Is migraine a lateralization defect?

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Migraine often co-occurs with patent foramen ovale (PFO), and some people have suggested surgical closure as an efficient treatment for migraine. Prospective studies, however, do not report radical effect of PFO surgery on migraine. Here, we examined the hypothesis that PFO and migraine may cooccur as two independent manifestations of lateralization defect during embryonic development. We measured the absolute displacement of a midline structure, the pineal gland, on brain scans of 39 migraineurs and 26 controls. We found a significant asymmetry of the pineal gland in migraineurs compared with controls. Our data suggest that migraine's circadian component and its association with PFO may be linked to a lateralization defect during embryogenesis, which could be a result from abnormal serotonin regulation. *NeuroReport* 19:1351–1353 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Migraine is a disabling neurological disease that affects millions of people worldwide. Although some aspects of its pathophysiology are becoming clearer, the underlying cause of migraine still remains a mystery.

A patent foramen ovale (PFO) is a frequent comorbidity of migraine. The foramen ovale is a hole located in the atrial septum of the heart that remains open during fetal stage to allow fetal blood circulation to bypass the lungs, and that normally it functionally closes at birth. In some cases, the closure is incomplete, or even absent, creating a right-left shunt.

The comorbidity of migraine and PFO was originally described in a study by Del Sette *et al.* [1]. Later, Wilmshurst *et al.* [2] reported that the closure of interatrial shunts in patients for decompression illness, stroke, or large septal defect alleviated the pain episodes and frequency of migraine attacks in those who had a history of migraine, in some cases even resulting in cessation of the attacks. Several studies have since then reported an increased PFO prevalence in migraineurs, especially in migraine with aura (MWA) (for review, see Ref. [3]).

Speculations have been advanced on the causality of PFO and migraine attacks. Two main hypotheses were put forward: first, the shunt could allow microemboli to reach the brain circulation and provoke migraine (and white matter lesions as described by Kruit *et al.* [4]). Alternatively, this shunt could allow substances (serotonin, norepinephrin) to bypass filtration by the lungs [5] and circulate through the brain, where they might trigger migraine attacks in predisposed individuals. These theories, however, experienced a serious setback after the large, randomized, placebo-controlled Migraine Intervention with STARFlex Technology (MIST) indicated that the closure of shunts does not have a desired effect on migrainous symptoms [3].

Here, we examined the hypothesis that the link between PFO and migraine is not one of causality, but that these two conditions cooccur because they share a common etiology in embryogenesis. We propose that both conditions arise from a lateralization defect early in the fetal development.

Our hypothesis is based on the anecdotal evidence that PFO may result from a lateralization defect in embryogenesis. First, exposure to selective serotonin uptake inhibitors such as paroxetin during the first trimester of pregnancy has been linked to heart malformations [6], including septal defects [7]. Second, serotonin exerts its effect through nodal signaling and the disturbances in the nodal pathway have been linked to numerous lateralization defects, including atrioventricular septal defects [8,9]. As serotonin is an important regulator of lateralization in the early development and plays a crucial role in heart morphogenesis [10], any deviations from the optimal serotonin levels may lead to lateralization defects of varying degrees. The link to migraine comes from the interplay of serotonin and nodal signaling in brain embryogenesis, it has been shown in the zebrafish that abnormal nodal expression results in a displacement from the midline to a lateral position of the pineal gland [11].

On the basis of these observations, we explored the hypothesis that migraine may have a common etiology with PFO in the developmental pathway, and that both conditions may arise from abnormal serotonin levels during embryogenesis. We predicted that migraineurs have a higher incidence of pineal displacement than healthy

controls, and that among migraineurs those with aura would have more displacement than those without aura.

Methods

We measured the distance between the center of the pineal gland in magnetic resonance images of migraineurs and controls. All patients were recruited from headache clinics in the area and by advertisement in the hospital. Each patient was screened with a detailed clinical interview. Exclusion criteria included pregnancy, breast-feeding, claustrophobia, and any MRI incompatibility. The hospital internal review board approved this study. Patients were classified into two groups, MWA or migraine without aura (MWoA) following the International Headache Society Classification.

Sixty-five participants were scanned in this study: 21 MWA (11 females, mean age=35.8±12.7 years), 18 MWoA (11 females, mean age=35.7±6.8 years), and 26 healthy controls (15 females, mean age=32±8.3 years). The study was conducted according to the Helsinki Declarations on human experimentation, and was approved by the Institutional Review Boards of the Massachusetts General Hospital.

Brain images were obtained and three-dimensional images reconstructed by two high-resolution magnetization-prepared rapid acquisitions with gradient echoes on a 3.0T Siemens Trio equipped with an 8-channel coil and on 1 1.5T Siemens Allegra equipped with a 23-channel coil (Erlangen, Germany). Both magnetization prepared rapid acquisitions with gradient echoes sequences [$1 \times 1 \times 1.3$ mm, 128 slices, 256×256 matrix, echo time=3.45/3.31 ms; repetition time=2530/2500 ms; flip=7°] were motion corrected and averaged to create one image volume.

Images were registered in Montreal Neurological Institute space. The pineal gland was located, and the coordinates of its center were recorded by two observers blinded to the diagnosis.

A two-tailed *t*-test, Welch's corrected was performed in the absolute distance in millimeters from the midline between migraineurs and controls. Analysis of variance was computed for the comparison between the three groups. One-tailed Mann–Whitney test was used to compare migraineurs subgroups, to take into account the non-Gaussian distribution of the data.

Results

We found significant differences in the absolute pineal displacement from the midline in migraineurs compared with controls. Migraineurs [mean, SEM (mm)]: 0.65±0.07, N=39; controls: 0.38±0.06, N=26; P=0.006 (t=2.85; d.f.=62).

When performing an analysis of variance on the three groups separately, we found that the means were significantly different (F=3.84, P=0.03). Pineal gland was significantly more lateralized in MWA compared with controls (P=0.049), and in MWoA compared with controls (P=0.012) but no difference was present between MWA and MWoA (P=0.47).

Discussion

We considered pineal displacement as an index of lateralization defect during embryogenesis [11]. We found a significant difference between migraineurs and controls in the amount of pineal displacement from the midline, supporting our hypothesis of a common developmental origin for migraine and PFO. Our second prediction, which the pineal displacement should be greater in MWA than MWoA, however, was not fulfilled and needs to be addressed in further studies.

A number of disorders, including bipolar disorders and cluster headache, exhibit seasonal behavior, and the role of the pineal gland in the chronobiology of our organism is well known. Bipolar disorders are frequently associated with migraine [12]. Cluster headache is noteworthily accompanied by a higher prevalence of PFO [13].

Pineal dysfunction may contribute to migraine. Migraine has a strong chronobiological component: attacks usually take place between 04:00 and 09:00 h, and migraine is linked to impaired sleep quality and disturbances in the sleep–wake cycle in children. In Arctic areas, MWA has been reported to be more prevalent in the light season than in the dark.

The circadian clockwork, which generates endogenous rhythmic phenomena, relies on light–dark transitions. Light itself may play a role in migraine chronobiology because migraineurs have a different sensitivity of S-cones, the detectors of short wavelength as blue [14]. Short wavelength visible or blue light is the most efficient to suppress melatonin production by the pineal gland [15].

The pineal produces melatonin from serotonin, itself a derivative from tryptophan. A disturbance in the process of tryptophan to melatonin biosynthesis could lead to an imbalance of the two substances, leading to abnormal levels of both melatonin and serotonin. Serotonin production is increased by light [16], whereas melatonin secretion is inhibited by light [17].

Serotoninergic neurotransmission seems to be altered in migraine [18,19], and low serotonin may facilitate the activation of the trigeminovascular nociceptive pathway [18]; levels of melatonin on the other hand are pronouncedly reduced in migraineurs [20]. These observations suggest that the control of serotonin-melatonin axis is disturbed both in migraine and bipolar disorder and may explain their comorbidity.

Phosphatidylinositol 3-kinase (PI3K) is an enzyme mediating the effects of serotonin through 5-HT1A receptor activation. During embryogenesis, PI3K inhibits nodal-induced cell differentiation [21], and abnormal levels of PI3K could lead to lateralization defect including PFO and pineal displacement. This in turn could later in life result in the abnormal serotonin–melatonin pattern observed in migraine.

Serotonin receptors are the target of numerous antimigraine drugs. Selective serotonin 1B/1D receptor agonists triptans act in the dorsal raphe, the periacqueductal gray, and the trigeminal nucleus caudalis [22]. In addition, new data suggest a potential effect of triptans in the ventroposteromedial nucleus of the thalamus acting through 5-HT(1A/1B/1D) mechanisms [23].

Cortical spreading depression is the probable mechanism of migraine aura [24]. The blockade of cortical spreading depression can be achieved by the action on inhibitory 5-HT1A receptors [25]. In addition to stopping migraine attacks, dihydroergotamine is an efficient drug for migraine prophylaxis. Through their actions at 5-HT1A autoreceptors (in the dorsal raphe nucleus) and heteroreceptors (notably in the hippocampus), dihydroergotamine and its metabolite

can exert an inhibitory influence on neuronal excitability, which might contribute to their antimigraine prophylactic efficiency [26].

In conclusion, this study indicates that there might be a common embryologic origin between PFO and migraine, and these two ailments may not have a causal relationship. It is not known yet whether the abnormal serotonin or melatonin levels can induce the migrainous attacks directly or whether they are surrogate rather than specific markers of a deeper underlying pathology. Further studies should address our hypothesis of PI3K abnormalities in migraine and other chronobiological disorders.

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