

Brain Stem and Cerebellar Hyperintense Lesions in Migraine

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Abstract

Background and Purpose— Migraineurs are at increased risk of cerebellar infarcts and supratentorial white matter lesions. The prevalence, frequency, and distribution of infratentorial hyperintense lesions in migraine are unknown.

Methods— Migraineurs with aura (n=161), without aura (n=134), and controls (n=140) from a population-based sample of adults (30 to 60 years of age) were evaluated with MRI.

Results— Infratentorial hyperintensities were identified in 13 of 295 (4.4%) migraineurs and in 1 of 140 (0.7%) controls ($P=0.04$). Twelve cases had hyperintensities, mostly bilaterally, in the dorsal basis pontis. Those with infratentorial hyperintensities also had supratentorial white matter lesions more often.

Conclusion— We found an increased prevalence of infratentorial (mostly pontine) hyperintensities in migraineurs from the general population. This extends the knowledge about vulnerable brain regions and type of lesions in migraine brains. A hemodynamic ischemic pathogenesis is likely, but further research is needed.

Key Words: cerebellum • cerebral ischemia • cerebrovascular disorders • magnetic resonance imaging • migraine • Pons

Introduction

We showed in a population-based MRI study that migraineurs with aura (MA) have a 12-fold increased risk of cerebellar infarcts, and that female migraineurs had more supratentorial deep white matter lesions (DWMLs) than non-migraineurs.¹ The risk of lesions increased with attack frequency, independent of cardiovascular risk factors.

Based on the same population-based study, we now describe the prevalence, distribution pattern, and associated neuroimaging characteristics of infratentorial hyperintense lesions (IHLs).

Methods

The Dutch population-based Genetic Epidemiology of Migraine (GEM) and its substudy, the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) MRI Study have been described previously.^{1,2} In brief, 863 migraineurs and 5628 controls were identified in the GEM study according to the IHS criteria.³ From those 30 to 60 years of age, we randomly selected for the MRI study 134 migraineurs without aura (MO), 161 MA, and 140 controls frequency matched by sex, 5-year age strata, and place of residence. Neither cases and controls nor responders (69%) and nonresponders differed by age, sex, and cardiovascular risk factors.

Three-millimeter axial slices of brain MRI were acquired with proton density (PD), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. Blinded to clinical status, 1 neuroradiologist read all images and recorded topographic details of observed abnormalities. IHLs were hyperintense on PD and T2 images and were not hypointense on FLAIR images.⁴⁻⁷ Periventricular white matter lesions (PVWMLs) and DWMLs (subcortical) were scored with semiquantitative scales with known reliability and validity.⁸ In addition, the white matter lesion Scheltens score was calculated.⁹ PVWML scores >3 (of 15) and the highest 20% volumes of total DWML load were classified in the analyses as high load.

Results

IHLs were identified in 1 of 140 controls (0.7%) and 13 of 295 migraineurs (4.4%; $P=0.04$), slightly more in MA (8 of 161; 5.0%) than in MO (5 of 134; 3.7%; Table). All subjects had a normal standard neurological examination and no history of transient ischemic attack or stroke.

Case Summary of Participants With Infratentorial Hyperintense Lesions

Cases	Age/Sex	Risk Factors*	Migraine Characteristics			Brain Lesions [†]			
			Diagnosis	Age of Onset-End	Average Attacks per Year	Infratentorial Hyperintensity	DWML [‡] Score	PVWML [‡] Score	Infarcts
1	41/Female	ht, hcr	MA	33-	18	Pons (3)	1	1	...
2	42/Female	ht	MO	11-	7	Cerebellum (1)	1	2	...
3	43/Female	ht	MA	14-	43	Cerebellum (3)	0	0	...
4	52/Male	ht	MA	32-	14	Pons (5)	1	2	...
5	52/Female	ht	MO	33-51	12	Cerebellum (3)	7 [§]	4 [¶]	1 temporal lobe (10 mm)
6	52/Female	ht	MO	25-	6	Pons (5)	11 [§]	2	...
7	55/Male	ht	MA	25-	6	Pons (5)	0	1	...
8	56/Male	ht, hcr	MO	20-	15	Pons (5)	9 [§]	5 [§]	...
9	60/Female		MO	14-54	12	Pons (5)	6 [§]	2	...
10	61/Male	ht	MA	7-	3	Pons (5)	3	0	1 corona radiate (4 mm)
11	61/Female	ht	MA	20-	6	Pons (5)	13 [§]	3 [§]	...
12	61/Female	ht	MA	15-56	32	Pons (5)	10 [§]	2	...
13	61/Female	hcr	Co	Pons (5)	17 [§]	4 [§]	2 capsula interna (both 3 mm); 1 thalamus (2 mm)
14	63/Female	ht, hcr	MA	30-	30	Pons (5)	6	3 [§]	...

* ht indicates hypertension; hcr, high cholesterol ratio.
[†]Location (Scheltens score/size);
[‡]Scheltens score;
[§]also classified as having "high DWML load" or "high PVWML load";
[¶] large confluent white matter lesion.

Of the 14 cases with IHLs, 3 had ≥ 1 small to medium size (2 to 5 mm) lesions in the deep cerebellar white matter that were hyperintense on all pulse sequences (Figure 1) and confined to the posterior inferior cerebellar artery territory. Twelve cases had IHLs located in the pons (pontine hyperintense lesions [PHLs]): 1 of 140 controls (0.7%), 7 of 161 MA (4.3%; $P=0.05$ versus controls), and 4 of 134 MO (3.0%). PHLs were visible on ≥ 2 , to a maximum of 6, slices. All were in the dorsal basis pontis, adjacent to the tegmentum, at the level of, and slightly cranial to, the entry zone of the trigeminal nerve (Figure 2). None reached the surface. In 4 cases, the lesions extended to the midline. In 11 of 12 cases, PHLs were bilateral and more or less symmetrical. Lesions seem to involve the pontocerebellar fibers, the pontine nuclei, or the nucleus reticularis tegmenti pontis, and, in some cases, parts of the corticopontine (pyramidal tract) or medial lemniscus fibers. PHLs were in the territories supplied by the anteromedial and anterolateral groups arising from the basilar artery.

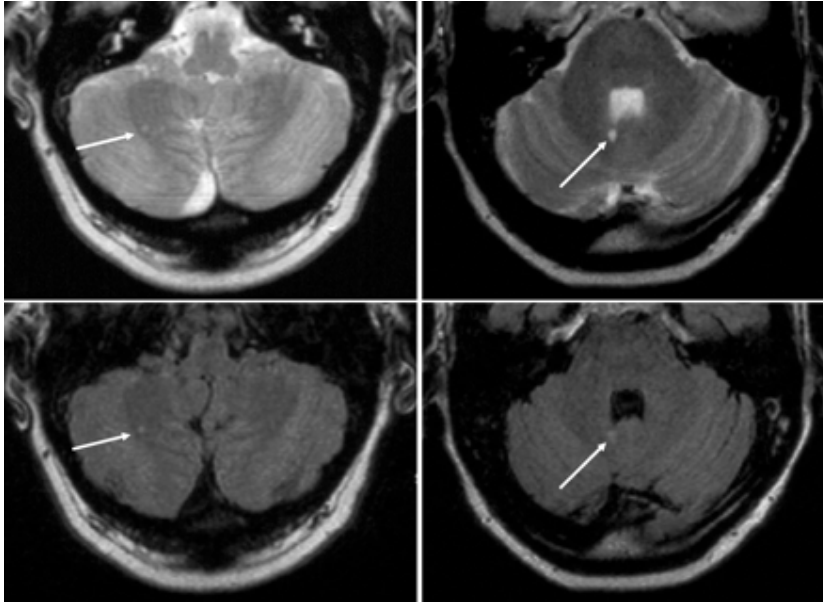


Figure 1. T2 and FLAIR images of 2 cases with cerebellar hyperintense lesions.

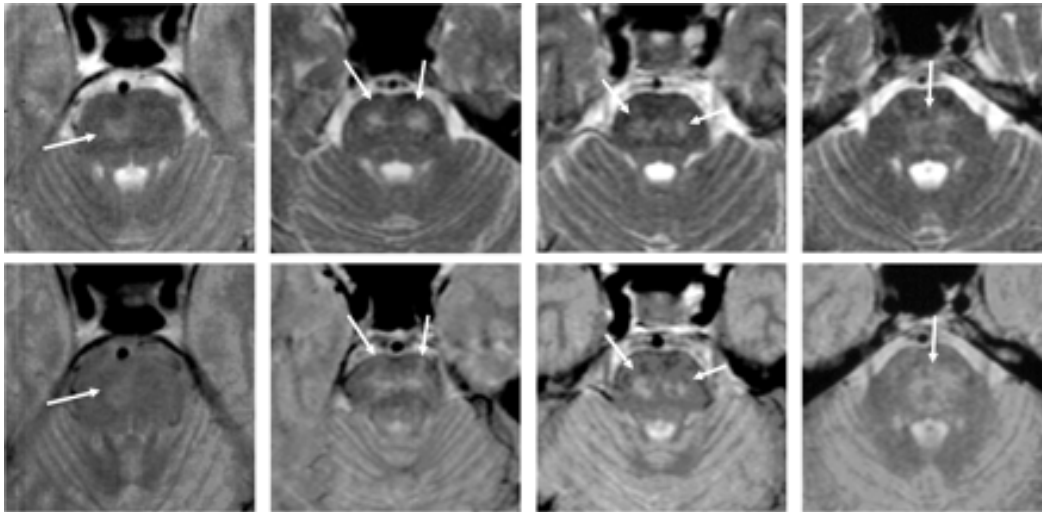


Figure 2. T2 and PD images at the midpontine level showing PHLs in 4 cases. Conspicuity of the lesions differed between T2- and PD-weighted images from case to case.

Compared with those without, those with IHLs significantly more often had high PVWML load (8% versus 31%; $P < 0.005$) and high DWML load (19% versus 43%; $P < 0.05$), but there were no significant differences in infarct prevalence (7% versus 18%) or, more specifically, in cerebellar infarct prevalence (4% versus 0%). Migraine cases with and without IHLs were similar with respect to migraine type, attack frequency, age at onset, or treatment status.

Discussion

Population-based migraineurs had IHLs more often than controls. IHLs were associated with PVWML and DWML but not with cerebellar infarcts, as described previously in migraineurs.¹ In the majority of cases (86%), hyperintensities were located in the midpontine parenchyma (PHLs). The brain stem is involved in migraine pathophysiology, and specific activation of the dorsal rostral pons and periaqueductal gray matter have been reported during migraine.¹⁰ However, the specific "migraine areas" were not involved in our cases.

In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a disorder in which MA often is the presenting symptom, similar brain stem hyperintensities are frequent.⁶ In CADASIL, decreased cerebral perfusion secondary to changes in the wall of cerebral arteries leads to early damage of the periventricular and deep supratentorial white matter. Those regions are irrigated by the longest perforating arteries and are thus the most vulnerable to hypoperfusion. This is particularly the case for the central part of the pons. Repeated or prolonged reduced perfusion has been described in migraine attacks, although not specifically in the pons.¹¹ There is evidence for impaired adaptive cerebral hemodynamic mechanisms in the posterior circulation of migraine patients.¹²

We are not aware of reports on PHLs in migraine. Most reports on PHLs describe an association with an increased cardiovascular burden,^{4,5,7} leukoaraiosis, lacunar infarcts,⁵ and poor clinical outcome.⁷ A histopathological study reported a good correlation between PHLs and MRI changes.⁴ Symmetrical PHLs (histologically corresponding to myelin pallor and reactive astrocytosis) have a comparable pathophysiology as lesions in subcortical arteriosclerotic encephalopathy, ie, ischemia secondary to small-artery sclerosis. Small vessel disease or repetitive perfusion deficits are likely to be common pathophysiological mechanisms for PHLs, DWMLs and PVWMLs, and lacunar infarction.^{4,5}

The origin of PHLs is not known. A number of specific relatively infrequent clinical entities, including multiple sclerosis, encephalitis, Behçet disease, osmotic myelinolysis, hypertensive encephalopathy, neoplasm, chemotherapy, and radiation, have been implicated but were excluded in our sample. Similarly, enlarged perivascular spaces or brain stem infarcts as a cause for pontine T2 hyperintensities were excluded because of the absence of concomitant hypointense changes on T1 or FLAIR images.¹³

In summary, we found an increased prevalence of infratentorial (mostly pontine) hyperintensities in migraineurs from the general population. This extends the knowledge about vulnerable brain regions and type of lesions in migraine brains. The etiology of these lesions in migraine is unknown but likely attributable to small-vessel disease (arteriosclerosis), repetitive perfusion deficits, or both; further research is needed.

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