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Migraine with and without aura—two distinct entities? A narrative review

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Abstract

Migraine is a primary headache disorder, with a prevalence estimated at approximately 15% globally. According to the International Classification of Headache Disorders, 3rd edition (ICHD3), there are three significant types of migraine: migraine without aura (MO), migraine with aura (MA), and chronic migraine (CM), the former being the most common. Migraine diagnosis is based on official criteria specific to each type. Although a lot is already known about the origin of migraine aura, its pathophysiology is still an object of research.

Long-term discussions have been held about MO and MA, with some evidence for the same underlying pathogenesis of both and other arguments against it. In this narrative review, we decided to analyse multiple factors from the perspective of similarities and differences between these two types of migraine. The aim was to understand better the bases underlying both types of migraine.

Aspects such as genetics, molecular bases, relation with hormones, epidemiological and clinical features, neuroimaging, neurophysiology, treatment response, and migraine complications are covered to find similarities and differences between MO and MA. Although epidemiology shares similarities for both types, there are slight alterations in sex and age distribution. Genetics and pathogenesis showed some crucial differences. Conditions, such as vestibular symptoms and depression, were found to correlate similarly with both types of migraine. For some features, including increased cardiovascular risk, the tendency appeared to be the same; however, migraine types differ in the strength of correlation. Finally, in cases such as hormones, the influence has shown opposite directions. Therefore, although migraine with and without aura are considered two types of the same disease, more research should focus on their differences, thus finally enabling better specific treatment options for both types of migraine.

Keywords Headaches, Migraine with aura, Migraine without aura, Primary headache disorder, Migraine aura

Introduction

According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), migraine is a primary headache disorder [1] with a prevalence estimated at 14–17%, depending on the source and global region [2, 3]. The most common group affected by migraine is young women of reproductive age; however, migraine can also appear in childhood or older adults, and migraine types differ in frequency according to age [4]. The diagnosis is based on the official ICHD-3 criteria [1], including pain type, duration, influence on daily life, and

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associated symptoms [5]. Migraine is divided into three major types: migraine without aura (MO), which is the most common one; migraine with aura (MA), accounting for approximately one-third of migraine cases; and chronic migraine, which may include either migraine with or without aura. A recent study highlighted the importance of the individual approach to every migraine patient [6]. Although people with migraines share a lot of similar features, there are a lot of differentiating hallmarks, such as frequency of attacks, response to therapy, associated comorbidities or other symptoms, and, finally, aura presence. All these features are crucial for an individualised treatment for each patient to achieve the best effects [6]. Several studies have focused on multiple aspects of the differences between MA and MO. Firstly, the epidemiology of both types shows slight variation in age and sex distribution [7]. Other differences can be found in genetics, molecular bases, and relationships with hormones [8]. Literature also indicates unique neuroimaging and electroencephalography (EEG) features [9, 10] and diverse treatment responses, which may suggest different entities of both types. Figure 1 summarises key issues discussed in the following work. Considering all the above, this narrative review aims to thoroughly explore the differences between MO and MA, analysing them from various perspectives. Based on the available literature, we aim to discuss whether MO and MA could be two types of the same entity or two different diseases. To our knowledge, this is the first work covering all the abovementioned aspects.

Methodology

The review was performed primarily narratively; however, some critical aspects of methodology should be pointed out. The literature search was conducted between June 2024 and December 2024. The following databases have been included: PubMed Database and Cochrane Database. In the narrative review, Medical Subject Headings (MeSH) terms: "migraine with aura" and "migraine without aura" were used together with the additional keyword "differences." Other implemented keywords were unique for each paragraph: for the *genetics* paragraph: "genetics," "genes," and "inheritance"; for the *molecular bases* paragraph: "molecular bases," "pathogenesis," and "cortical spreading depression"; for the *hormones* paragraph: "hormones," "menstruation," "menstrual cycle," and "hormonal contraceptives"; for *differences in epidemiology and clinical presentation* paragraph: "patients' characteristics," "patients' features," and "epidemiology"; for *neuroimaging* paragraph: "neuroimaging," "brain MRI," "brain CT," and "brain imaging"; for *neurophysiology* paragraph: "electroencephalography," "EEG," and "habituation deficit"; for *treatment response* paragraph: "treatment response" and "response to therapy"" and for *risk and complications* paragraph: "risk," "complications," "cardiovascular disease," and "stroke". Additional studies were indicated from the reference lists of identified articles. The graphical presentation of the process of article identification to include in the narrative review is shown in Fig. 2.

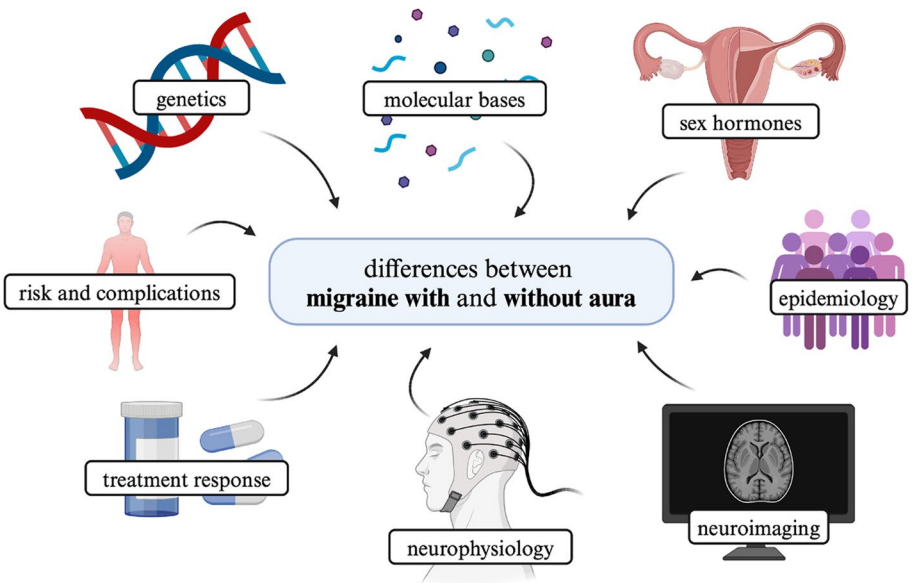

Fig. 1 A graphical summary of key aspects covered in the article

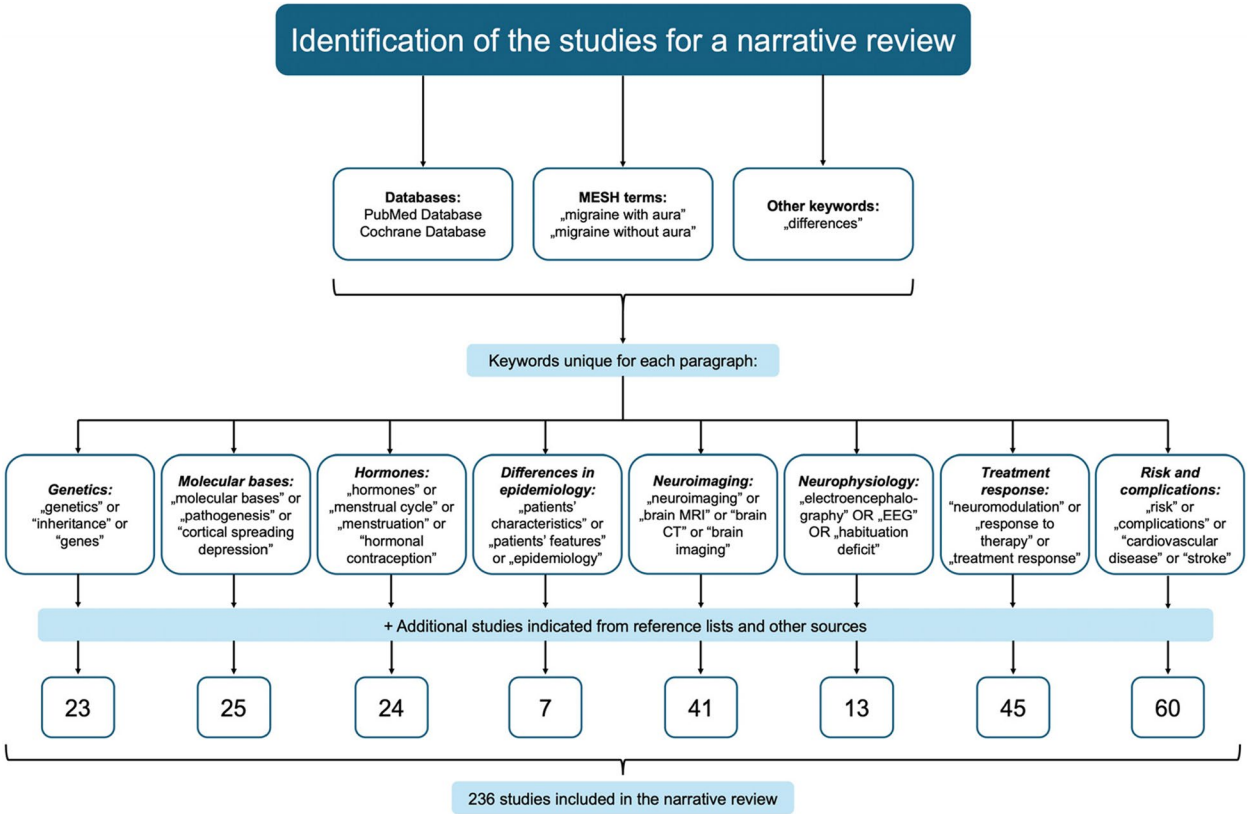

Fig. 2 A graphical presentation of the process led to identifying articles included in the narrative review. MESH, Medical Subject Headings

Findings

Genetics

Delving into MA/MO genetics is critical in understanding the differences between the causes and development of both types. This paragraph indicated two crucial questions: whether there was significant disproportionality in the association of each specific monogenic disorder with either MA or MO and whether polygenic MA and MO had overlapping gene associations.

Since one single gene mutation is usually a causative factor in monogenic disorders, we hypothesised that if MA and MO are genuinely two different diseases, each monogenic disorder should be associated with either MA or MO without significant overlapping. However, in migraine not related to monogenic disorders, not only genetics but multiple other factors may play a role; therefore, a problem is much more complex. Heritability of migraine is estimated to range from 35 to 60%, according to the family and twin studies conducted in 1993 and 1995 as cited in a review article in 2023 [11, 12]. The relative risk of MO in first-degree relatives of probands with MO was 1.9, while the risk of MA in first-degree relatives of probands with MA was 3.8, suggesting a much higher genetic influence in MA. The risk in first-degree relatives of probands with both types of migraine was 1.6 for MO and 2.2 for MA [12].

Monogenic migraine

The most studied type of monogenic migraine is hemiplegic migraine, caused by mutations in one of the following genes: calcium voltage-gated channel subunit alpha 1A (*CACNA1A)*, ATPase Na^+/K^+ Transporting Subunit Alpha 2 (*ATP1A2)*, or sodium voltage-gated channel alpha subunit 1 (*SCN1A),* inherited in an autosomal dominant manner [13]. All three genes have been associated with either familial (FHM) or sporadic (SHM) hemiplegic migraine, classified as types of migraine with non-visual aura [13, 14]. FHM1 is caused by a gain-of-function mutation of the *CACNA1A* gene, which causes calcium influx into neurons, enhanced glutamatergic neurotransmission, cortical hyperexcitability, and increased susceptibility to cortical spreading depression (CSD) [13, 14]; however, there is only a link to CSD and not to migraine with a typical aura. Condliffe et al. described a gain of function missense mutation E1015K associated with hemiplegic migraine and MA [15]. On the other hand, FHM2 and FHM3, caused by mutations of the A*TP1A2* gene and *SCN1A* gene, respectively [13], have not been

widely associated with sole MO, corresponding to the theory regarding their different pathophysiology. In 2022, Riant et al. also suggested a proline-rich transmembrane protein 2 (*PRRT2*) gene as a fourth autosomal dominant cause of FHM [16]. This gene encodes proline-rich transmembrane protein 2, which is highly expressed in the cerebral cortex, basal ganglia, and cerebellum [17]. Out of that, one can speculate that hemiplegic migraine should be a separate entity from migraine with a typical aura, and it is wrong to generalise to the whole MA.

However, the literature on differentiating its role in MA/MO is still scarce.

Other single-gene mutations related to migraine. In patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), caused by the NOTCH receptor 3 (*NOTCH3*) gene mutation and with a phenotype characterised by migraine, MA is five times more prevalent than in the general population. At the same time, the prevalence of MO does not differ between CADASIL and the general population [18].

Familial advanced sleep-phase syndrome (FASPS), a disorder characterised by a short circadian rhythm, early sleep onset, and early awakening, is caused by a missense mutation in the casein kinase one delta (*CSNK1D*) gene [19, 20]. Brennan et al. described two families with two variants of the *CSNK1D* gene, which were absent in all controls [21]. In the first family, five carriers of the altered allele had FASPS and MA, one carrier had MO, four non-carriers had MA only, and four non-carriers were asymptomatic. In a second family, two carriers of the altered allele had FASPS and aura without migraine. One female carrier had both FASPS and MA, one male carrier had aura without migraine and unknown sleep phenotype, and one male carrier did not complain of migraine or aura and had an unknown sleep phenotype [21]. The highly conservative nature of these loci and the absence of the variants in controls suggest a causative role in FASPS, MA, and CSD.

The mutation of the potassium channel subfamily K member 18 (*KCNK18*) gene, which encodes the TWIK-related spinal cord potassium channel (TRESK), increased susceptibility to MA. Lafrenière et al. first identified it in 2010 in a large multigenerational family with MA [22]. However, since no other migraine families have been reported with a frameshift mutation of *TRESK* and complete loss of function mutations have been observed in control groups, *KCNK18* is more likely to be a genetic modifier rather than a cause of the autosomal dominant migraine phenotype [23, 24].

Finally, Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations (RVCL-S) was first described in a Chinese American family. Seven out of 11 affected members had experienced migraine attacks, and one of the patients suffered from visual auras. The original article does not clarify the presence of auras in other affected individuals [25]. Further studies did not distinguish between MA and MO [26]. Table 1 presents the connections between several genes and migraine, mostly MA.

Polygenic migraine

Even though the heritability of MA is higher than MO, which indicates the higher role of genetics in MA genesis, the search for genetic risk factors associated with polygenic MA has been unsuccessful. Several candidate gene association studies (CGAS) focusing on the ion transporter coding genes found no significant associations with MA [27]. CGAS studies focusing on the methylenetetrahydrofolate reductase (*MTHFR*) gene found that one of the polymorphisms correlated with migraine, specifically MA (but no MO) [19]. Several studies conducted between 1998 and 2008 using family-based traditional linkage studies suggested loci for MA, MO, and

Table 1 A summary of genes possibly associated with migraine

Gene	Mutation	Phenotype	Migraine type	Inheritance pattern
CACNA1A	GOF	FHM1; MA	MA	AD
	LOF	EA2	MA/MO	AD
ATP1A2	LOF	FHM2, seizures; intellectual disability	MA	AD
SCN1A	GOF	FHM3	MA	AD
NOTCH3	GOF	CADASIL1	MA	AD
CSNK1D	LOF	FASPS	MA	AD
KCNK18	LOF	MA	MA	Dominant negative
TREX1	LOF	HERNS	MA (lack of evidence)	AD

AD Autosomal dominant, *CADASIL* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *EA2* Episodic ataxia type 2, *FASPS* Familial advanced sleep-phase syndrome, *FHM* Familial hemiplegic migraine, *GOF* Gain of function, *HERNS* Hereditary endotheliopathy with retinopathy, nephropathy, and stroke, *LOF* Loss of function, *MA* Migraine with aura, *MO* Migraine without aura, *SCA* Spinocerebellar ataxia

MA/MO phenotypes; however, except for two loci (4q24 in a Finnish study of MA families and 4q21 in an Icelandic survey on MO families), replication success was low. Furthermore, whether the two loci mentioned refer to different genes for MA and MO or a single gene causing both [28–30] is unclear. Furthermore, a recent genome-wide association study, including 59,674 migraine cases and 316,078 controls, found seven loci associated with MO, while none were associated with MA [27]. Polygenetic risk score analysis of 21 migraine-associated single nucleotide polymorphisms (SNPs) conducted by Pisanu et al. showed an association with MO but not MA [31]. In contrast, Zhao et al. identified six genes associated with MA and MO. This study identified a significant gene-based overlap between MA and MO, suggesting a shared genetic susceptibility of MA and MO, at least in pain genesis [32]. Furthermore, an analysis of shared heritability in 25 common brain disorders conducted in 2018 showed a substantial genetic correlation between MA and MO [33].

In conclusion, based on the evidence on polygenic migraines, MO and MA are more likely to share a significant genetic basis, which could be explained by shared aetiology or pathophysiology.

Molecular bases of MA and MO

Calcitonin gene-related peptide

The trigeminovascular system is a key element of the neurovascular theory of migraine headache development. Calcitonin Gene-Related Peptide (CGRP) is a neuropeptide associated with trigeminal nerves from which the blood concentration increases during migraine attacks [34, 35]. Goadsby et al. compared the CGRP level in 10 patients with MA and 12 with MO. Although CGRP concentrations were not elevated in peripheral blood, they increased in both groups' cranial circulation. Interestingly, authors reported that this level was higher in patients with MA, which could have implications for treatment focused on CGRP (receptor) antagonism [36].

Pituitary Adenylate Cyclase-Activating Peptide

Additionally, other substances, including Pituitary Adenylate Cyclase-Activating Peptide (isoforms PACAP-38 and PACAP-27), may play a role in the neurovascular aspects of migraine. This seems crucial in migraine management, mainly due to the most recent reports about the efficacy of treatment targeting PACAP in disease prevention [37]. Ghanizada et al. found that infusing PACAP-27 causes migraine attacks, precisely without aura, significantly more often than placebo [34, 38]. The study conducted by Schytz et al. demonstrated that PACAP-38 infusion also resulted in the onset of headache and vasodilatation in healthy subjects and migraine patients and caused delayed migraine-like attacks in migraineurs, similarly as in the previous study, experienced attacks both by migraineurs and healthy individuals were without aura [39]. Therefore, these findings suggest that PACAP molecules may relate more to MO than MA. On the contrary, infusion of CGRP in another study led to both migraine aura (in 38% of participants) and migraine headache (in 71% of participants) [40].

Cortical spreading depression

Cortical spreading depression is a well-known phenomenon suggested to play a significant role in aura development [41]. Headache is undoubtedly suggested to be linked with aura; however, the direct mechanism of its development remains unknown, with several hypotheses regarding its origin [42]. Some evidence indicates that CSD encourages trigeminovascular mechanisms of pain development [42, 43]. Moreover, studies analysing CGRP show that this molecule can play a role in inducing both aura and migraine headaches [40], as well as particularly in the CSD phenomenon [44]. Apart from MA, researchers hypothesise that MO can also be related to CSD (called "silent CSD"), causing a "silent aura" not accompanied by clinical aura symptoms [45]. This suggests MA and MO can be in a spectrum of one disorder with diverse clinical manifestations. Finally, a recent study showed aura may be an epiphenomenon unrelated to migraine pain; therefore, it promotes the hypothesis that aura is a disorder independent of headache. In their study, the authors presented that hyperactivation of the hypothalamus preceding migraine was present two days before the headache attack, regardless of aura presence [46].

Magnesium

The role of magnesium in migraine pathogenesis is well-described, with deficiencies known to promote CSD, alter nociceptive processing and neurotransmitter release, and encourage the hyperaggregation of platelets, all significant elements of migraine development. While magnesium blood serum levels in patients with MA and MO were shown to be within normal ranges, the evidence suggests this ion can be lower in their neurons [47]. Cegielska et al. found that more patients with MA than those with MO and healthy control groups presented positive results on the ischemic tetany test (87.5%, 59.3%, and 45.8%, respectively) [48]. An electrophysiological tetany test was used to evaluate intracellular magnesium levels, thus demonstrating possible latent deficiencies. Therefore, this indicates a potential for a reduced intracellular magnesium concentration in those patients. Low cerebral magnesium levels may cause glutamate release, which is associated with CSD and aura [34, 48].

Oxidative stress

Additionally, oxidative stress appears to be a significant contributing factor to the onset of migraine attacks. Superoxide dismutase (SOD) is an enzyme that accounts for defending cells against oxidative stress. Tuncel et al. found that erythrocyte SOD activity is considerably higher in patients with MA in comparison to patients with MO [49]. Aura is commonly suggested to be associated with vasoconstriction. Therefore, authors hypothesise the possible explanation of their findings in SOD being a protector against vasoconstriction induced by reactive oxygen species. However, more research is required on this topic.

Vascular disease biomarkers

The vascular theory of developing migraine is frequently the subject of discussion. Tietjen et al. evaluated the serum levels of vascular disease biomarkers in migraineurs compared to a control group [50]. It was found that molecules such as fibrinogen and high-sensitivity C-reactive protein (hs-CRP) were elevated in people with migraine and, importantly, were more linked with MA than with MO. Patients with MA had a higher likelihood of increased Factor II, also known as plasma prothrombin, and hs-CRP. Interestingly, women with MA presented with elevated fibrinogen and Factor II. The study also found that the total number of years of aura (not migraine headache) predicted increased hs-CRP level. An average number of aura attacks predicted all biomarkers, excluding Factor II [50]. In another study, Tietjen et al. found that endothelial activation biomarkers like von Willebrand factor activity and hs-CRP level were increased, and nitrate levels were decreased in premenopausal women with migraine, notably with MA [51]. The study revealed that endothelial microparticles, which are involved in endothelial dysfunction, were elevated in women with MA. Conclusively, it seems that endothelial activation plays a role in the development of migraine, particularly MA [52]. It was furthermore emphasised by a study by Petrusic et al. [53], in which researchers showed that microembolic signals were significantly more often detectable in patients with higher cortical dysfunction during aura compared to those with visual and/or somatosensory aura and healthy controls (29.4%, 3.2%, 5.9%, respectively). This suggests potential differences in the development of different aura types.

Haematological parameters and inflammatory biomarkers

Levels of haematological parameters and inflammatory biomarkers were also investigated in migraineurs [54]. Neutrophil/monocyte ratio (NMR), generally used in evaluating systemic inflammation, was higher in patients with MA than in the control group. In contrast, CRP, platelet/lymphocyte ratio, and NMR were increased in patients with MO compared to the control group [54]. Additionally, serum lymphocyte levels seemed to be lower, and the neutrophil/leukocyte ratio was higher in patients with MA than in patients with MO [55]. Interleukins are a class of molecules involved in migraine development. Ramezani et al. found that interleukin-6 (IL-6) expression was elevated in patients with aura compared to people without migraine. However, there was no increase in IL-6 in participants with MO [56]. The other factors that play a role in migraine development are vaspin, chemerin, visfatin, and interleukin-18, which are elevated in migraineurs compared to healthy individuals. Although inflammatory processes are thought to be more closely linked to MA, no significant differences were observed in the levels of the above-mentioned molecules between MA and MO patients. The levels of these substances were elevated in both groups compared to healthy individuals. Accordingly, inflammation is a significant trigger of migraine headaches [57]. Furthermore, some studies found that the other important biomarker, homocysteine, which is associated with cardiovascular diseases (CVD), such as coronary artery disease, may be elevated in people with MA in comparison to the MO and control groups but more likely in men than women [58]. Importantly, in most of the abovementioned studies [50–52, 56–58], the number of included patients was similar in both MA/MO groups. However, in three of them, [49, 54, 55] MO groups were at least two times bigger than MA groups, which might have influenced the statistical power to observe differences with controls for both forms of migraine.

Hormones

Migraine, apart from neuroinflammation, is intrinsically linked to female sex hormones and their cycles, often aligning with puberty onset, remission post-menopause, and variation in severity and frequency across the menstrual cycle and during the perimenopausal period [59–61]. However, sex hormones and reproductive events modulate MO and MA differently.

Menstrually-related migraine, occurring from two days before menstruation to day three of menstruation, is more common in MO patients than MA patients [59, 62–64]. Reports indicate that 53–56.4% of MO patients experience menstrually-related migraine attacks, and for 21% of MO patients, at least 75% of their monthly attacks are menstrually related. In contrast, 15–33.3% of MA patients experience menstrually-related migraine attacks, with only 4% of MA patients experiencing the majority of their attacks during menstruation [59, 62, 64]. However, other studies found no significant difference in migraine prevalence during menstruation between MO and MA

patients, indicating further research is needed [65, 66]. Interestingly, regardless of whether the patient is diagnosed with MO or MA, the migraine attacks that occur during the perimenstrual and menstrual periods are primarily without aura, indicating that the mechanisms that drive menstrually-related migraine attacks may be distinct from attacks with aura for MA patients [63, 64, 66]. In addition, although MA patients have not an increased risk of attacks with aura during the perimenstrual phase, the risk of attacks without aura was similar for women with MO (OR [95%CI]:1.53 [1.44–1.62]) and those with MA (1.53 [1.44–1.62]). Finally, premenstrual syndrome is significantly more common for MA patients than for MO patients [62, 65].

Changes in female sex hormone cycling and reproductive events also alter the migraine profile, impacting MA and MO patients uniquely. Both MA and MO patients experience favourable effects of pregnancy on their migraines, including decreased attack frequency and symptoms and complete remission for some. A lower percentage of MA patients (43.6–65.5%) experience remission during pregnancy compared to MO patients (76.8–79.3%), who also often gain relief earlier in pregnancy [62, 67, 68]. However, attack frequency may also increase during pregnancy for some MA patients, and new migraine onset during pregnancy is more likely to be associated with aura [59, 66]. Breastfeeding is protective for MO patients, whereas MA patients may experience an increased attack frequency [66, 67]. Menopause decreases attack frequency and severity for MO patients; however, a similar reduction with age is not seen for MA patients [64].

Responses to exogenous female sex hormones also differ between MA and MO. A higher percentage of MA patients (56.4%) experience worsening migraines with hormonal contraceptives compared to MO patients (25.3%) [62]. Estrogen treatment can lead to the development or worsening of aura [69]. Significantly higher estrogen levels during ovulation in MA suggest high estrogen may contribute to aura development, which may explain why menstrually-related migraine (with low levels of estrogens during menstruation) is mainly without aura [70, 71]. Conversely, high progesterone levels from progesterone-only contraceptives reduce migraine attack frequency for both MO and MA and decrease visual aura duration for MA patients [72, 73]. Hormonal contraceptives and stroke risk vary between MA and MO patients. One study showed that without contraceptives, both migraine subtypes have similar odds ratios (2.65 MA vs 2.24 MO) for stroke [74].

Nevertheless, different conclusions can be drawn from the work conducted by Kurth et al., [75] in which the analysis after adjustment of several confounding factors, including the use of hormones ever in life, showed more increased risk for stroke for MA (OR [95%CI]: 3.36 [2.72–3.99]) in comparison to MO (OR [95%CI]: 2.11 (1.98–2.24)]. Additionally, combined hormonal contraceptives increased stroke risk more pronounced for MA patients (OR 6.08) than for MO patients (OR 1.77) [74]. Thus, combined contraceptives are contraindicated for patients with MA.

It is unclear how sex hormones modulate aura in migraine, though preclinical studies suggest they may influence CSD, a key event in aura development. Both estrogen and progesterone can increase CSD rate, amplitude, and duration, contrasting with clinical data that suggest progesterone can be beneficial [76–79]. There is little or no difference in CSD susceptibility or frequency across the estrous cycle, aligning with clinical observations that the frequency of attacks with aura does not differ across the menstrual cycle [79]. Additionally, testosterone appears protective, decreasing CSD frequency and speed [80]. Consistently, studies showed lower testosterone levels in men with migraine compared to healthy controls [81, 82]. However, studies regarding testosterone differences between MA and MO are lacking.

Differences in epidemiology and clinical presentation

When moving from the molecular point of view to the clinical one, first, the general characteristics of patients who come to the outpatient clinic due to headache problems appear. It is well known that young women of reproductive age are the most common group affected by migraine headaches. However, the question remains: do the numbers differ for MA and MO? For more than three decades, it has been known that these two types of migraine differ in sex-related distribution and age of onset. A study performed by Rasmussen et al. comprehensively compared the epidemiology of MA and MO and included a total of 1000 participants. The male-to-female ratio in MO was established at 1:7, while in MA, it was only 1:2, showing a substantially greater predominance of women over men in the more common type of migraine. Moreover, in the same study, the age of onset appeared to be significantly higher for MA than for MO. Although the percentage of onset in the third decade was similar for both types of migraine, amounting to 30%, the onset in the second decennium was almost twice more common for MO than MA (43% to 24%). An inverse relationship was observed for the onset in the fourth decade (32% of MA and 17% of MO) [83]. The recent epidemiological study conducted by Chalmer et al. demonstrated similar tendencies thirty years later, analysing almost 13,000 migraine patients (and 63,000 participants overall). MO appeared significantly

more frequently in females than males (OR 1.22), with the highest peak of incidence observed in the reproductive age. Interestingly, MA presented no difference in sex distribution and was not age-related [84]. Focusing more on differences between females and males, apart from the distinct sex distribution of MO and MA, age distribution also seems to differ between sexes. Studies have shown that males are more prone to develop migraine at younger ages than females, with the percentage of men in migraine population decreasing from childhood to adulthood [85]. Additionally, another study showed that the age of onset is lower for males only for MO (16.5 years versus 21.5 years), while for MA, there was no significant difference in the age of onset between men and women (20.8 years versus 21.8 years, respectively) [86].

Furthermore, some slight differences were observed between MA and MO in body weight and dietary patterns [87, 88]. Rossoni de Oliveira et al. studied anthropological parameters and body fat percentage in female migraineurs with or without aura. Researchers demonstrated that for MA, there was a positive correlation between attack frequency and both body mass index (BMI) and waist circumference, which was not present for MO. However, the difference between MA and MO in BMI and waist circumference was not significant [88]. Interesting observations were made by Rist et al. according to dietary patterns. It was shown that MA patients had a lower intake of food such as chocolate, ice cream, hot dogs, and processed meats, which can be considered potential trigger factors [87].

Finally, a study by Kallela et al. observed differences between MA and MO strictly in migraine presentation. Unilateral pain and photophobia were more typical for MA, while nausea was more typical for MO. Moreover, headache lasted longer in patients suffering from MA than those with MO [89].

Some of the complaints may be considered either a feature of a patient with migraine, which could also differentiate MA and MO, or a complication of migraine, and it is not always directly known which term should be used. Therefore, the co-existing disorders and conditions have been described in paragraph 8.

Neuroimaging

Structural imaging

In recent years, multiple studies have assessed morphological brain differences, such as changes in structure and volume between MO and MA.

Volumetric and cortical thickness changes

Recent research has shown that migraineurs have a greater medulla volume compared to healthy controls, with MA and MO having similar whole brainstem volume [90]. On the other hand, morphological brain differences between MA and MO were observed in higher cortical areas [91–94]. Although one study found no dissimilarity in cortical thickness between MA and MO [95], a study with a larger sample suggested that MA had a thicker cortex in somatosensory areas, occipitotemporal gyrus, and cuneus compared to MO [93]. Changes in the occipital cortex volume, such as a thicker occipital cortex [96] and an increased grey matter volume in the occipital gyrus [91], seem to be promising biomarkers of MA. Moreover, MA showed a higher occipital bending compared to MO [92]. However, grey matter volume dissimilarities were also observed in other brain areas: MA had a reduction in cerebellum and temporal lobe volume and an increase in frontal lobe volume compared to MO [94].

White matter microstructure

Differences in white matter microstructure assessed with diffusion tensor imaging (DTI) between MA and MO have also been reported [97–99]. Compared to MO, MA had increased structural connectivity between the left parietal and occipital areas [97] and decreased structural connectivity between the postcentral gyrus and insula and between the precuneus and lateral occipital cortex [98]. However, a study that showed no differences in DTI between MA and MO did not support these results [100]. Previous research also had heterogeneous results, with one study finding differences in DTI between MA and MO, showing significantly more radiological changes in MA patients, [101] and one not [102].

White matter hyperintensities

According to a systematic review of 30 eligible studies published before 2022 involving 3,502 migraineurs [103–106], the presence of aura was associated with an increased risk of having white matter lesions (White Matter Hyperintensities (WMHs)) [99]. The prevalence of WMHs in MO and MA was 38% and 45%, respectively [99], compared to 5.3% of age-matched healthy controls [107]. MA had a six-fold increased risk, and MO had a four-fold increased risk of WMHs compared to healthy individuals [99]. A recent study published after the review showed that the number and volume of WMHs were similar between 15 MA and 15 MO patients. However, the study found a positive correlation between the frequency of aura and the number and volume of WMHs in the frontal and temporal lobes [108], the brain areas most affected by WMHs [99]. Overall, these results show some relationship between aura presence and WMH formation, not providing enough evidence for the causality between WMH formation and aura. The mechanism underlying this correlation could be the CSD-induced

prolonged oligemia potentially causing ischemic/hypoxic injury in hemodynamically vulnerable brain areas, which could contribute to WMH formation [109]. However, as no causal relations has been proven between MA and WMHs [110], it is also possible that a certain background of a patient makes her/him more susceptible to both aura and WMH.

Vascular structure

Apart from structural alterations involving neural tissue in the brain, vascular abnormalities have also been observed in MA compared to MO. Basilar artery (BA) displacement was greater in MA compared to MO [111, 112], with every millimetre of lateral BA displacement associated with a 4% greater odds of having MA [111]. On the other hand, large artery atherosclerosis in extracranial and intracranial arteries seems to be similar in MA and MO patients who recovered from their first-ever ischemic stroke [113].

Vascular perfusion

Ictal studies

An early study published in 1999 compared changes in cerebral perfusion between MO and MA during the ictal and the interictal phase. In MA, cerebral hypoperfusion in the contralateral occipital cortex was observed during aura, with no changes in cerebral perfusion occurring in MO during the ictal phase or in MO and MA interictally [45]. These results were confirmed by recent research, which showed biphasic cerebral perfusion changes in MA patients, occurring mainly unilaterally in posterior brain areas: cerebral hypoperfusion occurred during the aura phase, sometimes continuing in the first hours of headache attack, before hyperperfusion sets in during the ictal phase [114, 115]. On the other hand, results in MO are inconsistent, with some studies showing an ictal increase and others an ictal decrease in cerebral perfusion [115]. Recently, mean flow velocity reduction in the middle cerebral artery and the posterior cerebral artery during a CGRP-induced migraine attack was also found in MA compared to MO [116].

Interictal studies

Differences in cerebral perfusion between MA and MO have also been also reported during the interictal phase [95, 117, 118]. In children, 75% of migraine patients with aura had perfusion changes compared to 13% without (90% hyperperfusion, 10% hypoperfusion) [118]. In adults, one study showed that MA but not MO had cerebral hyperperfusion in the middle temporal gyrus and superior temporal gyrus compared to healthy controls [95]. Another study found that MA had hyperperfusion in the bilateral superior frontal gyrus, bilateral postcentral gyrus, and cerebellum and hypoperfusion in the bilateral middle frontal gyrus, thalamus, and medioventral occipital cortex compared to MO [117]. No changes in flow velocity in the anterior, middle, or posterior cerebral artery or vertebral artery were observed interictally between MA and MO [119].

Functional imaging

Functional magnetic resonance imaging (fMRI) could assess resting-state functional connectivity between distinct brain areas and brain activity during a stimulus. Unfortunately, although multiple studies assessed differences in fMRI between MA and MO during the interictal phase, studies comparing these patients during the ictal phase are lacking. There is consistent evidence that MA and MO exhibit different resting-state functional connectivity patterns between brain areas [98, 100, 120–124], suggesting a heterogeneity in brain functionality between these two subgroups. Differences between MA and MO were also observed in brain activation during a stimulus. Compared to MO, MA had higher brain activity, particularly of the visual cortex [125–127], during visual stimuli [9, 128]. MA also had higher activation of the left lingual gyrus, inferior parietal lobe, inferior frontal gyrus, and cerebellum following a trigeminal painful stimulus [114]. Additionally, in the case of functional near-infrared spectroscopy (fNIRS), the findings were similar for both MA and MO [129, 130].

Neurophysiology

Electroencephalography

Electroencephalography has been widely used to assess electrocortical phenomena in migraine patients [131]. Recordings can be performed during rest (resting-state EEG) or external stimulation (event-related potential (ERP)) [131].

Resting-state EEG

Differences in resting-state EEG during the interictal phase have been observed between MA and MO. Particularly, MA seems to have an excess of slow and hyper-synchronized alpha rhythmic activity [131]. More recent studies have confirmed these results, which show disparities in interictal resting-state EEG recording between MA and MO [132, 133]. MA and MO showed differences in the theta band's microstate dynamics [132] and functional connectivity [133]. Also, a recent article focused on high-density EEG in patients suffering from MA but without comparison to MO, which is the main topic of the narrative review. Nevertheless, researchers observed the decrease in alpha-power contralaterally to visual symptoms, which was consistent with the observed

effects of CSD. However, the presented changes were not specific to MA patients [134].

Event-related potentials

Even if both MO and MA seem to have an interictal cortical hyper-reactivity to sensory stimuli, the amplitude of the response appears to be more pronounced in MA [131]. Three recent studies showed that MA has a higher interictal cortical response during visual stimuli compared to MO [135–137]. However, two studies did not confirm these results, with one finding no differences between MA and MO [138] and another showing a higher cortical response in MO compared to MA [139]. On the other hand, the amplitude of interictal cortical response during somatosensory stimuli seemed to be similar between MO and MA [131, 140]. However, a recent study showed that MA and MO had a different EEG spatial distribution during a trigeminal cutaneous mechanical stimulus, with MA showing an increased signal in the cerebellum cortex [141]. The discrepancy in results between studies assessing event-related potentials in MA and MO could be due to methodological differences, such as the population included, the stimulus application, and the EEG recording procedure.

Habituation deficit

An interictal lack of habituation in cortical response during repeated visual, auditory, or somatosensory stimuli, which normalizes during the ictal phase, has been considered a neurophysiological hallmark of migraine [142]. Even if the interictal lack of habituation during repeated visual stimuli has been observed both in MO and MA, this impairment seemed more pronounced in MA patients [131, 136].

Treatment response

Currently, guidelines for abortive and preventive treatment for MA and MO are similar [143]. However, emerging evidence suggests that the response to therapies between these subtypes may not be identical, raising questions about whether more tailored treatment strategies are needed [144, 145]. Randomized clinical trials typically include mixed cohorts of MA and MO patients and the primary objective of these trials tends to focus on reducing headache days or the time to pain relief rather than addressing aura-specific symptoms [143–145].

Aura targeted treatment

No treatments have been approved solely for the aura, although some drugs such as ketamine, magnesium sulphate, aspirin, or ginkgolide have shown promising results in reducing aura symptoms in preliminary research, often involving small sample sizes [146–152]. Another interesting medication analysed specifically in aura was tonabersat, a neuronal-glial gap junction inhibitor [153]. It was demonstrated in the randomised control trial that tonabersat was effective in the reduction of aura attacks in comparison to placebo (median number of attacks per 12 weeks: 1.0 compared to 3.2). Interestingly, results regarding other outcomes, such as migraine headache days, either with or without aura, did not reach significance [153].

Abortive treatment

When examining abortive treatment, there is evidence that triptans may be less effective in MA patients compared to those with MO [154–156]. A recent survey of 1,394 patients rated triptans significantly more effective than ibuprofen, especially for MO [157]. One possible explanation for the reduced efficacy in MA may be more diffuse derangements of brain physiology during attacks involving the cerebral cortex, which are, therefore, more difficult in therapy [144]. However, there may also be deeper biological differences that make MA less responsive to these treatments. This discrepancy warrants further investigation, particularly to clarify why abortive treatments appear less effective in patients with aura. Although new medications like gepants and ditans have been approved for both types as acute or preventive treatment, no data is yet available on their specific efficacy differences between MA and MO [158–161].

Preventive treatment

Preventive treatment offers another perspective on the distinction between MA and MO. The role of CSD, a phenomenon more prominent in MA, may influence treatment efficacy. Several prophylactic drugs, including topiramate, valproate, lamotrigine, propranolol, and amitriptyline, are known to suppress CSD in animal models, suggesting that these treatments might offer specific benefits for MA patients [161–163]. However, this hypothesis has not been systematically validated in clinical studies [160, 164]. Moreover, propranolol has also been demonstrated to inhibit cerebral blood flow induced by CSD and trigeminovascular activity, which suggests MA and MO should respond differently to the prevention treatment with propranolol [153].

Among the newer preventive treatments, monoclonal antibodies targeting CGRP or its receptors (anti-CGRP mAbs) have revolutionised migraine management, they have not been systematically studied in terms of their effects on the aura [165–168]. Some observational studies suggest a reduction in headache days but no change in aura frequency for MA patients, possibly because anti-CGRP mAbs counteract trigeminovascular sensitisation without directly affecting CSD [169, 170]. A

post-hoc analysis by Ashina et al. found that erenumab reduced migraine days in both MA and MO patients, although its impact on aura was not directly assessed [171]. Similarly, a post-analysis of PROMISE studies with eptinezumab demonstrated efficacy and safety in patients with aura, comparable to the overall study populations [172]. Additionally, one study showed that galcanezumab reduced headache incidence following aura, particularly in patients who responded well to treatment [173]. More research is needed to understand whether anti-CGRP mAbs can address both the headache and aura phases in MA patients.

Anticonvulsants in migraine treatment

Other treatment options have shown mixed results. Anticonvulsants, like lamotrigine and levetiracetam, have gained attention for their potential to reduce aura symptoms [163, 164, 167]. Lamotrigine, in particular, appears to have a more significant impact on the aura phase, though its efficacy in treating the headache phase of migraine remains debated [164, 165, 169–172, 174, 175]. Similarly, levetiracetam has also been proposed as an alternative preventive option, though its benefits in MA versus MO remain unclear [166, 167, 173, 176]. These drugs may represent an option for patients who experience limited success with conventional therapies, particularly those targeting the aura component.

Non-pharmacological treatment options

Neuromodulation, including transcranial magnetic stimulation (TMS) and non-invasive vagal nerve stimulation, has shown mixed results for migraine management [143–145, 158, 177]. TMS is divided into two main forms: single-pulse TMS (sTMS) and repetitive TMS (rTMS). Transcranial magnetic stimulation was initially designed for the acute treatment of MA, but some recent reviews found no evidence of differences between MA and MO populations [178]. However, the randomised control trial performed by Lipton et al. showed efficacy in the acute treatment of MA for specifically sTMS [179]. Moreover, studies suggest that sTMS can be a valuable option in the therapy of both episodic and chronic migraine regardless of the aura presence [180, 181]. Apart from sTMS studies, some research shows the possible effectiveness of rTMS in migraine therapy [182]; nevertheless, only sTMS was approved by the Food and Drug Administration (FDA) in the United States of America [183].

Complex aura treatment

Finally, another complexity in treating MA arises in patients with more prolonged or complex aura presentations [184]. Case reports suggest that drugs like verapamil and acetazolamide may be effective in reducing the severity and frequency of these attacks, although these treatments are not typically used in standard care for MO patients [185]. Studies exploring treatment responses in MA and MO patients with both simple and complex aura found no significant differences in outcomes between these groups. However, patients with aura, particularly complex aura, tend to show better responses to preventive treatment such as with topiramate, valproate, or anti-CGRP mAbs, suggesting that aura may be a marker for a distinct subgroup responding differently to certain therapies [186]. For aura complexity assessment, a tool proposed by Petrusic et al. was used, called a Migraine Aura Complexity Score [187]. The analysis of complexity was performed based on three major components: aura's influence on higher cortical functions, the degree of involvement of the surface of primary visual and somatosensory areas, and the involvement of hand and head by somatosensory aura. Those three domains combined result in a better complexity assessment than all of them alone. The issue of aura complexity is another that requires further investigation due to the putative differences in the pathogenesis of each aura subtype, as mentioned before [53]. However, these divagations are beyond the topic of the narrative review.

Risk and complications

Cardiovascular diseases

A considerable number of studies conducted on different populations elaborated on the topic of migraine and CVD. It has been estimated that MA is a significant and independent risk factor of major cardiovascular events, comparable in risk stratification to high values of systolic blood pressure and high total cholesterol levels [75, 188] Compared to healthy populations, patients suffering from MA are reported to have approximately a two-fold increase in the total cardiovascular risk [75, 189]. Interestingly, higher headache frequency has been found to be an additional, independent factor that can further increase the cardiovascular risk for both types of migraine [190]. Available data is inconsistent when it comes to increased cardiovascular risk in the case of MO, yet few recent studies have shown a positive correlation between CVD prevalence and MO [75, 191–194]. Winsvold et al. reported that patients with MO have a higher prevalence of other CVD risk factors, such as high BMI, smoking, and low physical activity, which could be related to lifestyle changes, whereas no such significant correlation was found for MA [190]. Furthermore, genetic studies showed that migraine and several CVDs share genetic variants as risk factors, while this effect seems stronger for MO than MA [195–198]. However, slightly different observations were made in the recent study conducted on a large cohort of patients (140,915

participants in total, 25,915 with prevalent migraine, 2,224 with incident migraine) [199]. Although many studies showed higher cardiovascular risk scores are correlated with a history of migraine, active migraine does not necessarily increase those risk scores [199]. Similar observations were made in another study, which, compared to the previous one, focused only on women [200]. Results showed that the odds of having active migraine or developing it in the future decreased with increasing cardiovascular risk scores, which may be explained by the hypothesis of a positive correlation between a relatively healthy cardiovascular system and the presence of active migraine.

Nevertheless, several cardiovascular risk factors have been reported as more common in migraine patients than in the general population.

Atrial fibrillation

The estimated prevalence of atrial fibrillation (AF) was higher in MA than in MO patients, especially those with visual-type aura [201, 202]. Gollion et al. proved that AF is one of the leading causes of ischemic strokes in young patients with MA [203]. Chiang et al. conducted a study comparing the artificial intelligence-enabled electrocardiogram AF prediction model output in both groups of migraine patients. A higher probability of AF was demonstrated in MA than in MO in both women and men [204]. However, a large-scale study conducted on the Norwegian population presented contradictory results. A nine-year observation of the population of nearly 40,000 patients showed no increased risk of AF and stroke in migraine patients. Moreover, in the group of at least 55-year-old patients, migraine was connected to a decreased risk of AF [205].

Atherosclerosis

In 2019, Magalhães et al. reported an association between atherosclerosis of carotid arteries and migraine among women. In this study, MA was proved to be positively correlated with hypertension and diffuse carotid thickening, while MO patients had lower rates of arterial stiffening and carotid plaques [206]. Later studies did not confirm these findings, as no positive association between migraine and atherosclerosis was found [113, 207]. Furthermore, it was found in the Rotterdam study that migraineurs, regardless of migraine subtype, had less calcification in the intracranial arteries than subjects without migraine [208]. Moreover, Gollion et al. reported a significant negative correlation between any type of migraine and atherosclerosis of large arteries among migraineurs of both sexes [113].

Arterial dissection

Another type of vascular condition related to migraine is arterial dissection. It has been estimated that cervical artery dissection is associated with MO but not with MA [209]. Furthermore, it has been shown that artery dissection is a more common cause of ischemic stroke in the subgroup of MO compared to both MA and non-migraine stroke patients [203].

Patent foramen ovale

An interesting point is the presence of patent foramen ovale (PFO) in migraine patients. It is suggested that this right-to-left shunt is more common in patients with MA, while such correlations are not observed for MO [210, 211]. In the study conducted by Snijder et al., PFO with atrial septal aneurysm was significantly more frequent in patients with MA in comparison to healthy individuals (18.1% and 6.1%, respectively, OR 3.72) [210]. Consistent observations were made by Domitrz et al., who performed a study comparing the prevalence of PFO in MA, MO patients, and healthy volunteers. Results showed that PFO was significantly more often in the MA group than in both the MO and control groups (54%, 25%, and 25%, respectively) [211]. Moreover, some studies have focused on an increased risk of ischemic stroke in patients with MA due to the higher presence of PFO. More precisely, in patients with cryptogenic ischemic stroke (CIS), MA was associated with possibly causal PFO (OR = 4.0) and probably causal PFO (OR = 5.4) [212]. Noteworthy, Martinez-Majander et al. estimated that the increased risk of CIS in adults with MA was not linked to the presence of PFO. However, higher right-left shunt intensity increased the prevalence of MA [213]. These findings were consistent with other recent studies [203, 214]. Interestingly, limited research suggests that PFO may also be related to MO. Tang et al. conducted a cross-sectional study in China comparing the frequency of MO in patients with and without PFO. It was demonstrated that the former group suffered from MO significantly more commonly than the latter (13% and 8%, respectively) [215]. However, these observations require further investigation. Regardless of migraine type, Bank et al. suggested that more focus should be put into the management of co-existing CVD risk factors because a considerable number of middle-aged women with migraine do not achieve proper control over already diagnosed factors (e.g., blood pressure) [216]. Nevertheless, CVD risk due to migraine is so impactful that it was recognised and implemented in the most recent version of the Cardiovascular Risk Score (QRISK) 3 algorithm for the estimation of 10-year CVD risk [217].

Visual symptoms

Moving from the broad field of cardiovascular disorders, MA can be associated with an increased risk of different types of permanent visual symptoms. A few case reports presented MA patients with retinal migraine and typical visual aura who suffered from permanent monocular visual loss and positive visual symptoms (e.g., scotoma) after migraine attacks. Further investigation diagnosed several underlying causes, such as ischemic optic neuropathy, retinal artery occlusion, eye vasculitis, and retinal haemorrhage [218, 219]. Al-Moujahed et al. confirmed that migraine, especially MA, significantly increased the risk of retinal artery occlusion [220].

Recently, a phenomenon called visual snow syndrome (VSS) gained more attention in migraine studies due to its high prevalence in patients with migraine [221]. Interestingly, studies analyzing neurotransmitters' connectivity suggested some relation between VSS and particularly MA. More precisely, although serotoninergic connectivity was independent of migraine presence in VSS, the changes were comparable to those in MA patients. Therefore, similar pathogenesis may be shared by VSS and MA [222].

Hormonal diseases

Since, as already discussed, migraine pathogenesis is associated with sex hormones, some studies explored its relation to other hormone-related conditions. Several meta-analysis studies have reported the protective impact of migraine on the development of breast cancer [223–225]. However, Fang et al. provided evidence for the association of MO with an increased prevalence of estrogen receptor-negative breast cancer, while no such risk has been found for MA [226].

Other neurological diseases

Various studies reported evidence of an association between migraine and neurodegenerative diseases, dementia, and cognitive impairment; however, usually without differentiation between MA or MO [227, 228]. One study found a significant difference between MA and MO, which increased the risk of developing dementia by 2.11- and 1.19-fold, respectively [229]. The explanation for the increased risk of dementia for MA compared to MO may be found in the genetic background of both MA and some dementia forms [230], since, as previously mentioned, the evidence for genetic bases of MA is more clear compared to MO.

Migraine was estimated to be the most common type of headache in the population of multiple sclerosis (MS) patients, with a prevalence of around 31% [231]. Rościszewska et al. reported a significantly higher incidence of MA among migraineurs diagnosed with MS (45.9%) [232]. Recent studies have not confirmed a causal effect of migraine on MS, although mutual factors in the pathogenesis of both diseases have been found, such as shared genetic variants among major histocompatibility complex genes, regardless of migraine type [233, 234].

Vestibular disorders

Some evidence was also reported for the positive association of migraine with vestibular disorder. MA was estimated to increase the risk of Meniere's Disease (MD) slightly more than MO (HR = 2.13, 1.93, respectively). Conversely, a similar correlation was observed, as it has been proved that MD increases the risk of both MO and MA (HR = 2.23 and 2.0, respectively) [235]. Another study reported that vestibular symptoms were more likely to appear in the group of MA (85%) than MO patients (70%) [236].

Dermatological diseases

In the field of dermatology, Sarkhani et al. presented an observational study that proved an association between psoriasis and migraine. The prevalence of migraine was significantly higher in the psoriasis patients compared to the non-psoriasis control group (21% vs 9%). Furthermore, it has been reported that the prevalence of MA among migraine patients was significantly higher in the psoriasis than in the no-psoriasis group (53% vs 22%) [237]. These findings were coherent with previous studies, which also reported a higher ratio of MA among migraine-psoriasis patients compared to migraine patients in the general population [238, 239].

Psychiatric disorders

The comorbidity rate of psychiatric disorders, such as depression, sleep disorders, and anxiety in migraine, is established as high [240, 241]. MA is estimated to be more frequently associated with depression than MO [242, 243]. Moreover, patients who attend headache clinics due to suffering from MA and depression have a significantly higher rate of suicide risk, while the highest risk is reported for chronic MA patients (47% for self-reported suicide ideation and 14% for self-reported suicide attempts) [244]. However, the limitation of that study was that it included only hospital patients and not the general population of migraine patients. In another study, Oedegaard et al. compared the frequency of depression, mixed anxiety and depression disorder (MADD), and pure anxiety disorder in patients with MA, MO, and healthy individuals. It appeared that depression and MADD were significantly more frequent in women with MA in comparison to MO. However, those observations were not found for men suffering from migraine, in whom there were no statistical differences.

Furthermore, pure anxiety did not differ in prevalence between MA and MO [245]. Finally, an interesting study was conducted by Tanik et al., who investigated anger and impulsiveness in migraine patients using appropriate scales. It was demonstrated that anger symptoms were substantially increased in MA patients compared to MO patients. No similar observations occurred in terms of impulsivity [246]. What should be remembered is the higher prevalence of migraine in women; thus, usually, a higher percentage of women in research groups, which might influence the statistics, especially statistical power for each group.

Although migraine, either with or without aura, can be associated with several conditions (Fig. 3), the underlying mechanisms of this phenomenon are still unknown, and further studies are needed.

The red outline represents the increased risk (positive correlation), while the green outline represents the decreased risk (negative correlation). The circle diameter corresponds to the estimated strength of the correlation. Background colours represent the category of conditions (light grey, associated diseases; white, cardiovascular risk; pink, hormones; light blue, psychiatric symptoms; dark blue, inflammation; dark grey, neuroimaging). CGRP, calcitonin gene-related peptide; ER-, estrogen receptor-negative; ER+, estrogen receptor-positive.

Conclusions and future perspectives

In conclusion, the abundance of available literature comparing MA and MO shows similarities and differences when looking at from different perspectives and different aspects being analysed. A complex summary has been presented in Table 2. Potential confounding factors for studies reporting differences between MA and MO could be that, possibly, the diagnosis of MA may be more specific and discriminating than the diagnosis of MO in large cohort studies. On the other hand, the higher prevalence of MO may provide more statistical power to discern specific features for this group. However, literature not only mentions quantitative differences between MA and MO, pointing in the same direction. There are also intriguing qualitative differences between these two migraine types that cannot be explained by the above-mentioned potentially confounding factors, urging to take MA and MO as two different types of migraine always into account when making a diagnosis. The clue of these divagations is to achieve a full understanding of the underlying pathopsychological mechanisms of both types and identify differences that may influence the management of each. An in-depth analysis is needed to understand migraine genetic and molecular bases, which may allow researchers to use this knowledge in a proper, even more targeted treatment and even in novel drug discoveries. Any unique features of each type may also determine a specific response to the applied therapy. Finally, an additional advantage of seeing subtle differences in a

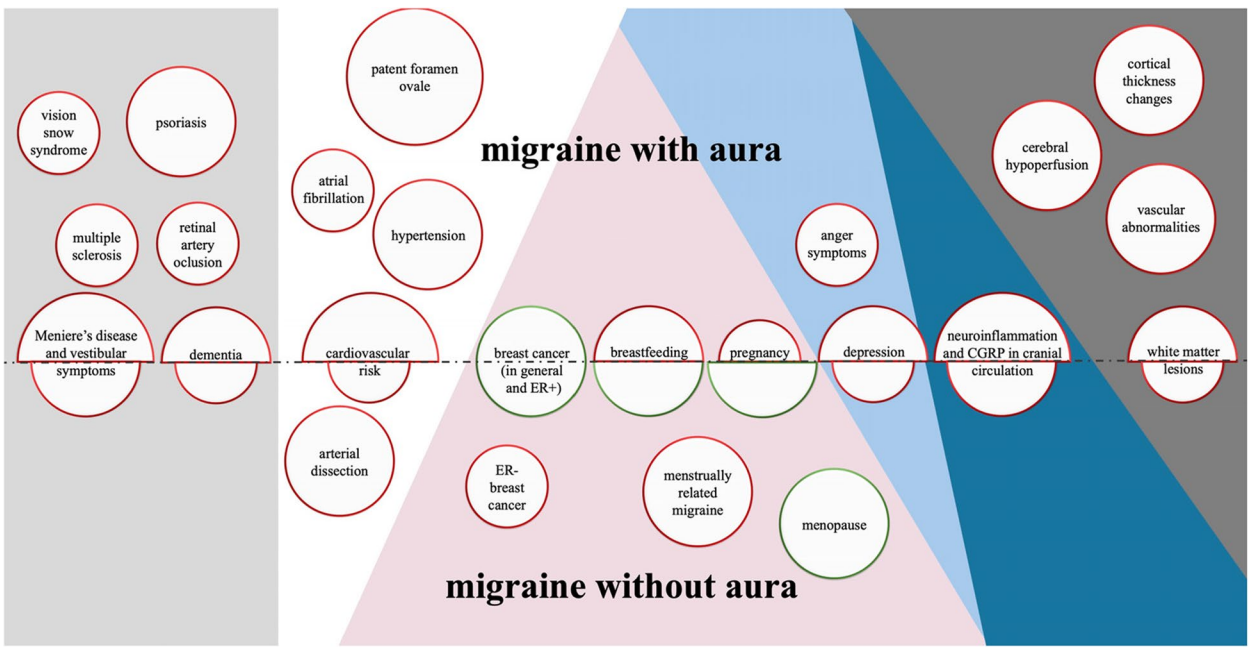

Fig. 3 Conditions and alterations associated with different types of migraines

Table 2 A summary of the original studies analysing differences between MA and MO with a specification of which study showed significant differences and which did not

	MA compared to MO
Pathogenesis	
Molecules' levels	MA > ↑ CGRP [36]; MA > ↑ fibrinogen, factor II, CRP [50]; MO > ↑ lymphocytes; MA > ↑ NMR [54]; MA > ↑ IL-6 [56]; MA > ↑ homocysteine [58]; = chemerin, visfatin, IL-18 [57]
Ischemic tetany tests (related to Mg levels)	MA > positive tetany test [48]
Hormones	
Menstrually-related migraine	MO > [59, 62–64]; = [65, 66]
Pregnancy influence	MO > ↑ remission [62, 67, 68]; MA > ↑ attack frequency, new migraine onset [59, 62, 66–68]
Breastfeeding influence	MA > ↑ attack frequency [66, 67]
Menopause influence	MO > ↓ attack frequency and severity [64]
Relation with hormones levels	MA > aura worsening after estrogen treatment [69]; = progesterone [72, 73]
Patients' characteristics	
Age and sex distribution	MO > ↑ female to male ratio [83, 84]
Age of onset	MO > ↓ in males than females [86]
Clinical presentation	MO > ↑ nausea, MA > ↑ unilateral pain, photofobia, headache duration [89]
Dietary patterns	MA > ↓ intake of chocolate, ice cream, hot dogs, and processed meats [87]
Anthropological measurements	= BMI, waist circumference [88] MO > attack frequency positively correlated with BMI, waist circumference [88]
Neuroimaging: morphological changes	
Volumetric and cortical thickness changes	MA > ↑ occipital bending [92]; MA > ↑ cortical thickness [93]; = brainstem volume [90]; = cortical thickness [95]
SC calculated from the DTI	MA > ↑ [98]; = [100]
White Matter Hyperintensities	MA > [103, 104, 106]; = [105, 108]
Basilar Artery displacement	MA > ↑ [111, 112]
Neuroimaging: vascular perfusion	MA > TCD abnormalities [116]; MA > CBF abnormalities [117, 118]; = TCD [119]; = CBF [95]
Functional neuroimaging	
Resting state functional connectivity	≠ different patterns between brain areas [98, 100, 120–124]
Brain activity during a task performance	MA > ↑ [115, 128]
Functional near-infrared spectroscopy	= [129, 130]
EEG	≠ resting state EEG [132, 133]; MA > ↑ cortical response during stimuli [135–137, 141]; MO > ↑ cortical response during stimuli [139]; = event-related potential EEG [138]
Treatment response	MO > ↑ triptans effectiveness [154–157]; MA > ↑ levetiracetam effectiveness [176]; MO > ↑ anti-CGRP mAbs influence on frequency) [169]; = anti-CGRP mAbs [171]; = anti-CGRP mAbs (on intensity and duration) [169]; = TMS results [178]; MA > single pulse TMS effectiveness; = vagal nerve stimulation [177]
Risks and complications	
CVD	MA > arteriosclerosis [206]; MO > arterial dissection [209]; MA > PFO [210, 211]; MA > atrial fibrillation [201, 202, 204]; = arteriosclerosis [113]
Breast cancer	MO > [226]
Neurodegenerative diseases	MA > dementia [229]; = Parkinson's disease [227]
Otolaryngology diseases	MA > vestibular symptoms [236]; = Meniere's disease [235]
Psoriasis	MA > [237, 238]
Psychiatric diseases and symptoms	MA > depression [244]; MA > depression, MADD in women [245]; = depression, MADD in men; anxiety in both sexes [245]

Table 2 (continued)

	MA compared to MO
Anger and impulsiveness	MA > anger symptoms [246]; = impulsiveness [246]

↑ Increase, ↓ Decrease, *BMI* Body mass index, *CBF* Cerebral blood flow, *CGRP* Calcitonin gene-related peptide, *CRP* C-reactive protein, *CVD* Cardiovascular diseases, *DTI* Diffusion tensor imaging, *EEG* Electroencephalography, *IL* Interleukin, *MA* Migraine with aura, *mAbs* Monoclonal antibodies, *MADD* Mixed anxiety depressive disorder, *MO* Migraine without aura, *NMR* < neutrophiles-monocytes ratio, *PFO* Patent foramen ovale, *SC* Structural connectivity, *TCD* Transcranial Doppler, *TMS* Transcranial magnetic stimulation

= No differences between MA and MO

MA > occurs more often in MA

MO > occurs more often in MO

≠ Differences between MA and MO without estimation of the direction

patient's clinical presentation or the results of additional tests or diagnostic tools is helping differentiate MA and MO, especially when the aura is atypical.

Apparently, female sex hormones modulate migraine with and without aura differently. MO is more common during menstruation and usually decreases post-menopause [59, 62, 64], which remains not at odds with MO being more common at a younger age and showing a more significant advantage of women than MA [83, 84]. Conversely, MA is less prevalent during menstruation [59, 62, 64].

Interestingly, although neuroimaging is not commonly used for migraine differentiation, patients seem to have neurovascular morphological [93, 94, 99, 104, 105, 107, 112, 113] and functional [99, 101, 116, 121–125, 129] alterations compared to healthy controls, suggesting the presence of a "higher brain excitability" in migraine patients. According to neuroimaging and EEG studies, these impairments could be more pronounced in MA patients compared to MO [136–138, 142], suggesting a further increase in brain excitability in this subgroup of patients. The difference observed between MA and MO mainly occurred in areas involved in visual processing [136–138]. As most studies included patients with visual aura, the most common type, these results could be due to the type of aura assessed. Although there are a few articles in this area [247–250], future neuroimaging and EEG studies should focus more on patients with different types of auras. Moreover, the heterogeneity in the methodology used by different studies makes results hard to compare. Thus, multicentre studies that include more patients using the same methods are needed to reach a definitive conclusion.

There are few clinical trials specifically comparing treatment outcomes between MO and MA patients. Further subgroup analysis or randomised studies containing a MA subgroup are needed to answer this important question. Also, currently, there are no approved treatments just for aura [147]. Understanding how CGRP impacts the neural and vascular components of migraine aura can provide insights into more effective treatments. Finally, preventive treatment response appears to be associated with different migraine aura subtypes, suggesting personalised treatment strategies could be beneficial in the future [186].

Many studies have also explored the association of migraine with several different conditions. Some significant disparities between MA and MO were found. MA is commonly suggested to be linked with a higher prevalence of major CVD events [75], while paradoxically, MO shares more genetic risk factors with CVD than MA [196–199]. However, some very recent evidence showed that particularly active migraine may be associated with a decreased cardiovascular risk score [199, 200]. Research on this topic should be prioritised since these findings are potentially crucial for applying adequate prevention. Several conditions are probably also associated strictly with MO, such as arterial dissection [209] or estrogen receptor-negative breast cancer, while breast cancer, in general, was observed to appear less frequently in migraine population [226]. The underlying pathomechanisms for such comorbidities are still poorly explored and require further investigation.

Although MO and MA share multiple similar features, diverse studies on different aspects of migraine suggest some crucial differences between both types. Moreover, the third possible option appears to be the aura separate from migraine pain, either preceded by an aura or not. Therefore, aura could be one disorder and migraine headache another. Specific features seen in clinical presentation, diagnosis, treatment, or outcomes differ between MA and MO. An important aim of recent studies was to understand migraine bases better, also for MA, MO, and aura separately.

The phenomenon of CSD seems to be an important factor in migraine pathogenesis; however, a conclusive answer to its role in MA, MO, and aura separately can not be found yet. This knowledge may be a missing piece

in achieving the most precise and effective treatment of each migraine type. Likely, exploring the molecular background of migraine pain development will bring the desired explanation for observed differences and allow researchers to answer the question, are MA and MO just two types or rather two distinct diseases? Nevertheless, seeing all the differences in various aspects of the disease, both pathogenetic and clinical, we propose that future research should consider MA and MO as being at least partially separate disorders.

Abbreviations

AF	Atrial fibrillation
ATP1A2	ATPase Na + /K + Transporting Subunit Alpha 2
BA	Basilar artery
BMI	Body mass index
CACNA1A	Calcium voltage-gated channel subunit alpha 1A
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CGAS	Candidate gene association studies
CGRP	Calcitonin gene-related peptide
CIS	Cryptogenic ischemic stroke
CSD	Cortical spreading depression
CSNK1D	Casein kinase 1 delta
CVD	Cardiovascular diseases
DTI	Diffusion tensor imaging
EA2	Episodic ataxia type 2
EEG	Electroencephalography
ERP	Event-related potential
FASPS	Familial advanced sleep-phase syndrome
FHM	Familial hemiplegic migraine
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
hs-CRP	High-sensitivity C-reactive protein
ICHD-3	International Classification of Headache Disorders, 3rd edition
IL-6	Interleukin-6
KCNK18	Potassium channel subfamily K member 18
MA	Migraine with aura
CGRP-mAbs	Monoclonal antibodies targeting calcitonin gene-related peptide or its receptor
MADD	Mixed anxiety and depression disorder
MD	Meniere's Disease
MO	Migraine without aura
MTHFR	Methylenetetrahydrofolate reductase
MS	Multiple sclerosis
NMR	Neutrophil/monocyte ratio
NOTCH3	NOTCH receptor 3
PACAP	Pituitary adenylate cyclase-activating peptide
PD	Parkinson's Disease
PFO	Patent foramen ovale
PRRT2	Proline-rich transmembrane protein 2
RCTs	Randomized clinical trials
RVCL-S	Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic manifestations
rTMS	Repetitive transcranial magnetic stimulation
SCN1A	Sodium voltage-gated channel alpha subunit 1
SHM	Sporadic hemiplegic migraine
SNPs	Single nucleotide polymorphisms
SOD	Superoxide dismutase
sTMS	Single-pulse transcranial magnetic stimulation
TMS	Transcranial magnetic stimulation
TRESK	TWIK-related spinal cord potassium channel
TREX	Carboxyl-terminus of three prime exonuclease-1
VSS	Visual snow syndrome
WMHs	White matter hyperintensities

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