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REVIEW

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Is migraine a common manifestation of CADASIL-Cons

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Abstract

Headaches and transient neurological symptoms that bear resemblances to clinical manifestations of migraine, especially migraine with aura, are common among patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or cysteine-altering *NOTCH3* genetic variants. However, according to the International Classification of Headache Disorders, Third Edition (ICHD-3), these patients should be diagnosed as headache attributed to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) rather than migraine with or without aura. Although transient focal neurological symptoms are often labeled as migraine aura, these symptoms are often atypical and complicated, and could not easily conform to the criteria for migraine with aura. Besides, the association between migraine and CADASIL could not be supported by population-based genetic studies, and cysteine-altering *NOTCH3* genetic variants are not more common among patients with migraine with or without aura compared with non-migraine controls. In addition, the underlying pathophysiology may be different between migraine and CADASIL. Although increased cortical spreading depression (CSD) susceptibility in mice harboring a human pathogenic *Notch3* variant is often regarded as supportive evidence for the association, CSD could been seen in conditions other than migraine, such as cerebral ischemia. The role of calcitonin gene-related peptide (CGRP), one of the most important molecules in migraine pathophysiology, in CADASIL patients with migraine-like manifestations is yet to be determined. To sum up, there remain uncertainties whether headache and migraine aura-like manifestations in CADASIL correspond to "ordinary" migraine with or without aura seen in routine clinical practice. Therefore, we are still a number of steps from a firm conclusion about the association between CADASIL and migraine.

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Migrainous headaches in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) are not equal to a migraine diagnosis

It was commonly reported that patients with CADASIL can have headaches with certain migrainous features, especially migrainous aura. However, a migrainous phenotype does not necessarily correspond to a migraine diagnosis. In the International Classification of Headache Disorders, Third Edition, (ICHD-3) criteria for migraine with (MA) and without aura (MO) (codes 1.1 and 1.2) [1], a diagnosis of migraine can be made when the clinical manifestations are "not better accounted for by another

ICHD-3 diagnosis." In fact, there is a diagnostic entity called "headache attributed to CADASIL" (code 6.8.1) (Table 1), in Chap. 6, headache attributed to cranial and/or cervical vascular disorder. It is described as "headache recurring in attacks resembling 1.2 migraine with aura, except for an unusual frequency of prolonged aura." In a similar sense, although the diagnostic entity "headache attributed to mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)" (code 6.8.2) could manifest with "recurrent migraine attacks with or without aura" (criterion C1), these patients should better be diagnosed as such rather than migraine. In fact, migraine is a specific diagnosis rather than just a symptom. From this perspective, migrainous headaches in patients with CADASIL should be diagnosed and coded as "headache attributed to CADASIL" (code 6.8.1) rather than MA or MO (codes 1.1 and 1.2) according to the ICHD-3.

Migrainous symptoms, including Aura, in CADASIL are often atypical

Patients with CADASIL can have transient neurological deficits accompanied or followed by headache, which are often regarded as "migraine aura." However, it is not uncommon that these symptoms may not conform to the classical manifestations of "migraine aura," and could not easily fulfill the criteria for MA (code 1.2) [1]. For instance, in one of the largest series from France and Germany ($n = 378$) [2], 59.3% of CADASIL patients with MA had atypical or complex forms of "auras", such as confusion, altered consciousness or hallucinations, acute-onset or long-lasting auras, etc., and 19.7% of patients reported that their "auras" were never accompanied by headache. The findings were actually consistent with those seen in a British cohort ($n = 300$) [3]. Even when the "auras" are considered typical, the distributions of individual aura symptoms are different from those seen in patients with "ordinary" MA. The majority of CADASIL patients had multiple aura types [2, 3], which were seen in only about one third of patients with "ordinary" MA [4]. Besides, sensory, speech, and motor auras seemed to be over-presented in patients with CADASIL [2, 4]. Based on these clinical observations, it is possible that the underlying mechanisms of episodic focal neurological symptoms in CADASIL could be different from those in "ordinary" forms of migraine aura. On the other hand, it is still possible that CADASIL patients could have "genuine" MA or MO (codes 1.1 and 1.2) aside from these atypical migrainous attacks, i.e., "headache attributed to CADASIL" (code 6.8.1). However, whether CADASIL patients are more likely to have MA or MO (codes 1.1 and 1.2) remains to be determined, as all these "migrainous headaches" were frequently lumped together as "migraine" in most prior studies [2, 3, 5–7].

Table 1 Diagnostic criteria for migraine and headache attributed to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [1]

1.1 Migraine without aura	**1.2 Migraine with aura**	**6.8.1 Headache attributed to Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)**
A. At least five attacks[1] fulfilling criteria B-D	A. At least two attacks fulfilling criteria B and C	A. Recurrent attacks of migraine with typical, hemiplegic or prolonged aura, fulfilling criterion C
B. Headache attacks lasting 4–72 hr (untreated or unsuccessfully treated)	B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal	B. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) has been demonstrated[1]
C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)	C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥ 5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5–60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache	C. Either or both of the following: 1. migraine with aura was the earliest clinical manifestation of CADASIL 2. attacks of migraine with aura improve or cease when other manifestations of CADASIL (*eg*, ischaemic stroke, mood disturbances and/or cognitive dysfunction) appear and worsen
D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia	D. Not better accounted for by another ICHD-3 diagnosis.	D. Not better accounted for by another ICHD-3 diagnosis.
E. Not better accounted for by another ICHD-3 diagnosis.		

There remain uncertainties regarding the association between migraine and genetic variants associated with CADASIL

Although individuals harboring cysteine-altering *NOTCH3* genetic variants, regardless of whether a diagnosis of CADASIL could be made, could have migrainous headaches, such variants do not appear to be more common among patients with MA or MO. For instance, the p.R544C variant, which is the predominant variant associated with CADASIL in certain regions of East Asia [8–11], was not more prevalent in migraine patients ($n = 2,884$) compared to non-headache population controls ($n = 3,502$) (1.1% vs. 1.0%, $p = 0.846$) in a study from Taiwan, and the percentages of MA were not different between migraine patients with and without the variant (6.2% vs. 11.3%, $p = 0.572$) [12]. Similarly, none of the patients in a Korean series of CADASIL patients had MA [13].

It is possible that racial or ethnic differences could play a role, although data in some other studies in Caucasians were not supportive of the association between *NOTCH3* genetic variants and migraine. In a cross-section study involving participants from the Geisinger DiscovEHR initiative cohort recruited in the United States, the proportions of patients with MA (4.2% vs. 6.0%, $p = 0.61$) and MO (14.3% vs. 21.7%, $p = 0.13$) were similar between cases with cysteine-altering *NOTCH3* variants and age- and sex-matched controls not harboring nonsynonymous variants in the *NOTCH3* gene. When migraine patients were looked upon separately, the percentage of patients with aura in cases (5/22 = 22.7%) was similar to that in controls (11/51 = 21.6%) [14]. In addition, the prevalence of migraine between individuals with and without cysteine-altering *NOTCH3* variants was not significantly different in the United Kingdom (UK) Biobank [15].

The underlying pathophysiology may be different between migraine and CADASIL

Cortical spreading depression (CSD) is widely believed to be the underlying mechanism of the migraine aura [16, 17], and increased susceptibility to CSD in transgenic mice expressing the p.R90C *Notch3* variant or a *Notch3* knockout mutation is commonly viewed as supportive evidence for the association between migraine and CADASIL [18]. However, skepticisms remain. Excitability of cortical neurons plays an important role in CSD susceptibility [16], although the pathology of CADASIL mainly involves subcortical small vessels rather than cortical neurons [7]. Besides, it remains to be determined whether there could be increased susceptibility to CSD in CADASIL patients. More importantly, CSD is an electrophysiological phenomenon neither specific nor limited to migraine, and it can also be observed in patients with subarachnoid hemorrhage, stroke and traumatic brain injury [16]. Therefore, whether increased susceptibility to CSD observed in transgenic mice might reflect cerebral ischemia or migraine aura needs to be further confirmed.

In the clinical phenomenology, there are considerable discrepancies between "aura" symptoms in CADASIL and those in "ordinary" MA [2, 4]. Atypical or complicated "aura" symptoms are reported in a significant proportion of CADASIL patients [2, 3], and the distributions of individual "aura" symptoms are different from those in "ordinary" MA patients [4]. This may imply that the underlying pathophysiology could be different between migraine and CADASIL. It is not without doubt whether some of the atypical "aura" symptoms of CADASIL, such as basilar symptoms, hallucinations, confusion, etc [2, 3, 19], could be accounted for by CSD. In particular, a history of cerebrovascular events is commonplace for these patients [2]. Under such circumstances, it may not be easy to make a distinction between "auras" and transient ischemic attacks (TIAs) in these patients [2]. As genetic variants association with CADASIL predisposes these patients to increased risks for cerebral ischemia, whether some of the "auras" in CADASIL could be symptoms of TIAs or even minor stroke in individuals with a history of headache needs to be further clarified.

On the other hand, recognition of the role of calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine is perhaps one of the most important progresses in headache medicine in the recent decade, and has been translated to routine clinical practice [20]. It was demonstrated the CGRP levels in the external jugular veins increased during the ictal phase, indicating CGRP release during migraine attacks [21], and the interictal plasma levels of CGRP were higher in patients with chronic migraine than in those with episodic migraine or healthy controls [22]. On the other hand, in an interesting study, it was shown that there was no difference in the CGRP levels in CADASIL patients with and without migraine [23]. In fact, there have been only limited data to date, and the association between CGRP and CADASIL is yet to be clarified. Taken together, more research is needed to persuade the scientific community that there is solid scientific evidence indicating shared pathophysiology between CADASIL and migraine.

Response to Chabriat H. The Journal of Headache and Pain 2025[24]

As pointed out by my opponent, Professor Hugues Chabriat, there is little doubt that patients with CADASIL or cysteine-altering *NOTCH3* variants and their family members could have clinical manifestations that bear similarities to aura and headache in migraine patients. However, I would like to emphasize that headache diagnoses should be made according to the ICHD-3 [1]. A diagnosis of "headache attributed to CADASIL" (code

6.8.1) would be more appropriate than MA or MO (codes 1.1 and 1.2) for these patients. Although migrainous features could be shared by headache disorders other than MA or MO, these patients should be categorized correctly based on the clinical phenomenology, genetic variants, substances used, or clues that indicate a specific etiology of the corresponding primary or secondary headache disorders. After all, the natural course, treatment, and even the prognosis could be different. More importantly, putting different headache disorders together would introduce heterogeneities that could complicate scientific research to understand the underlying pathophysiology of individual headache disorders.

As nicely quoted by Professor Chabriat, "MA corresponds to recurrent episodes of migraine headaches preceded or accompanied by transient focal neurological symptoms [1]." However, not all transient focal neurological symptoms followed or accompanied by migrainous headache are migraine aura. More importantly, based on the high prevalence of atypical presentations or even complicated forms of "aura" [2, 5, 6] and the strong associations with cerebral ischemic events and characteristic radiologic findings [7] in these patients, it is prudent to make a distinction between clinical manifestations of CADASIL and symptoms of MA or MO. In particular, in about one fifth of CADASIL patients categorized as having "MA", the aura has never been accompanied by headache [2]. Although there is an entity called "typical aura without headache" (code 1.2.1.2) in the ICHD-3 [1], the "aura" should be typical as implied by its name. Besides, in the comments for the diagnostic criteria of "typical aura without headache" in the ICHD-3 [1], it is recommended that proper investigations be carried out, as potentially serious conditions, such as TIAs and seizures, should be excluded [25]. To sum up, migraine-like presentations in patients with CADASIL are not the same as "ordinary" MA or MO seen in our daily practice.

Professor Chabriat talks about the role of preclinical evidence in transgenic mice as supportive evidence for the association between "MA" and CADASIL. More specifically, it has been demonstrated that mice harboring a human pathogenic *Notch3* variant could have increased susceptibility to CSD [18]. However, CSD is also seen in a number of conditions other than migraine, such as subarachnoid hemorrhage, stroke and traumatic brain injury [16]. In fact, CSD can also be induced experimentally by various noxious conditions, including ischemia [26]. Therefore, although some of the molecular mechanisms underlying or associated with CSD are shared by migraine, some of these could also be shared by ischemic stroke. We still need more work to demonstrate whether increased susceptibility of CSD in the preclinical model of CADASIL is more relevant to migraine aura or to cerebral ischemia. On the other hand, there are incongruences between laboratory findings and clinical observations. For instance, although hormonal fluctuations were shown to have an impact on CSD susceptibility in preclinical models [27, 28], menstrual migraine is usually, or even invariably, without aura clinically [29, 30]. Therefore, there remain uncertainties whether increased CSD susceptibility in the mouse model could be supportive of the association between CADASIL and "ordinary" migraine aura.

Professor Chabriat argues that the considerable increase in the prevalence of "MA" among patients with CADASIL compared to that in the general population cannot be explained only by chance. If these "MA" cases do align with our knowledge about "ordinary" MA, it would be expected that cysteine-altering *NOTCH3* genetic variants would be more common in patients with migraine than in individuals without migraine from a population perspective. In particular, *NOTCH3* cysteine-altering genetic variants are present in up to 1 in 400 in public exome data [14, 31], which are much common than we used to believe. However, in a relatively large study involving 2,884 migraine patients and 3,502 non-headache population controls, there was no association between MA or MO and the p.R544C variant, the predominant variant associated with CADASIL in certain regions of East Asia [12]. Besides, in an analysis involving 200,000 exome-sequenced UK Biobank participants, people with common forms of migraine, including MA and MO, were not more likely than those without migraine to have four of the most commonly encountered cysteine-altering *NOTCH3* genetic variants [32]. Also, the percentages of migraine were not significantly different between individuals with and without cysteine-altering *NOTCH3* variants in the UK Biobank [15]. The above findings are in sharp contrast to those in some of the largest European cohorts of CADASIL patients [2, 3]. One of the explanations is the positions of the *NOTCH3* variants. It was reported that patients harboring *NOTCH3* variants located in epidermal growth factor-like repeat (EGFR) domains 7–34, which are much more common in the general population, had a less severe phenotype than those with *NOTCH3* located in EGFR domains 1–6 [33]. However, the prevalence and age of onset of migraine are not different between patients with EGFR domains 1–6 and 7–34 variants [33, 34]. On the other hand, how migraine cases were defined or identified could also be an important issue. The attack frequencies of migraine with and without "aura" were very low in the European study, i.e., less than once a month in 80.2% and 64.4%, respectively [2]. The diagnoses could be delayed or missed if they were not proactively made. In fact, there are considerable variations in the percentages of "MA" in patients with CADASIL or *NOTCH3* variants and diagnosed as migraine in different reports, and could range from 0 to

100% [2, 8, 13, 35, 36], which could be accounted for, at least in part, by the heterogeneities in the definitions of "MA" and the attitude of the clinicians. In comparison, the estimate on the prevalence of migraine in the UK Biobank could also be inaccurate since cases were identified by using the International Classification of Diseases (ICD) codes [15], for which case ascertainment could be an inherent limitation. More importantly, it is also possible that "MA" in the European and British studies [2, 3] may not completely correspond to the "ordinary" forms of MA encountered in our routine practice or the ICHD-3 diagnosis of MA. Therefore, to what extent cysteine-altering *NOTCH3* genetic variants are associated with "ordinary" migraine remains an issue to be further investigated.

To sum up, Professor Chabriat's arguments has only convinced us that headaches with certain migrainous features are common among patients with *NOTCH3* genetic variants or CADASIL. However, we are uncertain whether these headaches and transient focal neurological symptoms correspond to "ordinary" MA and MO. It seems we are still a number of steps from a firm conclusion about the association between CADASIL and migraine.

Abbreviations

CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CGRP	Calcitonin gene-related peptide
CSD	Cortical spreading depression
EGFR	Epidermal growth factor-like repeat
ICD	International Classification of Diseases
ICHD-3	International Classification of Headache Disorders, Third Edition
MA	Migraine with aura
MELAS	Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
MO	Migraine without aura
TIA	Transient ischemic attacks
UK	United Kingdom

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
YFW has received personal fees as an advisor or a speaker from Allergan/AbbVie, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Hava Bio-Pharma, Lundbeck, Novartis, Orient EuroPharma, Pfizer, Sanofi, Teva, UCB, and Viatris. He has received research grants from the Taiwan National Science and Technology Council, and Taipei Veterans General Hospital.

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