The role of the brain in migraine disorders remains unclear, although recent findings link migraine to other neurological conditions, i.e., hemiplegic migraine is allelic with episodic ataxias and cerebellar disorders [1]. This possible link between different pathological conditions residing primarily in the central nervous system (CNS) supports the hypothesis that migraine represents a complex disease with episodic signs and symptoms variably manifesting during the lifetime of migraine patients. The international guidelines for diagnosing migraine provide criteria for different attacks, although some of the proposed subtypes may be present in the same patient, suggesting that the disease may have different clinical manifestations [2] and that the guidelines do not reflect the need of diagnosing complex phenotypes, apart from pooling together different diagnostic codes.

Unmasking latent migraine

Migraine is a heterogeneous disorder. In fact, there is extreme variability as far as several features are concerned, such as age at onset, presence or not of focal neurological...
signs (the aura), the evolution from adolescence to adulthood and the changes induced by exogenous substances. Family history of migraine in subjects who are apparently not affected may play a significant role when they receive migraine-triggering substances, such as hormones or nitric oxide (NO) donors. These may, in fact, trigger migraine-like headache in subjects without personal history of migraine, but harbouring the susceptibility in their family [3, 4]. The onset of migraine attacks following oral contraceptives (OCs) should be regarded as a possible side effect of OCs in prone women [5]. Endogenous hormones seem to act in a different manner in migraine women. Migraine without aura (MO) is more likely to appear for the first time at puberty and to be triggered by declining oestrogens, whereas migraine with aura (MA) more likely begins with sustained high sex hormone levels, during pregnancy or with oestrogen replacement [6]. The influence of OCs does not appear to be different in patients who have only MO and those who have MA+MO [7].

Among NO donors, nitroglycerin (NTG) has undergone extensive experimental investigation in the neurological field, because typical headaches develop in migraineurs (but not normals) with a 4–6 h latency after its administration [8]. In experimental animal models, NTG administration induces an up-regulation of pro-inflammatory genes (iNOS, interleukin-6, interleukin-1), mast cell and macrophage activation, with a subsequent, delayed inflammatory reaction in the dura mater of the rat (4–6 h) [9]. This could be the mechanism through which NTG induces the migraine attack in humans.

Migraine-like headache attacks also occur in non-migraineurs with family history of migraine, following NO-donor administration, therefore the susceptibility to the disorder can be unmasked using these substances. This is of extreme relevance in patients who receive nitrates for therapeutic purposes.

Taken together, these synthetically reported observations lead to an outline of the concept that migraine has an “organic” substrate on which the clinical pattern may be modulated by exogenous or endogenous substances.

Migraine and comorbid conditions

The heterogeneity of migraine also implies that there is an association with other neurological, psychiatric and cardiovascular diseases, the most common being epilepsy, cerebrovascular disorders, anxiety/depression, arterial hypertension, mitral valve prolapses and patent foramen ovale. The association is not coincidental and it may be due to a common genetic substrate and to the presence of different mutations in the same gene [10]. The hypothesis envisages common neurobiological mechanisms influencing the full expression of the clinical phenotype [11]. In this view, deranged brain oxidative metabolism, abnormal neuronal excitability, possibly due to altered membrane ion channels, and functional changes in receptor components, along with environmental factors, represent the mechanisms underlying the spectrum of migraine and comorbid conditions and the continuum among these disorders. Ion channel pathology, mitochondrial disorders and other gene mutations received attention in the genetic era and linked migraine to other paroxysmal episodic phenomena, raising the question of whether migraine is a genetically determined disorder [12, 13].

There is increasing concern about migraine and the risk of ischaemic stroke [14], although further studies are needed to explore the mechanism of this potential association. This topic seems crucial when OCs are prescribed in female migraine patients. There is no clear evidence that OCs increases the risk of stroke, however discontinuation of the substances is prudent in these patients, namely in the presence of other risk factors, smoking habit or middle age, for instance [14, 15]. Similar actions should be taken when screening patients to be treated with vasoconstrictor agents, such as ergots and the triptans. To summarise, accurate recognition of comorbid diseases, as well as increasing the list of differential diagnoses, provides epidemiological clues to the fundamental pathophysiology of migraine, and creates therapeutic opportunities and/or imposes therapeutic limitations.

Migraine evolution: born to be migrainous

Cyclic vomiting, abdominal migraine and paroxysmal vertigo represent precursors of adulthood migraine [2] to support the hypothesis that migrainous disorders are present early during the lifetime. The above manifestations seem to represent unspecific and low-grade paroxysmal events as if the brain would not yet be able to configure a clear migraine attack. As long as the “visceral organ brain” [16] develops, it becomes able to clearly organize a fully blown migraine attack and the former episodes tend to decrease and disappear. There is evidence that they are neurobiologically related to migraine [17, 18] and therefore the recognition of a migraine disorder should be considered in young children prior to submitting them to instrumental diagnostic procedures. Interestingly, the diagnosis of MA [2, 19] in adolescents is clearly unstable [20] and a large proportion of them convert to “probable migraine without aura” [2], previously coded as “migrainous disorder not fulfilling the criteria” [19], at 3-year follow up.
Migraine attacks tend to disappear following severe traumatic brain injury [21] and to recur after a certain degree of cognitive functioning is regained, thus suggesting that a certain degree of “high level” pain processing is needed in order to perceive the migraine pain along with premonitory and accompanying symptoms and the aura as well. Therefore, the more severe the brain damage, the later the recovery of a fully developed migraine attack. Furthermore, neurodegenerative diseases presenting with focal brain damage in dopaminergic areas, such as substantia nigra in Parkinson’s disease, may somehow shorten the lifetime clinical course of migraine, suggesting that an imbalance in the nociceptive system has an effect on migraine mechanisms [22].

According to the above consideration, the question of whether migraine has an evolutionary meaning arises [23]. Is migraine a natural selection product? Is migraine an alarm system to protect the brain from inner injuries? Trying to answer those questions will be one of the routes to travel to find interesting topics for understanding the evolution of human brain development.

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