

# Perfusion-weighted MR imaging in persistent hemiplegic migraine

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Received: 12 May 2011 / Accepted: 26 July 2011 / Published online: 11 August 2011  
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## Abstract

**Introduction** Hemiplegic migraine is a rare type of migraine that has an aura characterized by the presence of motor weakness, which may occasionally last up to several days, and then resolve without sequela. Pathogenesis of migraine remains unclear and, recently, perfusion-weighted imaging (PWI) has provided a non-invasive method to study hemodynamic changes during acute attacks.

**Methods** Two female patients were admitted in our hospital suffering from prolonged hemiparesis. In both cases, they underwent MRI examination using a 1.5 T magnet including axial diffusion-weighted and perfusion sequences. From each perfusion MRI acquisition two regions of interest were delineated on each hemisphere and, the index of flow, cerebral blood volume, mean transit time, and time to peak were recorded and asymmetry indices from each perfusion parameter were calculated.

**Results** Perfusion alterations were detected during the attacks. In one case, we observed, after 3 h of left hemiparesia, hypoperfusion of the right hemisphere. In the other case, who presented a familial hemiplegic migraine attack, on the third day of a persistent aura consisting of right hemiplegia and aphasia, PWI revealed hyperperfusion of the left hemisphere. Asymmetry indices for temporal

parameters (mean transit time and time to peak) were the most sensitive. These findings resolved spontaneously after the attacks without any permanent sequel or signs of cerebral ischemia on follow-up MRI.

**Conclusions** PWI should be indicated for patients with migraine attacks accompanied by auras to assess the sequential changes in cerebral perfusion and to better understand its pathogenesis.

**Keywords** Hemiplegic migraine · Familial hemiplegic migraine · MRI · Persistent aura

## Abbreviations

PWI	perfusion-weighted imaging
HM	Hemiplegic migraine
FHM	familial hemiplegic migraine
SHM	sporadic hemiplegic migraine
DWI	diffusion-weighted imaging
CBV	cerebral blood volume
FLAIR	fluid-attenuated inversion recovery
ICBF	Index of Cerebral Blood Flow
MTT	mean transit time
TTP	time to peak
TOF	3D time-of-flight
MRA	MR angiography

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## Introduction

Hemiplegic migraine (HM) is a rare variety of migraine defined by migraine attacks, which include the presence of motor weakness during the aura. HM has two main forms according to the familial history. Patients with at least one first- or second-degree relative, who presents with aura

characterized by motor weakness, fulfil the criteria for familial hemiplegic migraine (FHM), whereas patients without a familial history have a sporadic hemiplegic migraine (SHM). Molecular biology is increasingly being used to diagnose FHM, by screening for the three known genes involved in FHM (*CACNA1A*, *ATP1A2*, and *SCNA1*) [1]. FHM and SHM are equally frequent, and the prevalence of HM is ~1/10,000 people. Attacks usually start in childhood or adolescence. Although prognosis is usually good, severe attacks may occur with prolonged hemiplegia, confusion, coma, fever, and seizures [1]. Earlier reports have shown that attacks can last up to several hours or days, but without any permanent neurological deficit or infarct [2, 3].

The pathogenesis of migraine remains unclear, and conflicting theories between vascular or neuronal dysfunction have been suggested. In this context, imaging techniques have proved helpful in understanding the pathogenesis of migraine. Many reports have demonstrated changes in cerebral blood flow (CBF) in classic migraine attacks [2, 4–8]. However, there are still few reports on multimodal neuroimaging in HM [4, 9–16]. Collecting this information could provide important information about HM and help us understand its pathology.

The objective of this report is to describe two patients with HM, where perfusion-weighted imaging (PWI) was used at different time courses. This revealed opposite changes in cerebral perfusion during the migraine attacks. We also documented the course of neurological deficit in one patient who presented with a FHM attack, and whose aura persisted for >9 days, but did not cause any permanent sequela or ischemic lesion or infarct on follow-up MRI.

## Patients and methods

The patients underwent MRI examination using a 1.5 T magnet (Intera, Philips, Best, the Netherlands). The MRI protocol included T1-weighted images, T2-weighted images, axial fluid-attenuated inversion recovery (FLAIR) sequence, and axial isotropic diffusion-weighted EPI sequence (27 slices, slice thickness 5 mm, gap 0 mm) with  $b=0$  and  $b=1,000$  s/mm<sup>2</sup>, as well as a 3D time-of-flight (TOF) sequence, to determine intracranial abnormalities of the cerebral arteries. The ADC map was calculated in line on the acquisition station. A susceptibility-based MR perfusion sequence was performed as a 3D-segmented EPI technique (T2\*-weighted PRESTO). Twenty-seven slices, covering the entire brain (acquisition matrix size 64×64), were acquired with a time resolution of 1.2 s, with Phase array coil. The total scan time was 1 min and 17 s. A bolus of gadolinium (0.2 mmol/kg body weight) was

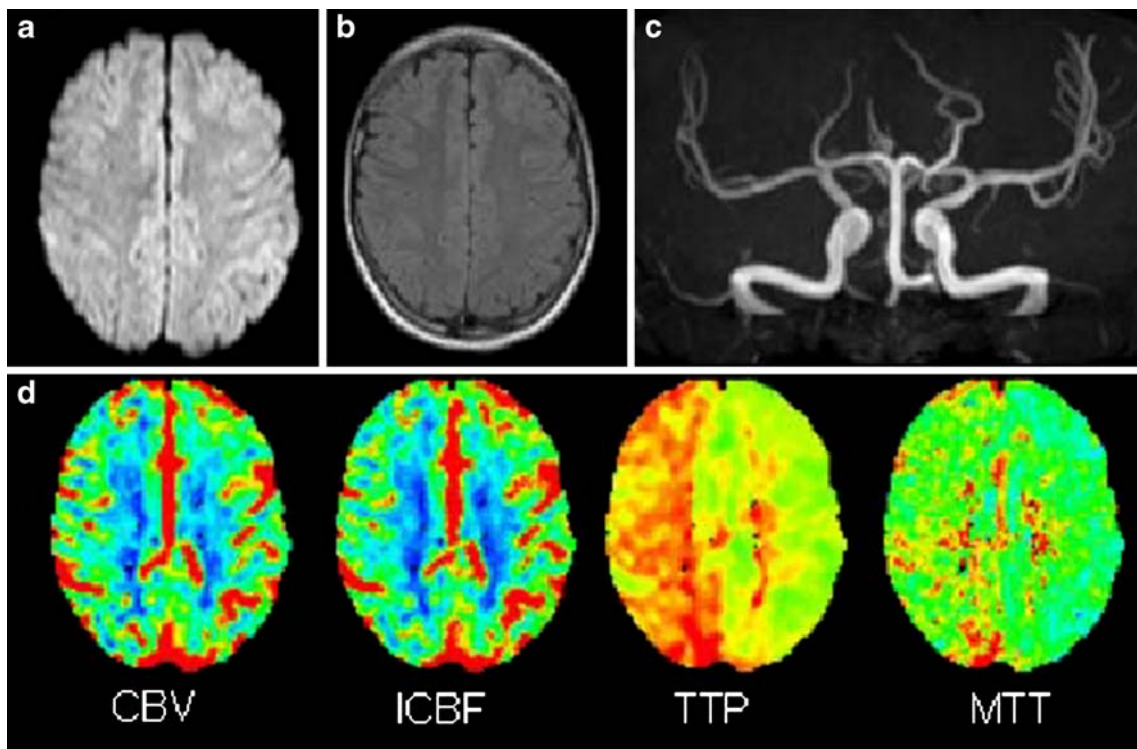
administered at an injection rate of 6 ml/s, and was then flushed with 20 ml of saline.

All perfusion data were processed at a workstation (View Forum, version 3.2, Philips Medical System) with commercially available software. The curve of the time-dependent concentration of the contrast bolus was analyzed. These curves were computed from the changes in signal intensity and were fitted to a  $\gamma$ -variate function to correct for recirculation. Perfusion-parameter maps were computed on a voxel, by voxel analysis. The negative integral under the curve corresponded to the relative CBV. The index map that corresponded to relative index of CBF was calculated as the ratio of the negative integral under the curve and the mean transit time (MTT). The time-to-peak was calculated pixel by pixel and corresponded to the signal drop was the largest. From each perfusion MRI acquisition, from all slices, two regions of interest were delineated on each hemisphere and, the index of flow (ICBF), CBV, MTT, and TTP were recorded. The mean of all brain analyses for each parameter were obtained and asymmetry indices (AIs; pathological hemisphere compared to controlateral hemisphere) from each perfusion parameter were calculated  $100 \times (\text{pathological hemisphere} - \text{controlateral hemisphere}) / [(\text{pathological hemisphere} + \text{controlateral hemisphere})/2]$ .

## Case 1

The first patient was a 12-year-old right-handed girl with a personal and family history of migraine without auras. She experienced sudden severe headache, nausea, and blurred vision with flashing red dots, followed by left-sided hemiparesis, dysarthria, and paresthesia of the left hand. She was admitted to our hospital 2 h after onset of symptoms with a persistent headache and vomiting. The neurological examination revealed left-sided hemiparesis. Routine blood tests, electroencephalography, visual-evoked potentials, brain angiography, computed tomography, and extracranial and transcranial Doppler were normal. Brain MRI examination with T1- and T2-weighted images, FLAIR, diffusion-weighted images (DWI), and MR angiography (MRA) showed no abnormalities (Fig. 1a–c). PWI performed 3 h after the onset of symptoms revealed hypoperfusion of the right cerebral (pathological) hemisphere compared to the left hemisphere (Fig. 1d). The AIs were very high for ICBF but were also moderate for CBV at that time (Table 1). All parameters of perfusion (ICBF, CBV, MTT, and TTP) were significantly modified (Wilcoxon test), as illustrated on Fig. 1d.

The condition of the patient gradually improved in a few hours and she completely recovered in less than 24 h. Since then, she has had no recurrent attack of HM. A search for mutations of the *CACNA1A* and



**Fig. 1** Multimodal MRI of case 1 after 3 h of left hemiplegia. DWI (a), FLAIR (b), and MRA (c) show no abnormality. Maps from PWI parameters (d) show an asymmetry of CBV, ICBF, and TTP

*ATP1A2* genes was negative. On the basis of these clinical findings, a diagnosis of SHM was considered the most likely, even if the diagnostic criteria for this disease were not fully satisfied.

Case 2

A 36-year-old woman was referred to our hospital for subacute development of right-sided hemiplegia, aphasia, and fever that had been developing for 60 h. She was

known to have suffered from FHM since the age of 9, but the auras she had usually lasted less than 2 h and always consisted of right-sided hemiplegia and aphasia. Only two attacks had occurred during the past year since FHM had been diagnosed. Her mother, her grandmother, and her 13-year-old daughter also suffered from migraine with intermittent neurological deficits. The patient’s FHM was linked to a mutation of the *CACNA1A* gene, as was her daughter’s.

At presentation, she reported global blurring of vision for a few minutes. Recognizing the first sign of a migraine

**Table 1** Analysis of MRI perfusion parameters during hemiplegic migraine

MRI delay	Case 1		Case 2				Evolution of MRI parameters	
	AI	<i>p</i>	AI	<i>p</i>	AI	<i>p</i>		
Parameters							Difference	<i>p</i>
CBV	-12.8%	0.0028	+49.8%	0.00047	+11.6%	0.00082	-82.7%	0.00047
ICBF	-40.2%	0.00032	+47.3%	0.00048	+13.9%	0.0082	-81.1%	0.00071
TTP	+14.1%	0.00032	-5.2%	0.00048	-2.3%	0.00070	-58.4%	0.00072
MTT	+26.9%	0.00032	+3.4%	0.23	-2.0%	0.33	NA	0.15

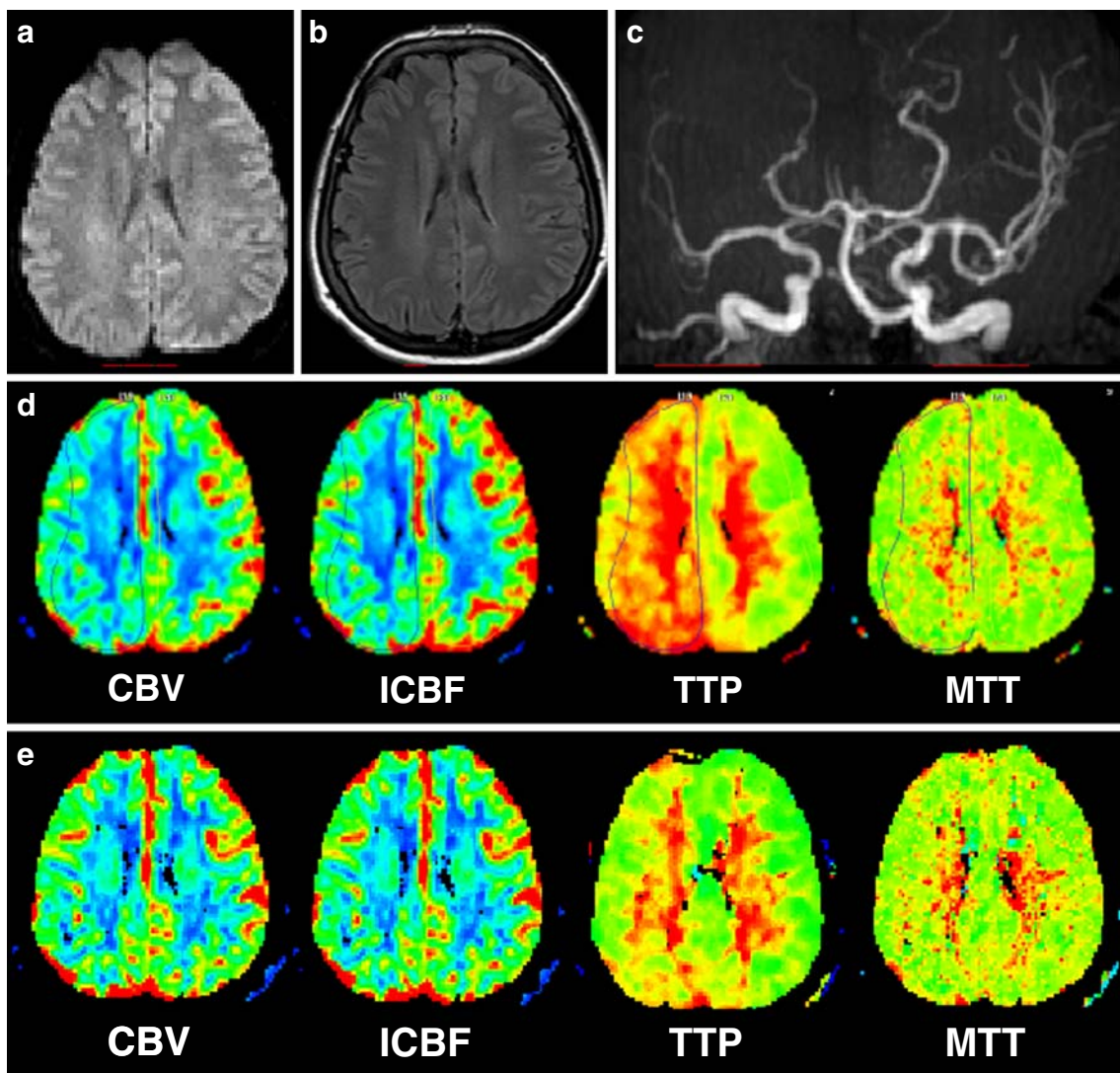
Asymmetry indices for the parameters of the PWI show a strong decrease in ICBF of the pathological hemisphere at 3 h after the onset of an aura in case 1. In contrast, the ICBF increases in case 2, and corresponds to hyperperfusion of the pathological hemisphere after 72 h, though this becomes less intense after 120 h. The difference (pathological hemisphere–controlateral hemisphere) strongly decreases from 72 to 120 h for CBV, ICBF, and TTP, and is then correlated with clinical improvement of the patient

attack, she took a naratriptan tablet (2.5 mg). In the following hour, she developed sudden-onset right-sided weakness with continuous headache and vomiting. Her mother gave her dihydroergotamine (nasal spray, 0.5 mg). On admission, a neurological examination demonstrated right hemiparesis and global aphasia. Routine blood tests, including an ionogram, complete blood count, and coagulation tests, were normal. An ECG was also normal.

An MRI was performed 72 h after the onset of symptoms. Routine T1- and T2-weighted images, FLAIR, and DWI did not show any pathological findings, in particular any cerebral tissue injury (Fig. 2a, b). MRA, performed with a 3D TOF sequence, did not show arterial occlusion (Fig. 2c). PWI revealed hyperperfusion of the left cerebral hemisphere (pathological) compared to the contralateral hemisphere

(Fig. 2d), demonstrating significant findings of ICBF, CBV, and TTP, but not MTT (Table 1). At the time, the AIs were very high for ICBF and CBV. ICBF and CBV maps showed asymmetry for these perfusion parameters.

A new PWI, performed 120 h after the onset of symptoms, while mild aphasia was still present, also showed asymmetry of perfusion, though this was then less marked (Table 1, Fig. 2e). Quantitative data for all PWI studies indicated a continuous decrease in the AIs of CBV, ICBF, TTP, and an increase in the AI of MTT in the first MRI (after 72 h) compared to the second MRI (after 120 h). Nevertheless, the differences between the two hemispheres remained significant (Wilcoxon test). At 9 days after the onset of the migraine attack, the patient was discharged. Neurological examination revealed only mild aphasia, with complete



**Fig. 2** Multimodal MRI of case 2 after 72 and 120 h of right hemiplegia and aphasia. DWI (a), FLAIR (b) show no abnormality. MRA (c) shows dilatation of the left ACM branches. Maps of PWI

parameters at 72 h (d) show important asymmetry of CBV, ICBF, and TTP, which tend to normalize after 120 h (e)

remission of hemiparesis. A migraine-preventive treatment, consisting of lamotrigine 100 mg/day, was introduced progressively. No HM attack has been reported since then.

## Discussion

In migraine with aura, the symptoms related to the cerebral cortex or to brain-stem dysfunction usually develop gradually over 5 min and then usually last for less than 60 min. Occasionally, the duration of the neurological deficit is prolonged over several hours or days. In the 2004 revision of the International Classification of Headache Disorders, a rare but well-documented complication of migraine was inserted, which was characterized by aura symptoms that persisted for more than 1 week without radiological evidence of tissue injury [10]. Effectively, HM may mimic an acute ischemic stroke, making clinical distinction challenging, especially considering the urgency of stroke treatment (thrombolysis) [11]. Clinically, HM attacks can be distinguished from stroke by the gradual development and progression of aura symptoms, the reporting of a migraine, and the patient's personal and family history regarding HM, if the information is available.

In case 1, the PWI examination was conducted 3 h after the onset of symptoms, and showed cortical hypoperfusion while the neurological symptoms were still present. The reduction of ICBF and the increase in TTP occurred concomitantly with the aura symptoms. These parameters' values seem to be above the ischemic threshold as a cerebral infarction did not develop, as assessed by DWI. These results are in concordance with Andersen's findings, who reported, by means of SPECT, initial hypoperfusion that persisted for up to 3 h in the appropriate hemisphere of a neurological deficit [17]. The results from case 1 are also in concordance with Kapinos and Linn' findings, who reported, by means of PWI in the hyperacute phase (2 h and 30 min), initial hypoperfusion above the ischemic threshold [11, 13].

In case 2, we report on a young woman suffering from FHM, who experienced a severe and long-lasting migraine attack. In contrast to case 1, PWI, performed several days after the onset of aura, showed persistent hyperperfusion of the pathological hemisphere. Moreover, we did not observe any abnormality of DWI, which is consistent with the literature for patients with migraine with aura [13]. These cases demonstrate the usefulness of multimodal MRI in patients with acute hemiparesis to distinguish between HM and ischemic lesion. To comfort us in the diagnostic of HM, hemodynamic changes observed, in both cases, during the acute phase, were not respecting any single arterial territory, DWI was negative and we did not see vascular occlusion on TOF.

Alterations in cerebral perfusion have been well documented in patients with migraine attacks. Hemodynamic changes have been observed in migraine patients with and without aura [10, 15, 18]. During a typical aura, transient hypoperfusion is usually observed [9, 15]. Linn et al. reported that clinical function can be restored before resolution of hypoperfusion in PWI [13]. In patients with a prolonged or persistent aura, some authors have described hyperperfusion [4, 12, 16] as well as hypoperfusion [14], as assessed by PWI and/or by SPECT. Findings in the literature may seem ambivalent because the temporal acquisition for perfusion imaging greatly influences the results, between initial hypoperfusion and subsequent hyperperfusion/hyperpermeability.

There are only a few reports on neuroimaging for HM [2, 4–8]. In case 2, PWI showed hyperperfusion at 72 h after the onset of hemiparesis and aphasia. At that time, the AIs were very high for ICBF and CBV (Table 1). In the second MRI, asymmetry of perfusion was still present, but was less marked. However, mild aphasia persisted, and the differences between the two hemispheres remained significant (Wilcoxon test). In this patient, PWI findings were concordant with the literature. Indeed, previous studies have reported normal DWI in patients with MHF, whereas PWI and SPECT revealed hyperperfusion in the affected hemisphere, in particular, in cases where there was a long-lasting migraine attack [6–8]. Nevertheless, it remains unclear why neurological deficits are still present under conditions of subsequent hyperperfusion. Hemispheric hyperperfusion in patients with FHM and long-lasting aura, as in case 2, could argue against an ischemia mechanism. The concomitant neurological deficit and elevated CBV and CBF, rather support the hypothesis that etiopathogenesis in migraine is caused by primary neuronal dysfunction. Although the spread of cortical depression [19] may well explain a typical migraine aura, as well as the initiation of a prolonged aura in FHM, it can hardly account for neuronal dysfunctions that can occur for days or weeks [2].

The two cases presented here nicely link to imaging data from the literature on migraine patients [6–9, 11–16]. Previous reports reveal a brief wave of initial hyperperfusion, followed by hypoperfusion of the affected hemisphere, which causes neurological symptoms and, later, a temporary and variable state of hyperperfusion [8, 17]. We observed, in both cases, that AI of ICBF was the parameter that showed the greatest variability (>40%) associated with either hypoperfusion or hyperperfusion. In contrast, the AIs of the temporal parameters, MTT and TTP, were most significant in the early scan of the patient with hypoperfusion (case 1). Thus, AIs for perfusion mapping temporal parameters could be the most sensitive markers for early hypoperfusion, whereas AI of CBV could be more representative of

hyperperfusion during a prolonged aura. These imaging findings may depend on the type of the migraine, on the delay between the onset of attack, and when a MRI is conducted.

## Conclusion

Many different findings from imaging have been described in patients with migraine, but observations of brain perfusion, as assessed by PWI during HM attacks, are rare. The changes depend, at least in part, on when the imaging is done and the course of the migraine attack. Thus, we suggest that DWI and PWI imaging are useful during HM attacks, not only to diagnose HM and exclude cerebral infarction, but to also play a role in our future understanding of the pathogenesis of HM. Further serial studies are required to confirm data and to better define the changes observed here.

**Conflict of interest** We declare that we have no conflict of interest.

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