (according to ICHD-3)

For instance, several randomized clinical trials have explored the potential impact of patent foramen ovale (PFO) closure on migraine with and without aura, yielding conflicting results [23–25]. While these trials failed to establish benefit in their primary outcome, meta-analyses revealed a discernible improvement in the frequency of migraine aura attacks or in the subgroup of patients experiencing predominantly aura-accompanied attacks [26, 27]. The lack of standardized terminology to distinguish between migraine attacks without aura and aura episodes with or without headache may have partially hampered the trial design and interpretation of results. Considering the frequency of aura episodes, regardless of their association with headache, as an inclusion criterion and clinical outcome might elucidate the potential "anti-aura" effect of some medication or interventions.

The term "migraine aura" has frequently been used to describe the occurrence of aura phenomenon in migraineurs, yet it lacks an official recognition and definition in the ICHD-3. Moreover, its linguistic similarity to both "*migraine with aura*" and "*migraine without aura*" complicates literature searches on the topic. Therefore, a redefined terminology to address these research and clinical limitations is warranted. Considering this, we propose the term "*Migrainous Aura*" for all cases of aura occurring in the context of a typical migraine attack. This term not only acknowledges the fundamental association between the aura phenomenon and migraine but also provides a clear distinction between these two entities. This approach would be consistent with the previous introduction of *"migrainous infarction"* in the ICHD-3, where the specific wording of "migrainous" replaced the more ambiguous "migraine stroke", mitigating any potential confusion.

In summary, we propose the term "*Migrainous Aura*" to denote the distinct clinical manifestations of the aura phenomenon, "*Migraine with aura attack*" to describe the multifaceted migraine headache plus aura attack, and "*Migraine with Aura*" to delineate the clinical condition of recurrent migraine with aura attacks, in line with the ICHD-3 (Fig. 1). In other words, a diagnosis of "Migraine with Aura" can be classified as either episodic or chronic based on the frequency of the "migraine with aura attacks". Therefore, the clinical efficacy of a medication for migraine with aura would be measured by its impact on the "migraine with aura attack" frequency.

This conceptual framework mirrors the relationship between epilepsy and seizures, where epilepsy represents the clinical condition that predisposes individuals to recurrent seizures (Table 2) [28]. Adopting the term "*Migrainous Aura*" could help define the factors putting individuals at risk of developing "*Migraine with Aura*", just as the distinction between epilepsy and seizures has advanced understanding in that field. Indeed, in patients who experience a first seizure, there are factors associated with an increased risk of recurrence—allowing a diagnosis of epilepsy— that critically inform management [28].

Non-migrainous aura

The aura phenomenon is most commonly associated with migraine, yet it is not exclusive to this condition. Aura-like clinical manifestations, likely associated with SD, can also be observed in a range of other neurological disorders, primarily of cerebrovascular origin. These include cerebral arteriovenous malformations [29, 30], cerebral venous thrombosis [31], sporadic and familial cerebral amyloid angiopathy [32, 33], Moyamoya disease [34, 35], and focal cerebral lesions [20, 36–39]. An enhanced clinical classification system that discriminates between these phenotypically similar events —whether of *Migrainous* or *Non-Migrainous* clinical etiologies— might deepen our understanding of this complex neurological phenomenon. Such a classification would not only better reflect the distinct clinical etiologies underlying aura-like phenomena but also facilitate cross-translation knowledge from various conditions associated with aura. This could yield important mechanistic and clinical implications, including potentially targeted therapeutic approaches [40, 41].

It is noteworthy to recognize that a broad range of monogenic disorders may manifest with aura and, in some cases, even present as a "true" *migraine with aura* – i.e., satisfying ICHD-3 diagnostic criteria. These conditions affect various biological pathways, including ion channels and pumps (as observed in familial hemiplegic migraine) [42], vascular proteins (as seen in hereditary small vessel disease) [43], , or mitochondrial metabolism (as evidenced in mitochondrial disorders) [44]. These genetic mutations arguably contribute to an increased

susceptibility to SD, the key mechanism underlying aura [17, 45]. Therefore, we propose that the aura associated with these hereditary conditions should be clinically classified as distinct from typical migraine, regardless of whether they present as "typical" or "atypical" aura, as patients with these conditions necessitate tailored management strategies. As our understanding progresses, we anticipate the identification of additional genes in the future whose pathological alteration may lead to the clinical picture of migraine with aura, resulting in more patients transitioning from the category of migraine with aura to the category of genetic aura conditions.

It is also important to acknowledge that other brain injury mechanisms can precipitate SD, including traumatic brain injury, seizures, subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, and subdural hematoma [19, 39, 46–48]. In patients admitted to neurocritical care for these conditions, detailed electrocorticographic measurement of the SDs is possible, with a small subset of patients remaining awake and oriented during the recordings. Notably, the classical clinical manifestations of aura have been described in only one case where SDs were simultaneously recorded [49]. On the other hand, in most neurocritical patients, the clinical correlate of SDs, especially SD clusters, usually consists of both transient and permanent neurological deficits associated with a deterioration of consciousness, which often makes a detailed history challenging to collect [47]. However, SDs can also be observed on the monitor in alert and fully oriented patients without any corresponding clinical manifestations [46].

Finally, the relationship between distinctive extracranial factors and the predisposition to aura phenomena warrants further discussion. Animal and human studies suggest an association between right-left shunts, particularly PFO, and increased aura frequency in migraine patients [24, 50, 51]. Very different factors may contribute to this mechanism, such as the coagulation tendency of the venous system, the size of any emboli, and the susceptibility of the cerebral cortex to SDs and their widespread propagation.

In summary, we propose the introduction of the term "*Non-Migrainous Aura*" to distinguish aura phenomena with different clinical etiologies from classical migraine (Fig. 1). This framework mirrors the nomenclature adopted for epilepsy, which distinguishes between "provoked" and "unprovoked" seizures based on their underlying clinical etiology (Table 2). In this analogy, the "*migrainous aura*" is considered "unprovoked" as it arises spontaneously from a susceptible migraine brain, whereas the "*non-migrainous aura*" is deemed "provoked" as it requires a different cause to initiate SD. Moreover, just as the diagnosis of epilepsy necessitates the occurrence of recurrent unprovoked seizures [28], the diagnosis of migraine with aura similarly necessitates recurrent episodes of "*migrainous aura*" [5].

Table 3 Clinical features associated with a high likelihood of migrainous aura and red flags for a low likelihood of migrainous aura

Clinical Features	Migrainous Aura typical features	Red flags for non-migrainous aura or migrainous infarction
Symptoms	Unilateral visual symptom followed or not by other focal symptoms	Prominent non-visual symptoms
Evolution and duration	Gradually spreading, fully reversible in 60 min	Duration of an individual aura symptoms < 5 min or > 60 min, evolution not consistent with consequent eloquent brain areas, alternating-side symptoms
Age at onset	< 40 years old	Older age at onset
Frequency	Low frequency	High or increasing frequency (e.g. > 3 aura events/month)
Headache	Followed or accompanied by headache with migraine features	Not associated headache *
Medical History	Migraine, family history of migraine	Cerebrovascular disorders, onset in concomitance with an acute neurological insult (e.g. head trauma)

* even if ICHD-3 criteria for "Typical aura without headache" are satisfied

The authors of this manuscript have agreed upon red flags based on their current experience with headache and cerebrovascular disorders. Further studies are needed to identify relevant features discriminating "*migrainous aura*" from other etiologies of aura

Aura of uncertain clinical etiology

An aura phenomenon may sometimes defy straightforward clinical etiological classification, presenting without a clear and discernible underlying cause. For instance, an aura can present as a first episode or without an accompanying migraine headache (*"typical aura without headache"*), failing to satisfy, at least initially, the stringent ICHD-3 diagnostic criteria for migraine with aura. Additionally, the presence of atypical features or red flags, such as onset at an advanced age, atypical manifestations or duration, or heightened frequency, may foster uncertainty regarding a possible alternative etiology to migraine (Table 3) [52–55]. In these challenging presentations, we advocate for adopting the term "*aura of uncertain clinical etiology*". While the prevailing clinical etiological hypothesis may still be migraine with aura, with its inherent connotation of a benign clinical course, this term underscores the need for additional longitudinal observation and, potentially, further diagnostic investigations to clarify the underlying etiology [56]. This new definition can guide prompt and individualized management in challenging aura presentations (Fig. 1). Over time, the "*aura of uncertain clinical etiology*" may be reclassified as a "*migrainous*" or "*non-migrainous aura*",

or it may remain "*of uncertain clinical etiology*". Yet, since aura is a clinical diagnosis, subsequent diagnostic evaluations can change the underlying suspected etiology but should not question the diagnosis of aura itself.

Migrainous infarction

Ischemic stroke in patients with migraine presents a unique classification, falling into two categories: "*migrainous infarction*" and "*non-migrainous infarction*" [17, 57]. "*Migrainous infarction*" mostly occurs in younger women and typically involves the posterior circulation [58]. According to ICHD-3 criteria, this type of infarction is defined by the presence of one or more typical aura symptoms, accompanied by unequivocal neuroimaging evidence of ischemic infarction in a subject with a known history of migraine with aura [5]. Crucially, the infarction must be precisely localized in the brain territory corresponding to the aura symptoms [5]. Conversely, infarctions occurring in migraine patients but not meeting these criteria are classified as "*non-migrainous infarctions*". To further complicate the relationship between stroke and migraine with aura, anti-platelet therapy has shown some benefits in reducing the frequency of aura events in exploratory studies [59, 60].

The accurate differentiation between "*migrainous aura*" and "*migrainous infarction*" can pose a significant clinical challenge [9, 61]. Clinical characteristics such as symptom nature, duration, and progression can substantially guide diagnosis (Fig. 1) [62]. Specifically, red flags that may suggest an ischemic etiology include onset at an older age, absence of accompanying headache, increasing frequency of episodes, prominent non-visual symptoms, alternating sides, and prolonged duration of symptoms (Table 3) [57, 58, 61–65]. However, there is a clear need for prospective cohort studies to better characterize the clinical features of "*migrainous infarction*" and, more importantly, the risk of stroke recurrence [63]. Due to our limited capacity to clinically differentiate these two conditions—"*migrainous aura*" and "*migrainous infarction*"— and the potential implications of misdiagnosis, acute multimodal neuroimaging is essential in some cases to rule out an underlying ischemic stroke, particularly when red flags are present [66]. In previous clinical studies of migraine patients with ischemic stroke, the distinction between "*migrainous*" and "*non-migrainous infarction*" has rarely been made, hampering the possibility of exploring potential pathophysiological and clinical differences. However, these conditions likely share overlapping pathogenic mechanisms.

The underpinning biology of migrainous infarction remains incompletely understood, yet it likely involves multiple factors, including brain metabolic dysfunction, hypercoagulability, vasospasm, endothelial dysfunction, and paradoxical embolism [17, 58, 64]. "*Migrainous infarctions*" are often associated with cerebral vessel occlusion, mainly the posterior cerebral artery [58], with only anecdotal reports of infarctions lacking a clear arterial distribution [58]. Notably, paradoxical embolism through a PFO occurs preferentially in the posterior circulation [67], and randomized trials have shown a reduced incidence of ischemic stroke following PFO closure in stroke patients under 60 years old [68–70]. Although all large trials investigating PFO closure in migraine have failed to meet their primary endpoints [23–25], meta-analyses pooling these data demonstrated a reduced headache frequency, especially in patients with migraine with aura [26, 27]. However, the specific impact of PFO closure on the "*migrainous aura*" or "*migrainous infarction*" has not been thoroughly investigated, leaving the pathogenic role of PFO and the potential benefit of closure in these conditions unclear. Taken together, these data suggest ischemic damage as the primary initiator and cortical SD – aura symptoms – as a consequential element in the pathogenic progression of "*migrainous infarction*".

An alternative hypothesis suggests that spontaneous SD is the primary initiator of "*migrainous infarction*", leading to ischemic damage through vasospasm [71] or as a direct metabolic consequence of SD [20]. This latter stroke subtype is thought to arise from a mismatch between tissue metabolic supply and demand in individuals experiencing "*migrainous aura*", especially those with additional susceptibility risk factors [17]. Stroke-like episodes in patients affected by mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) represent a potential framework model where SD is the primary trigger for the development of metabolic infarction [44, 72]. However, direct measurements to support this hypothesis are still lacking [73].

To underscore the susceptible metabolic signature of migraineurs' brains, migraine patients who experience ischemic stroke often exhibit greater or more rapid ischemic core extension, especially those with migraine with aura [74]. This suggests a poor ischemic tolerance driven by an inherent cerebral metabolic supply-demand mismatch [74]. This is also supported by studies on genetic conditions associated with aura. For instance, studies on genetically modified mice carrying familial hemiplegic migraine type-1 mutations showed increased vulnerability to middle cerebral artery occlusion [75, 76].

It is conceivable that distinct subgroups of patients exhibit varied clinical etiologies or that multiple pathophysiological etiological mechanisms operate synergistically in certain patients. However, the current scientific literature lacks a reliable etiological classification of migrainous infarction. We encourage future clinical studies to differentiate between "*migrainous infarction*" and "*non-migrainous infarction*" and to delve into their potential underlying causes. A deeper

understanding of the pathophysiological mechanisms behind "*migrainous infarction*", whether non-SD-related (e.g., embolic) or primary SD-related (e.g., metabolic, vasospasm, and non-thrombotic mechanisms), would significantly enhance our approach to managing both migraine and non-migraine patients. Nevertheless, determining whether cortical SD is the root cause, a mediator, or a bystander in "*migrainous infarction*" remains challenging. Notably, robust evidence suggests that cortical SD exacerbates the progression of ischemic penumbra into the ischemic core, leading to a larger final infarct volume [39]. Therefore, SD plays a critical role in the progression of cerebral ischemic lesions, regardless of the initial underlying etiology, further complicating its involvement in "*migrainous infarction*" [39].

Conclusion

In the ever-evolving field of neurology, refining our terminology is paramount to promoting effective communication, improving clinical care, advancing scientific research, and fostering global collaboration. Clear definitions are critical for accurate phenotyping of different clinical entities, which is a crucial step for translational mechanistic research. In this context, we advocate for a nuanced terminological framework to redefine the aura clinical phenomenon and its underlying clinical etiologies – both migraine and non-migraine-related. Notably, our proposal is intended to be harmonious with, rather than in opposition to, the diagnostic criteria outlined in the ICHD-3, and be used as an adjunctive instrument for a more accurate terminology and classification of aura-related conditions, and, potentially, inform future updates of the ICHD. While the ICHD-3 is centered on the headache symptom, we propose a complementary aura-centered clinical classification. Our framework encourages clinical reasoning around the aura phenomenon itself. Ultimately, we aim to stimulate research to deepen our understanding of this complex phenomenon, which has critical clinical implications beyond the confines of headache medicine.

Box 1. Aura phenomenon

Aura is a clinical phenomenon characterized by transient, unilateral visual, somatosensory, or other focal central nervous system symptoms that usually develop and resolve gradually [5, 6]. When multiple symptoms occur during a single episode, they generally follow a sequential pattern, each lasting between 5 and 60 min. These symptoms are typically "positive" in nature, progressing slowly in a topographical fashion that reflects the underlying cortical spreading depolarization across the contiguous brain cortex [15, 49]. The diagnosis of aura relies solely on clinical evaluation – neurological examination and medical history – without the need for additional diagnostic tests [5, 6]. Given the lack of supportive physiological markers, a well-defined phenotypic presentation of the phenomenon is necessary for the diagnosis. Etymologically, the term "aura" traces back to the sanscrit root "av" and derives from the Greek word Αὔρα (Aúra), originally used to describe a gentle breeze.

Box 2. Spreading depolarization continuum

Spreading depolarization (SD) is an evolutionarily conserved phenomenon observed in the brain cortex across different species, from insects to humans [20]. It was first described by the pioneering Brazilian physiologist Aristides Leão in a series of four papers between 1944 and 1947. SD is characterized by a self-propagating wave that causes a rapid and dramatic disruption of transmembrane ion gradients in neurons and astrocytes, spreading through contiguous cerebral grey matter at ~3 mm/min.[39] In experimental settings, there is consistently severe dysfunction at the site where SD develops, yet this dysfunction may be reversible. In normal brain tissue, SD can lead to variable effects on cortical activity, either causing a depression of activity – so-called *spreading depression* – and/or an increase in activity -– so-called *boom* [39, 76]. SD is known to be provoked under various pathological conditions such as seizures, hypoxia, hypoglycemia, ischemia, and mechanical, chemical, or electrical injury, highlighting its role as a critical response mechanism to metabolic insults. In cases of severe ischemia, an immediate and complete suppression of cortical activity develops simultaneously across all hypoperfused tissue – so-called *non-spreading depression* – and provoked SD develops a few minutes later. In such scenarios, the duration of SD is dependent on the tissue's metabolic state, ranging from transient and short-lasting, to prolonged or persistent in severely compromised tissue [39]. Overwhelming evidence supports the detrimental role of provoked SD in the development and progression of acute gray matter lesions, including ischemic stroke, subarachnoid hemorrhage, traumatic brain injury, and cardiac arrest [20, 39, 46].

Taken together, this evidence suggests that cortical SD exists along a continuum, from short-lasting and relatively harmless episodes, to prolonged or persistent, harmful events with significant diagnostic and prognostic implications. Although the practical bench-to-bedside implications of SD are still evolving, spontaneous benign SD likely underlies the distinctive clinical manifestations of migrainous aura, whereas only a small proportion of provoked SD is likely to exhibit aura symptoms – "*non-migrainous aura*" – as other neurological manifestations typically are more relevant in the clinical presentation.

Abbreviations

ICHD	International Classification of Headache Disorders
PFO	Patent Foramen Ovale
SD	Spreading Depolarization

Supplementary Information

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Supplementary material 1: Vignette of six representative cases

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Author contributions

UP, MR, and SS conceived the study.UP drafted the manuscript.All Authors reviewed the manuscript for content. All Authors approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
N/A.

Consent for publication
N/A.

Competing interests
The authors declare no competing interests.

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