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## Comorbid neuropathologies in migraine

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**Abstract** The identification of comorbid disorders in migraineurs is important since it may impose therapeutic challenges and limit treatment options. Moreover, the study of comorbidity might lead to improve our knowledge about causes and consequences of migraine. Comorbid neuropathologies in migraine may involve mood disorders (depression, mania, anxiety, panic attacks), epilepsy, essential tremor, stroke, and white matter abnormalities. Particularly, a complex bidirectional relation exists between migraine and stroke, including migraine as a risk factor for cerebral ischemia, migraine caused by cerebral ischemia, migraine as a cause of stroke, migraine mimicking cerebral ischemia, migraine and cerebral ischemia sharing a common

cause, and migraine associated with subclinical vascular brain lesions.

**Key words** Migraine · Depression · Epilepsy · Tremor · Stroke · White matter lesions · Patent foramen ovale

### Introduction

Comorbidity may be defined as the presence of any additional coexistent condition in a patient with an index disease or as an association between two disorders that is more than coincidental [1]. The presence of a comorbidity may complicate diagnosis because of overlapping symptoms. As stated by Lipton and Silberstein [2], comor-

bidity may arise by coincidence or selection bias, one condition may cause the other, both conditions may be related to shared environmental genetic risk factors, and the same environmental or genetic risk factors may determine a brain state that gives rise to both conditions.

Comorbid neuropathologies in migraine, as shown in Table 1, may involve mood disorders (depression, mania, anxiety, panic attacks), epilepsy, essential tremor, stroke and white matter abnormalities [1].

**Table 1** Comorbid neuropathologies in migraine

Psychiatric disorders
Epilepsy
Essential tremor
Stroke
White matter abnormalities

### Migraine and psychiatric disorders

The prevalence of behavioural disorders such as major depression, mania or hypomania, generalised anxiety and social phobia is higher in subjects with migraine than in those without migraine [3]. Epidemiologic studies report an association between migraine headache and major depression [3–6]. The association might be noncausal, reflecting shared genetic or environmental pathogenic determinants. Alternatively, migraine might cause major depression or might be caused by it. The hypothesis that depression in persons with migraine may reflect a psychological response to the stress of recurrent severe headaches would predict an influence only from migraine to depression but not from depression to migraine. In contrast, the hypothesis of shared causes would predict that each disorder might increase the risk of first-time occurrence of the other. Some studies suggested bidirectional influences between migraine and major depression, with each disorder increasing the risk of first onset of the other [6, 7]. Moreover, the fact that prevention of migraine attacks might benefit from treatments with some antidepressant agents (Table 2) supports the presence of shared mechanisms.

Besides, the association between migraine and depression is better proven for migraine with aura than for migraine without aura [8].

### Migraine and epilepsy

Migraine and epilepsy are both chronic neurologic disorders with episodic attacks. Both migraine and epilep-

**Table 2** Antidepressants used for migraine prevention

Amitriptyline
Fluvoxamine
Paroxetine
Sertraline
Phenelzine
Bupropion
Mirtazapine
Trazodone
Venlafaxine

**Table 3** Antiepileptic drugs used for migraine prevention

Gabapentin
Levetiracetam
Topiramate
Valproate
Zonisamide

sy represent distinct families of neurological disorders with typical constellations of symptoms. Migraine is characterised by recurrent attacks of pain and associated symptoms. Epilepsy is characterised by recurrent attacks of positive neurological symptoms, often progressing to altered or lost consciousness and, at times, by convulsive features. The sensory, motor and cognitive characteristics of migraine and epilepsy often overlap. Auras, hallucinations, changes in mood and behaviour or consciousness, and focal sensory or motor symptoms may occur in both conditions. Both disorders may present with headache. Furthermore, as migraine and epilepsy are highly comorbid, many individuals have both disorders, further complicating accurate diagnosis. Many patients complain of headaches after seizures and in some cases the migraine aura can trigger seizures, as anticipated by Andermann and Andermann [9], who coined the term *migralepsy* specifically referring to this condition. However, in many patients, migraine and epileptic attacks are not temporally related. According to Lipton et al. [10], the risk of migraine is more than twice as high in persons with epilepsy, whether probands or relatives, than in persons without epilepsy. Besides, the risk of migraine is increased in persons with epilepsy caused by head trauma and is present in every subgroup of epileptic patients, defined by seizure type, age at onset, aetiology or family history. The prevalence of epilepsy in patients with migraine ranges from 1% to 17%, with a median of 5.9%. This percentage greatly exceeds that found in the general population, which is approximately 0.5% [11]. In contrast, the prevalence of migraine in patients with epilepsy ranges from 8% to 15% [12]. Additionally, the therapeutic options for the two disorders overlap, as antiepileptic drugs such as currently used also for migraine prevention (Table 3).

### Migraine and tremor

As reported by Biary et al. [13], unexplainably, essential tremor and migraine occur together more frequently than just by chance alone. Accordingly, the prevalence of migraine in patients with essential tremor is 36% com-

pared with a prevalence of 18% in normal controls. Similarly, essential tremor occurs in about 17% of patients with migraine, compared with only 1% of controls.

### Migraine and stroke

A complex bidirectional relationship exists between migraine and stroke (Table 4), including migraine as a risk factor for cerebral ischaemia, migraine caused by cerebral ischaemia, migraine as a cause of stroke, migraine mimicking cerebral ischaemia, migraine and cerebral ischaemia sharing a common cause, and migraine associated with subclinical vascular brain lesions [14–16].

#### Migraine as a risk factor for cerebral ischaemia

The fact that migraine might be considered as a risk factor for cerebral ischaemia has long been debated [17]. To speak of this possibility, a clearly clinically defined stroke syndrome must occur remotely in time from a typical attack of migraine [18]. History of migraine may contribute to the risk of stroke through an unspecified mechanism. Several case-control studies investigated the relationship between migraine and stroke: the odds ratio was 4.3 (1.2–16.3; 95% CI) in women under 45 years of age according to Tzourio et al. [19] and 3.7 (1.5–9.0; 95% CI) according to Carolei et al. [20]. Besides, odds ratios were higher in patients with a history of migraine with aura than in patients with a history of migraine without aura. According to Carolei et al. [20], the rare association between migraine and cerebral ischaemia was limited to women below the age of 35 years and suggests careful clinical evaluation of comorbidity in the presence of migraine with aura [20]. The added risk of stroke (odds ratios) to a female migraineur under the age of 45 doubles from 3 (in the presence of migraine without aura) to 6 (in the presence of migraine with aura), to 13.9 (in the presence of migraine and oral contraceptives use). A more recent study confirmed the increased risk of total and ischaemic stroke for

**Table 4** Relationship between migraine and stroke

Migraine as a risk factor for cerebral ischaemia
Migraine caused by cerebral ischaemia
Migraine as a cause of stroke
Migraine mimicking cerebral ischaemia
Migraine and cerebral ischaemia sharing a common cause
Migraine associated with subclinical vascular brain lesions

migraineurs with aura with respect to migraineurs without aura indicating a low absolute risk increase, with 3.8 additional cases per year per 10,000 women [21]. This fact might be due to a higher cardiovascular risk profile of migraineurs with respect to controls and particularly of migraineurs with aura. The GEM population-based study reported that, compared to controls, migraineurs were more likely to smoke, less likely to drink alcohol and more likely to report a parental history of early myocardial infarction. Migraineurs with aura were more likely to have an unfavourable cholesterol profile, to have elevated blood pressure and to report a history of early onset coronary heart disease or stroke; female migraineurs with aura were more likely to be using oral contraceptives [22].

#### Migraine caused by cerebral ischaemia

Migraine caused by cerebral ischaemia is also referred to as symptomatic migraine. It is diagnosed when an established structural central nervous system lesion produces typical episodes of migraine with or without neurologic aura. This is the case of migraine-like headaches that are attributed to ischaemic stroke or transient ischaemic attack but also the case of migraine-like headaches attributed to nontraumatic intracranial haemorrhage, which are extensively described in Chapter 6 of *The International Classification of Headache Disorders*, second edition (ICHD-II) (Table 5) [23].

The close temporal relation between the stroke and the onset of the headache is the main factor supporting the diagnosis as well as the resolution of the headache after the acute phase, although in some cases headache may become chronic. A migraine-like headache is often the presenting clinical feature in patients with arterial dissection and it is reported in the ICHD as *headache or facial or neck pain attributed to arterial dissection* (ICHD-II, 6.5.1) (Table 6) [23].

It usually precedes the onset of retinal or brain ischaemia by hours or days. The presence of a new onset migraine headache in association with an ipsilateral Horner's syndrome is highly suggestive of carotid dissection and requires mandatory and urgent neurovascular investigations (Fig. 1) [24].

#### Migraine as a cause of stroke

Migraine as a cause of stroke was first recognised by Charcot. As suggested by Welch [18], to diagnose

**Table 5** Diagnostic criteria of migraine-like headaches induced by stroke according to ICHD-II (Chapter 6)

- 6.1 Headache attributed to ischaemic stroke or transient ischaemic attack
- 6.1.1 Headache attributed to ischaemic stroke (cerebral infarction)
- Diagnostic criteria:
- Any new acute headache fulfilling criterion C
  - Neurological signs and/or neuroimaging evidence of a recent ischaemic stroke
  - Headache develops simultaneously with or in close temporal relation to signs or other evidence of ischaemic stroke
- 6.1.2 Headache attributed to transient ischaemic attack
- Diagnostic criteria:
- Any new acute headache fulfilling criteria C and D
  - Focal neurological deficit of ischaemic origin lasting <24 h
  - Headache develops simultaneously with onset of focal deficits
  - Headache resolves within 24 h
- 6.2 Headache attributed to nontraumatic intracranial haemorrhage
- 6.2.1 Headache attributed to intracerebral haemorrhage
- Diagnostic criteria:
- Any new acute headache fulfilling criterion C
  - Neurological signs or neuroimaging evidence of recent nontraumatic intracerebral haemorrhage
  - Headache develops simultaneously with or in close temporal relation to intracerebral haemorrhage
- 6.2.2 Headache attributed to subarachnoid haemorrhage
- Diagnostic criteria
- Severe headache of sudden onset fulfilling criteria C and D
  - Neuroimaging (CT or MRI T<sub>2</sub> or FLAIR) or cerebrospinal fluid evidence of nontraumatic subarachnoid haemorrhage with or without other neurological signs
  - Headache develops simultaneously with haemorrhage
  - Headache resolves within 1 month

**Table 6** Diagnostic criteria of migraine-like headache attributed to arterial dissection according to ICHD-II (Chapter 6)

- 6.5 Carotid or vertebral artery pain
- 6.5.1 Headache or facial or neck pain attributed to arterial dissection
- Diagnostic criteria:
- Any new headache, facial pain or neck pain of acute onset, with or without other neurological symptoms or signs and fulfilling criteria C and D
  - Dissection demonstrated by appropriate vascular and/or neuroimaging investigations
  - Pain develops in a close temporal relation to and on the same side as the dissection
  - Pain resolves within 1 month

**Fig. 1** Digital angiography showing a dissection of the left internal carotid artery in a patient presenting with a new onset migraine-like headache associated with ipsilateral Horner's syndrome

migraine-induced stroke the neurological deficit must exactly mimic the migrainous symptoms of previous attacks; the stroke must occur during the course of a typical migraine attack; all other causes of stroke must be excluded although stroke risk factors may be present. Besides migraine as a cause of cerebral infarction is extremely rare, is vastly over diagnosed and should be diagnosed only by exclusion. Migraine-induced stroke represents the same clinical entity considered in the ICHD-II as *migrainous infarction* (ICHD-II, 1.5.4) [23], occurring when one or more symptoms and signs of migrainous aura persist for more than 60 min and are associated with neuroimaging confirmation of ischaemic infarction in a relevant area (Table 7 and Fig. 2).

Migrainous infarcts are considered a direct consequence of an unusually severe hypoperfusion during aura. There is no consistent pattern of infarction, as infarcts

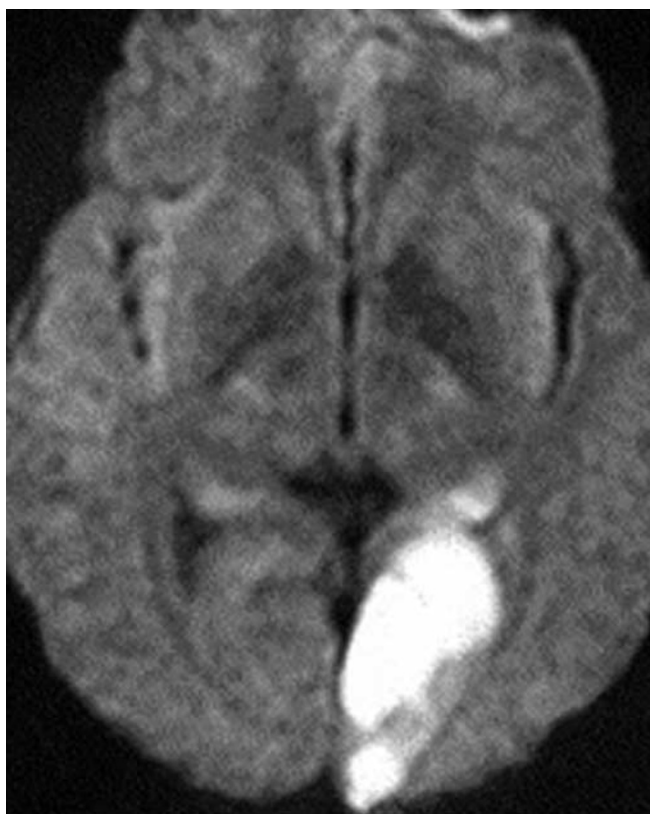
**Table 7** Diagnostic criteria of *migrainous infarction* according to ICHD-II (Chapter 1)

## 1.5 Complications of migraine

## 1.5.4 Migrainous infarction

## Diagnostic criteria:

- A. The present attack in a patient with 1.2. *Migraine with aura* is typical of previous attacks except that one or more aura symptoms persists for >60 min
- B. Neuroimaging demonstrates ischaemic infarction in a relevant area
- C. Not attributed to another disorder

**Fig. 2** Brain magnetic resonance imaging (diffusion-weighted images) showing a migraine-induced stroke in the left occipital lobe

may be large, small, single, multiple, cortical, subcortical and involve both carotid and vertebral-basilar territories. However, the most common pattern is an infarction involving the posterior cerebral artery presenting as a visual field defect.

**Migraine mimicking cerebral ischaemia**

Migraine mimicking cerebral ischaemia refers to cases of stroke caused by acute and progressive structural disease accompanied by headache and focal neurologic symptoms that are difficult to distinguish from migraine with aura. A differential diagnosis is particularly trou-

blesome in patients who continue to have migraine with aura late in life when the incidence of cerebrovascular disease increases. The differential diagnosis between a migraine aura and a transient ischaemic attack may be particularly challenging in some cases. The helpful criteria to differentiate the two conditions are summarised in Table 8.

**Migraine and cerebral ischaemia sharing a common cause**

Migraine and cerebral ischaemia sharing a common cause include syndromes in which both migraine and stroke are major clinical features. These conditions are characterised by chronic alterations of the vessel wall of small arteries and include cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), and autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. The first two conditions are also described in Chapter 6 of ICHD-II (6.7.1 and 6.7.2) (Table 9) [23].

CADASIL is an autosomal dominant disease, affecting smooth muscle cells of cerebral arteries, caused by a mutation in the gene Notch 3. It is characterised by recurrent strokes or transient ischaemic attacks, subcortical vascular dementia and migraine with aura. Migraine with aura is the most common clinical feature of the disease, present in one third of cases and is also the first clinical manifestation. It appears around the age of 30 years and precedes stroke by about 15–20 years and death by about 20–30 years. In CADASIL aura attacks tend to be particularly prolonged and frequent and they are not always followed by a typical migraine headache. Brain magnetic resonance imaging (Fig. 3) is always abnormal in CADASIL patients, showing ischaemic areas and white matter changes on T<sub>2</sub>-weighted images; the diagnosis may be further confirmed by a skin biopsy with immunostaining of Notch 3 antibodies [25–27].

MELAS is an inherited disease caused by a point mutation in the mitochondrial DNA. It is characterised by migraine with or without aura, stroke episodes and

**Table 8** Criteria to differentiate a migraine aura from a transient ischaemic attack

Migraine with aura	Transient ischaemic attack
Slow evolution of visual and sensory symptoms	Sudden onset
Serial progression of symptoms	Quick progression
Two or more identical attacks	No identical attacks
Complete recovery from attacks	Usually precede stroke
Duration longer than 20 min	Brief duration (1–30 min)
Followed by migraine headache	Rarely followed by nonmigraine headache
Most common in the young	Most common in middle-aged and elderly persons

**Table 9** Diagnostic criteria of *headache attributed to other intracranial vascular disorders* according to ICHD-II (Chapter 6)

## 6.7 Headache attributed to other intracranial vascular disorders

## 6.7.1 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

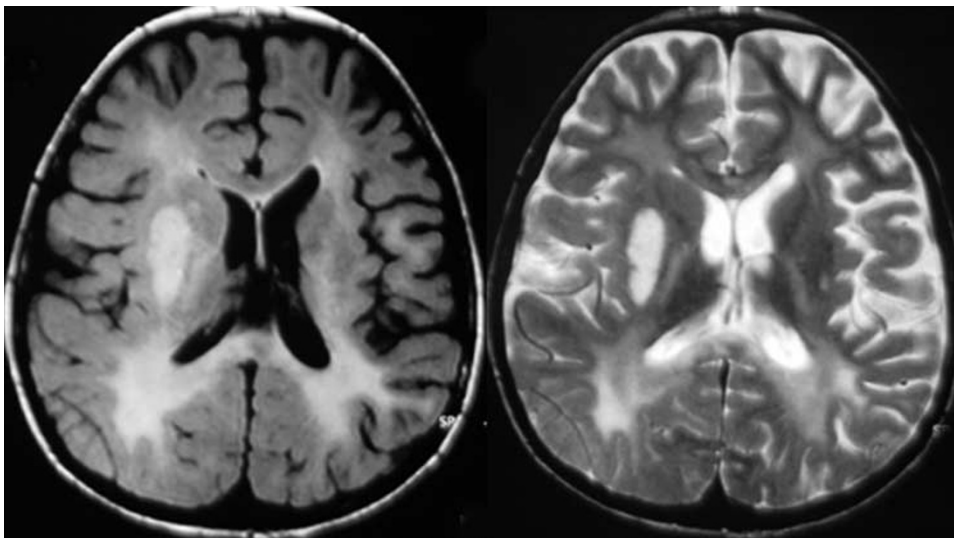
## Diagnostic criteria:

- A. Attacks of migraine with aura with or without neurological signs
- B. Typical white matter changes on T<sub>2</sub> weighted images
- C. Diagnostic confirmation from skin biopsy evidence or genetic testing (Notch 3 mutations)

## 6.7.2 Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)

## Diagnostic criteria:

- A. Attacks of migraine with or without aura
- B. Stroke-like episodes and seizures
- C. Genetic abnormality (3243 point mitochondrial DNA mutation in the tRNA Leu gene or other DNA MELAS point mutation)

**Fig. 3** Brain magnetic resonance imaging (T<sub>1</sub>-weighted images on the left and T<sub>2</sub> FLAIR images on the right) in a patient diagnosed with CADASIL

seizures [28, 29]. Another condition in which both migraine and stroke might share a common cause is patent foramen ovale (PFO) [30–32]. PFO has been associated with cryptogenic stroke episodes caused by paradoxical embolism through the PFO. The incidence of migraine with aura is about 50% in cryptogenic stroke patients who have a PFO, instead of the 12% found in the general population. Moreover, the closure of the PFO has been associated with suppression of migraine attacks [33, 34].

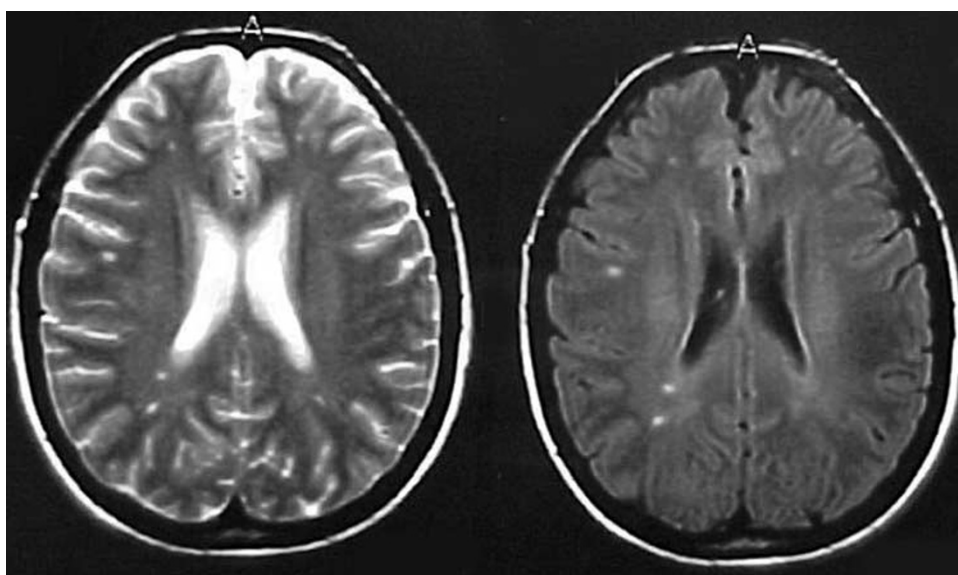
Migraine associated with subclinical vascular brain lesions

Migraine has also been associated with subclinical vascular brain lesions (Fig. 4) [35]. A Dutch study [36], however, did not show any significant difference in infarct prevalence between migraineurs and nonmigraineurs, although cerebellar lesions were more common in patients with migraine, particularly in those with aura and with frequent attacks, than in people who did not have migraine. Among

women, but not men, deep white matter lesions were more prevalent in those with migraine irrespective of type and increased with the frequency of the attacks. Oral contraceptive use further increased the risk of deep lesions, while triptans use did not confer an increased risk of subclinical lesions. The results of the Dutch study support the hypothesis that the brain parenchyma supplied by the posterior



**Fig. 4** Brain magnetic resonance imaging (T<sub>2</sub>-weighted images) showing subcortical asymptomatic brain lesions in a migrainous patient



**Fig. 5** Brain magnetic resonance imaging (T<sub>2</sub>-weighted images on the left and FLAIR images on the right) showing subcortical white matter abnormalities in a migrainous patient

circulation is a well known and particularly common site of migraine-related stroke.

### Migraine and white matter abnormalities

Since the advent of magnetic resonance imaging, white matter abnormalities (Fig. 5) have been described in subjects with migraine, although there has been some debate over whether the prevalence exceeds that found in patients without migraine.

The cause of these lesions has still not been clarified. However their presence in migraineurs has been associated with increased age and increased prevalence of cerebrovascular risk factors [16]. A meta-analysis summarised the results from seven case-control studies that considered the possible association between migraine and white matter abnormalities [37]. The pooled risk of white matter abnormalities associated with migraine from those studies was approximately four-fold (OR 3.9; 95% CI 2.3–6.7), with the odds ratios similar for studies that included (OR 3.6; 95% CI 1.5–8.4) or excluded (OR 4.1; 95% CI 2.1–8.4) individuals with risk factors for cerebrovascular disease [37].

### Conclusions

The identification of comorbid disorders in migraineurs is important as it may impose therapeutic challenges and limit treatment options. Moreover, the study of comorbidity might lead to improve our knowledge about causes and consequences of migraine.

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