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Two cases of delayed onset, fully reversible cortical oedema and signal intensity on brain MRI without infarction caused by prolonged migraine aura

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To the Editors

Migraine is a disabling primary headache disorder that makes up 88.2% of the burden of headache disorders. Roughly one in three individuals with migraine experiences an aura associated with at least some of their attacks [1].

The typical aura is defined as visual, sensory, and/or speech symptoms that have gradual onset, last for no longer than one hour, include both positive and negative manifestations, and resolve/reverse completely [2]. Aura symptoms typically start gradually, building up over five minutes, and can last for up to one hour, though usually for 20 to 30 minutes. Two or more aura symptoms may occur, but when present they begin gradually in succession, differentiating the event from ischaemia.

Two well-described complications of migraine are persistent aura without infarction, and probable migraine aura, which are diagnosed when aura symptoms persist for longer than the typical maximum 60 minutes. In exceedingly rare manifestations, symptoms can persist for months or even years without corresponding infarction [2].

A common hypothesis about the pathophysiology of aura is cortical spreading depression, initially described by Leão in the 1940s. This is a bioelectrical phenomenon where a wave of intense cortical neuronal depolarisation is followed by a more prolonged period of hyperpolarisation, beginning in the occipital cortex. These waves break down the ion gradients in the brain, cause swelling of the neurons and distortion of the dendritic spines, and change energy metabolism and regional cerebral blood flow [3–5].

While the pathophysiology of migraine with aura is still not completely understood, research has shed light on the association between the aura and reversible abnormalities on brain magnetic resonance imaging (MRI). These reversible changes have been discussed as potential markers of disease activity and can provide valuable insights into the underlying mechanisms of the migraine aura.

The purpose of this report was to demonstrate two cases of prolonged aura without infarction who showed transient and fully reversible MRI abnormalities developing in a subacute fashion, and compare them to the cases previously reported in the literature. Written informed consent was obtained from both patients.

Patient 1: A 73-year-old woman with history of breast adenocarcinoma (status post lumpectomy, stem cell transplant, chemotherapy, and radiation) in remission, small left frontal meningioma, and migraine with aura developed persistent aura without infarction at age 72. Her migraines had started after her breast cancer treatment 20 years earlier. At baseline, she had one migraine day per month, and two or three lifetime episodes of probable aura manifesting as disorientation, aphasia, hemianesthesia, and ataxia requiring hospitalisation. During each event, brain MRI, electroencephalogram (EEG), and lumbar puncture yielded normal findings.

Her most severe episode to date had lasted 14 days, during which she was obtunded, had a left gaze preference, and right sided hemiplegia. A 60-minute EEG showed left hemisphere slowing without epileptiform activity. Cerebrospinal fluid

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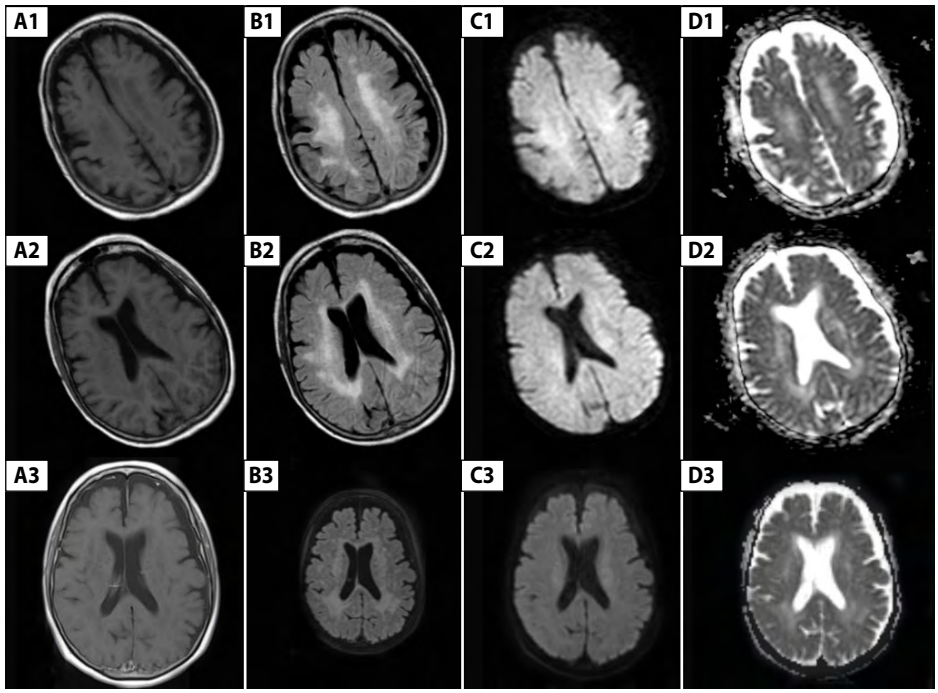

Figure 1. Brain MRI T1 (**A1**, **A2**), FLAIR (**B1**, **B2**), DWI (**C1**, **C2**), and ADC (**D1**, **D2**) showing left parietal and occipital lobe cortical thickening, FLAIR hyperintensity (**B1**, **B2**), and diffusion restriction (**C1, C2, D1, D2**) six days into prolonged aura event. EEG had shown corresponding slowing. Brain MRI T1 (**A3**), FLAIR (**B3**), DWI (**C3**), ADC (**D3**) showing resolution of previously seen cortical thickening and diffusion ribboning, 12 weeks after persistent aura event

(CSF) was normal. Brain MRI without gadolinium performed six days into the event showed cortical thickening/effaced sulci (T1 and T2), abnormal FLAIR signal, and diffusion restriction in the left parietal, occipital, and posterior temporal lobes with sparing of the subcortical white matter (Fig. 1). Repeating scanning with gadolinium three days later showed no abnormal enhancement. These changes were absent on the initial scanning four days prior. This care took place at an outside hospital. Thrombolysis was not administered. The initial decision-making of the treating physicians was unknown to these authors. The patient was treated with intravenous steroids, with improvement of the clinical syndrome. She required several weeks of outpatient rehabilitation. Follow-up brain MRI performed 12 weeks later showed the left-sided focal abnormalities had completely resolved with no appearance of infarction (Fig. 1). She was diagnosed with persistent aura without infarction. Genetic testing for familial hemiplegic migraine was negative. She underwent whole genome sequencing including mitochondrial DNA testing; no genetic aetiology was identified.

Patient 2: A 57-year-old man with migraine with aura (visual, sensory, language) was hospitalised for a stroke-like event lasting 5-6 days, and ultimately diagnosed with probable migraine aura (formerly termed 'prolonged aura'). The event began with his typical right periorbital headache triggered by exercise, followed by vision change (described by the patient as "Swiss cheese" vision), followed by expressive (more than receptive) aphasia and confusion. Examination also revealed right homonymous hemianopia, acalculia, and agraphia. He had no sensory or motor loss. These symptoms were consistent with his previous aura episodes, but were much longer and more severe. In hospital, he also developed visual hallucinations in part of his visual field. A computerised tomography angiogram (CTA) was within normal limits. Continuous EEG monitoring showed left hemisphere slowing. CSF analysis showed elevated erythrocytes (1,053), without any abnormalities to nuclear cells, protein, or glucose. CSF encephalitis/meningitis panel was negative including herpes simplex virus 1 and 2, polymerase chain reaction (PCR), and paraneoplastic antibody testing. Brain MRI with and without gadolinium performed on day 3 of the event showed gyriform T2 signal intensity involving the left posterior temporal, parietal, and occipital lobes without evidence of enhancement, restricted diffusion or susceptibility. There was relative hyperemia on perfusion imaging of the same regions (Fig. 2). These findings had been absent on brain MRI performed two days earlier. The patient was suspected to have 'complicated' migraine and was treated with intravenous valproate sodium, after which his clinical syndrome improved and gradually resolved. A follow-up brain MRI performed five weeks later showed resolution of all previously seen abnormalities (Fig. 2).

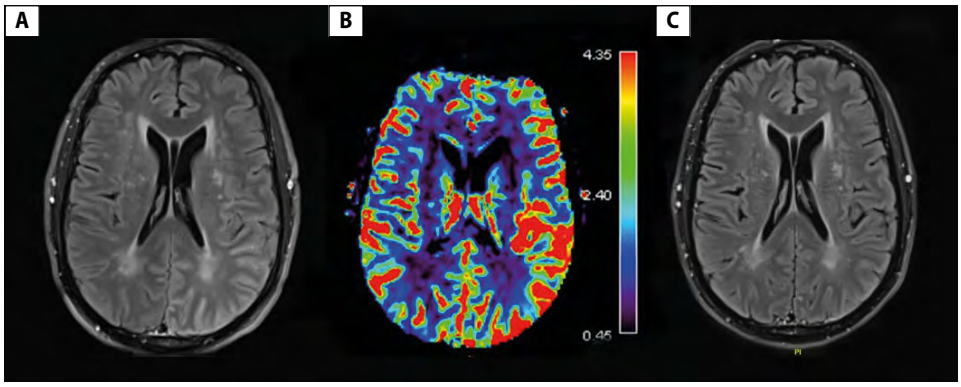

Figure 2. Brain MRI FLAIR (**A**) and perfusion imaging (**B**) three days into aura event, showing non-enhancing gyriform T2 signal intensity in left posterior temporal, parietal, occipital lobes, and relative hyperemia on perfusion imaging. Follow-up scan performed five weeks later (**C**) showed resolution of T2 signal changes

Both patients presented in this report were known migraineurs with aura. Both presented with identical cortical thickening/signal changes on brain MRI affecting the left posterior temporal, parietal, and occipital lobes, the second being associated with corresponding hyperemia. These radiographic changes were not present on baseline scans, scans performed early in the hospitalisations, nor on follow-up scans performed 1–3 months after the events.

The differential for these clinical syndromes included ischaemia, epileptiform activity, and infectious and autoimmune meningoencephalitis, all of which were ultimately excluded in both cases.

Both cases of older individuals with focal neurological symptoms presenting to Accident & Emergency first and foremost raise suspicion for vascular events. Patient 2 was treated in our own hospital. Upon arrival at A&E, an acute 'brain attack' protocol was initiated, with intravenous thrombolysis being deferred due to late patient presentation (20 hours since last time seen to be normal) and endovascular thrombolysis being deferred due to normal vascular imaging done in the emergent setting. Patient 1 was treated at an outside hospital, and events pertinent to this case report were reviewed in retrospect nine months later. We do not know whether Patient 1 was initially suspected to have acute ischaemia. She did not receive intravenous or endovascular thrombolysis, and whether this was due to a lack of suspicion or to a delayed presentation is unknown to these authors.

Both cases should be evaluated for acute ischaemia when presenting to an emergency setting. At the conclusion of the evaluation, in retrospect, the otherwise normal workup, reversibility of the imaging findings, known aura history, and clinical resolution of events with migraine treatments led to the diagnosis of persistent aura without infarction in Patient 1, and of probable migraine aura in Patient 2.

Persistent aura without infarction is defined as an aura symptom or symptoms that last longer than seven days without corresponding infarction on imaging [2]. Patient 1 had symptoms for two weeks and needed outpatient rehabilitation for a further two weeks or so to return fully to baseline, but was not found to have a stroke.

Probable migraine aura, previously called prolonged aura, is defined as an aura lasting > 1 hour but less than one week [2]. Patient 2 had symptoms for c.5–6 days without evidence of stroke on imaging five weeks later.

Our findings share similarities with cases of persistent aura or probable migraine aura reported in the literature and set out in Table 1. A characteristic common feature is the temporal nature of MRI abnormalities. For example, Resnick et al. [6] observed increased FLAIR signal along the parieto-occipital cortex during the attack, which exhibited complete resolution on repeat MRI after 12 days. This dynamic alteration hints at a potentially functional, reversible change, rather than a static structural abnormality.

The FLAIR sequence was previously reported to capture transient abnormalities associated with migraine with aura akin to our two patients [6, 11, 12]. This finding can be explained by alteration in the relaxation time of CSF that is associated with pathological conditions or artifacts. Pathological causes usually involve subarachnoid haemorrhage, meningitis, acute stroke, and fat-containing tumours [7]. Having this finding documented in persistent aura indicates the need for further study on the pathophysiology of aura and its role in changing the CSF composition and dynamics during the attack. This also suggests a migraine aura as being one of the differentials when having a similar clinical and radiological presentation.

Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps play a key role in detecting restricted diffusion, which is a marker of a potential ischaemic event. Although the absence of restricted diffusion on brain MRI may help exclude acute ischaemic stroke as a cause of the symptoms, Bereczki et al. presented a case demonstrating a shifting area of diffusion restriction on DWI during persistent visual aura. Brain MRI on day 56 after symptom onset showed normal findings, with complete resolution of the restriction [8].

Table 1. Summary of clinical and radiographic findings in published cases

Paper	Patient	Clinical findings	MRI findings	Treatment
Resnick et al. [6]	56-year-old man	Visual aura Right parietal syndrome lasting 18 hours	During attack/episode: — FLAIR: increased signal along parieto-occipital cortex associated with gyral effacement — DWI: high confluent signal along above-described distribution without restriction or low values on ADC After 12 days: — DWI and FLAIR: complete reversal and resolution of signal abnormality	i.v. valproic acid
Smith et al. [10]	66-year-old woman	Prolonged aura of: — right-sided neglect — global aphasia — right-sided pronator drift	During attack/episode: — T1 with gadolinium: abnormally increased signal and extravasation of contrast into subarachnoid space of left hemisphere After 4 days: — T1 with gadolinium: no focal deficits and an intact vasculature	Steroids and divalproex
Belvis et al. [11]	41-year-old woman	Visual aura Bilateral paresthesias in extremities lasting four days	During attack/episode: — Signal disturbance in left occipital lobe in ADC map — No lesions on T1, T2, FLAIR, and DWI series 8 days after attack/episode: — Disappearance of lesion in ADC map	Rizatriptan and ibuprofen (only for headache)
Bereczki et al. [8]	58-year-old man	Right-sided visual field defect lasting 15 days	During attack/episode: — DWI: region of restricted diffusion shifted forward from occipital to temporoparietal cortex between day 2 and day 17 (in accordance with change in clinical features) After attack/episode: — No tissue damage at day 56 after onset	
Kim et al. [9]	38-year-old man	Visual aura lasting more than 10–14 days	During attack/episode: — DWI and FLAIR: hyperintense signals in occipito-temporo-parietal cortex and adjacent subcortical white matter ADC: elevated After attack/episode: — Complete resolution of lesions/abnormal signals	Corticosteroids
Gómez-Chocoet al. [12]	22-year-old woman	Right hemihypoesthesia lasting more than one hour	During attack/episode: — FLAIR: sulcal hyperintensity in left temporal lobe 4 days after onset: — FLAIR: resolution of abnormal hyperintensity	

ADC apparent diffusion coefficient; BBB blood-brain barrier ; CSF cerebrospinal fluid; CTA computed tomography angiography; DWI diffusion-weighted imaging; EEG electroencephalogram; FLAIR fluid-attenuated inversion recovery; LP lumbar puncture; MRA magnetic resonance angiography; MRI magnetic resonance imaging; TSH thyroid stimulating hormone; TTE transthoracic echocardiogram; i.v. intravenous

While decreased values in an ADC map suggest cytotoxic oedema, elevated values usually accompany vasogenic oedema, and both findings have been reported to be seen in migraine. Brecezki et [8] al. described reduced ADC values that accompanied the diffusion restriction in their case, while Kim et al. [9] described elevated ADC values in persistent visual aura.

T1 sequences with contrast enhancement provide insights into blood-brain barrier integrity during the migraine episode. Smith et al. observed increased signal abnormality and extravasation of contrast into the subarachnoid space of the left hemisphere during an aura that lasted for more than one hour. Presumably, vasodilation and breakdown of the blood-brain barrier follows the initial vasoconstriction and preservation of endothelial junctions that take place at migraine onset. Overall, they considered this finding to be an indicator of reversible vasculopathy during the migraine aura [10].

On a treatment note, Resnick et al. described an aura lasting 18 hours and involving visual changes with right parietal syndrome that responded to valproic acid, similar to our Patient 2 who responded to intravenous valproate [6]. Additionally, cases described by Smith et al. [10] and Kim et al. [9] showed significant responses to steroids akin to our

Patient 1. The response to steroids may imply the presence of oedema and/or inflammation caused by the metabolic changes during the aura.

We conclude with the comment that both patients were scanned twice during their hospitalisations. It is notable that the first scans on presentation did not show any abnormalities. The gyriform cortical abnormalities appeared on day 6 (Patient 1) and day 3 (Patient 2). When patients present with focal neurological signs and symptoms, but the aetiology is not clear from initial evaluation, we suggest performing repeat imaging to evaluate for delayed imaging findings.

Our findings contribute insights into the reversible abnormalities observed on brain MRI during persistent migraine aura and probable migraine aura. They underline the dynamic nature of the underlying processes of the pathophysiology of aura, and prompt a call for more research into this topic, with the ultimatel goal of the optimisation of treatment strategies for individuals who experience this phenomenon.

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References

1. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2013; 53(8): 1278–1299, doi: 10.1111/head.12150, indexed in Pubmed: 23808666.
2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33(9): 629–808, doi: 10.1177/0333102413485658, indexed in Pubmed: 23771276.
3. Leao A. Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol. 1947; 10(6): 409–414, doi: 10.1152/jn.1947.10.6.409, indexed in Pubmed: 20268874.
4. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med. 2011; 17(4): 439–447, doi: 10.1038/nm.2333, indexed in Pubmed: 21475241.
5. Lauritzen M, Dreier JP, Fabricius M, et al. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab. 2011; 31(1): 17–35, doi: 10.1038/jcbfm.2010.191, indexed in Pubmed: 21045864.
6. Resnick S, Reyes-Iglesias Y, Carreras R, et al. Migraine with aura associated with reversible MRI abnormalities. Neurology. 2006; 66(6): 946–947, doi: 10.1212/01.wnl.0000203646.05540.ec, indexed in Pubmed: 16567723.
7. Stuckey SL, Goh TD, Heffernan T, et al. Hyperintensity in the subarachnoid space on FLAIR MRI. AJR Am J Roentgenol. 2007; 189(4): 913–921, doi: 10.2214/AJR.07.2424, indexed in Pubmed: 17885065.
8. Bereczki D, Kollár J, Kozák N, et al. Cortical spreading edema in persistent visual migraine aura. Headache. 2008; 48(8): 1226–1229, doi: 10.1111/j.1526-4610.2008.01183.x, indexed in Pubmed: 18819182.
9. Kim YJ, Kwon SU. Recurrent steroid-responsive cerebral vasogenic edema in status migrainosus and persistent aura. Cephalalgia. 2015; 35(8): 728–734, doi: 10.1177/0333102414553820, indexed in Pubmed: 25319965.
10. Smith M, Cros D, Sheen V. Hyperperfusion with vasogenic leakage by fMRI in migraine with prolonged aura. Neurology. 2002; 58(8): 1308–1310, doi: 10.1212/wnl.58.8.1308-a, indexed in Pubmed: 11971111.
11. Belvís R, Ramos R, Villa C, et al. Brain apparent water diffusion coefficient magnetic resonance image during a prolonged visual aura. Headache. 2010; 50(6): 1045–1049, doi: 10.1111/j.1526-4610.2010.01672.x, indexed in Pubmed: 20408884.
12. Gómez-Choco M, Capurro S, Obach V. Migraine with aura associated with reversible sulcal hyperintensity in FLAIR. Neurology. 2008; 70(24 Pt 2): 2416–2418, doi: 10.1212/01.wnl.0000314693.57386.f0, indexed in Pubmed: 18541878.