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## **Migraine in multiple sclerosis and other chronic inflammatory diseases.**

Xavier Moisset<sup>1</sup>, Pierric Giraud<sup>2</sup>, Radhouane Dallel<sup>1</sup>.

1- Université Clermont Auvergne, CHU de Clermont-Ferrand, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, France.

2- Annecy Genevois Hospital, F-74370, Annecy, France.

### **Corresponding author:**

Xavier MOISSET

Service de Neurologie, CHU Gabriel Montpied

58 rue Montalembert, F-63000 Clermont-Ferrand – France

E-mail: [xavier.moisset@gmail.com](mailto:xavier.moisset@gmail.com)

Tel: +33 4 73 75 22 01 – Fax: +33 4 73 75 22 02

### **Conflict of Interest Statement:**

Xavier Moisset reports fees from Allergan, Biogen, Bristol Myers Squibb, Grünenthal, Lilly, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, TBWA, and Teva and non-financial support from SOS Oxygène, Boehringer, not related to the submitted work.

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## **Migraine in multiple sclerosis and other chronic inflammatory diseases.**

### **Abstract**

Migraine is a very prevalent disease worldwide and is a major cause of disability. As known for a long time, migraine is associated with neurogenic inflammation. Epidemiological studies have shown that migraine is comorbid with several chronic inflammatory diseases, including multiple sclerosis (MS), chronic inflammatory rheumatic diseases (CIRDs) and inflammatory bowel diseases (IBDs). This brief narrative review highlights some recent data supporting a link between migraine and these three chronic inflammatory diseases. Studies found that migraine prevalence is approximately two-fold higher in these diseases compared to the general population. The causal link between migraine and these chronic inflammatory diseases has not been identified yet. Here, we suggest that systemic mediators (such as cytokines) and gut microbiome make migraine worse or add significant risks. Systemic inflammation biomarkers and gut microbiome modification are certainly avenues worth exploring.

### **Keywords**

Migraine, multiple sclerosis, chronic inflammatory rheumatic diseases, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic inflammation, gut microbiome

## **Abbreviations**

95% CI: 95% confidence interval

CCL20: C-C chemokine ligand 20

CD: Crohn's disease

CGRP: calcitonin gene related peptide

CIRD: chronic inflammatory rheumatic disease

CSF: cerebrospinal fluid

IBD: inflammatory bowel disease

IL: interleukin

MS: multiple sclerosis

OR: odds ratio

PsA: psoriatic arthritis

RA: rheumatoid arthritis

SP: substance P

SpA: spondyloarthritis

UC: ulcerative colitis

## **1. Introduction**

Migraine is currently the sixth most prevalent disease worldwide with a prevalence around 15% and is a major cause of disability [1]. It is well-known for decades that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of migraine attacks [2]. A large volume of work has also suggested an important role for inflammation, in particular neurogenic inflammation, in migraine pathophysiology (for review, see [3]). Several major cytokines, including tumor necrosis factor (TNF), IL-1 $\beta$  and IL-6, have been linked to migraine pathophysiology, as their levels are altered in individuals with this condition [4]. In addition, an inflammatory soup is frequently used in preclinical models to mimic migraine headaches and related trigeminal sensitization [5,6]. Indeed, neurogenic inflammation is characterized by the release of neuropeptides including substance P (SP) and calcitonin gene related peptide (CGRP) from the trigeminal innervation. This release leads to vasodilation, plasma extravasation secondary to capillary leakage, edema, and mast cell degranulation leading in turn to increased neuronal activation in the trigeminovascular system.

Thus, if inflammation is directly involved in the pathophysiology of migraine appearance or chronicization, another cause of chronic inflammation that would increase inflammatory mediators selectively in the brain or more globally would be able to increase migraine

prevalence and/or severity. Based on such observation, several epidemiological studies have been performed in chronic inflammatory diseases such as multiple sclerosis (MS), chronic inflammatory rheumatic diseases (CIRDs) and inflammatory bowel diseases (IBD). This brief review highlights some recent data on such association between migraine and some chronic inflammatory diseases. Speculation concerning the potential inflammatory mediators implicated in all these diseases will be provided.

## **2. Comorbid conditions in migraine**

### **2. 1. Migraine and multiple sclerosis**

MS is the most frequent chronic disease generating neurologic disability in young adults [7]. It continues to be a challenging and disabling condition but there is now greater understanding of the underlying genetic and environmental factors that drive this condition and many treatments are available [8]. The median age at disease onset is around 30 and 70% of patients are women. Overall, 85% of the patients begin with a relapsing-remitting disease, each relapse corresponding to an episode of inflammation. Thus, both sex ratio and age present similarities with migraine epidemiology. Several well-conducted studies have shown an increased prevalence of migraine in MS [9–12]. Conversely, it has also been suggested that being a migraineur was increasing the risk to present with MS [13]. Indeed, in a cohort of more than 100,000 female nurses, the relative risk of developing MS in migraineurs was 1.39 times higher than in non-migraineurs (95% CI 1.10-1.77,  $p=0.008$ ). Nonetheless, the absolute risk of developing MS in women migraineurs over a 15-year follow-up was still low (0.47%). According to a recent systematic review and meta-analysis, the overall migraine prevalence among MS patients was 31% [95%CI = 22 to 40], i.e. around two times more than in the general population [14].

As stated above, the link between migraine and MS could be bidirectional [13]. A bidirectional link between pain and MS has also been suggested by data obtained in animal models [15]. Indeed, Arima and collaborators demonstrated that a pain-mediated neural signal can be transformed into an inflammation reaction at specific vessels to induce disease relapse, thus making this signal a potential therapeutic target. Although pain relief should already be sought for patients' quality of life, if headache pain had also a direct role in the risk of relapse, it would need even more care for the treatment of this symptom. However, conflicting results have been published, with either a decrease MS activity among migraineurs [16] or a clear increase in the relapse rate among MS migraineurs [17]. Of note, these two studies were made by the same research group and were well-conducted. Thus, the link between MS activity and

migraine is still an open question. Presence of small cortical lesions or lesions within the midbrain could also make a link between the two conditions. Indeed, direct meningeal inflammation, dysregulation of areas implicated in pain control or facilitated cortical spreading depression could explain the increased occurrence of migraine in MS. It could be of interest to look at the temporal relationship between MS and migraine appearance, migraine frequency, migraine treatment and impact of the disease modifying treatment used for MS. Indeed, multiple interactions between these factors could exist and have not been taken into account in the studies published to date.

Interestingly, it has also been shown that migraine headache were frequent at the time of diagnosis [18].

A postal survey conducted in France to assess the prevalence of pain in a cohort of 1,300 patients with MS, 46% of the respondents (n = 673) had migraine [9]. Migraine was mostly episodic, but headaches were occurring on  $\geq 15$  days per month in 15% of those with migraine. Migraine was associated with younger age, disease duration, relapsing-remitting course, and interferon-beta treatment. Such association has been reported in other well-conducted studies [19,20] and could be in favor of a role of the inflammasome activation in migraine development [21]. Another link between MS, migraine and inflammation has been suggested in one study showing that high-sensitivity C-reactive protein (CRP) levels were higher in MS patients with migraine compared to patients without migraine [22]. Although such an inflammation marker is of low specificity, it is one indicator of the importance of inflammation in the coexistence of these two diseases.

## **2.2. Migraine in chronic inflammatory rheumatic diseases**

Chronic inflammatory rheumatic diseases (CIRDs), is a class of rheumatic diseases that is represented by rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). The common feature of these three diseases is that they include chronic inflammation, causing inflammatory pain, which leads to functional disability. The current therapeutic objective is to achieve clinical remission, that is, the absence of pain, joint swelling, spinal stiffness, and biological inflammatory syndrome. In a cross-sectional study, we assessed the prevalence of migraine in 499 patients with CIRDs, including 238 patients with RA, 188 with SpA and 72 with PsA [23]. Migraine was diagnosed according to IHS migraine diagnostic criteria [24]. The prevalence of migraine was 34%. Compared to the French general population, these patients had a significantly higher prevalence of migraine (two-fold). Risk factors for migraine were a high level of anxiety, female sex, young age, and TNF-alpha

inhibitor treatment (OR = 1.90 (1.13-3.25)). Besides, high disease activity was a risk factor in SpA. Blood CRP level was not significantly associated with migraine, but was low overall in those clinically well-controlled patients. This study showed that migraine frequently occurred in patients with rheumatic diseases. Therefore, upon reporting residual pain, we suggest that these patients should be checked for the presence of migraine, despite adequate clinical control of rheumatic disease.

In a population-based, propensity score-matched cohort study, it has been shown that compared to the non-migraine group, the multivariable-adjusted hazard ratio of RA for the migraine group was 1.91 (95% CI 1.58-2.31,  $p < 0.001$ ) [25]. Although this study had a major limit as only 60,000 migraineurs were identified among more than 20 million inhabitants, leading to a migraine prevalence around 0.3%, the matching was made properly and the result clearly suggest an association between migraine and RA.

Beside CIRDS, an even more frequent rheumatologic disease is arthritis. A study has shown, after adjusting for several potential confounders, that there was a significant association between arthritis and migraine (OR = 1.83, 95% CI = 1.20-2.81) [26]. The association was more significant in women aged  $<45$ . The mechanism for the coexistence of migraine and arthritis has not been explored, but it is well-known that the inflammasome is involved in arthritis inflammation and such inflammation could make a link between these two entities [27].

### **2.3. Migraine in inflammatory bowel diseases**

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are systemic, chronic inflammatory conditions that predominately affect the gastrointestinal tract but are also characterized by numerous extra-intestinal manifestations (articular, cutaneous, ocular). As brain-gut interactions are known to be bidirectional [28] and as many IBD patients complain about headaches in daily practice, we included 203 consecutive tertiary-care center patients to assess the prevalence of migraine in IBD patients [29]. In our cohort, migraine prevalence was two-fold higher in IBD patients compared to the general population (41% vs. 21.3%,  $p < 0.001$ ). Migraine was associated with younger age, female gender and higher depression scores. Among unexpected observations, one study [30] found that migraine, typically classified as a disease of the central nervous system, appears to be genetically most similar to irritable bowel syndrome and environmentally most similar to cystitis and urethritis, all of which are inflammatory diseases. Although migraine impact was very important for 30% of the patients, specific acute therapeutics were prescribed in only

22% of cases. Although further studies are needed to confirm whether migraine should be classified as IBD extra-intestinal manifestations, such association has been reported by other authors [31,32]. However, systematic screening is not recommended to date, as migraine is not considered as an extra-intestinal manifestation so far, although this co-occurrent symptom is far more frequent than joint involvement, which is considered to be the most frequent extra-intestinal manifestation [33]. We suggest adding systematic screening for migraine in the monitoring of IBD patients to provide appropriate treatment.

### **3. Putative pathophysiological mechanisms**

#### **3.1. Systemic inflammation**

Several authors have tried to find better biomarkers for inflammation in MS. In both plasma and cerebrospinal fluid (CSF), several biomarkers have been suggested but are not used in routine clinical practice [34]. C-C chemokine ligand 20 (CCL20) is a cytokine responsible for the chemoattraction of immature dendritic cells and its level seems associated with MS severity. It has also been suggested that CCL20 could be involved in RA [35] or IBD [36] pathogenesis. It is also known that high levels of T helper (Th) lymphocytes and related cytokines and chemokines have been found in central nervous system lesions and in CSF of MS patients, thus contributing to the breakdown of the blood-brain barrier, the activation of resident astrocytes and microglia, and finally the outcome of neuroinflammation [37]. To date, several types of Th cells have been discovered and designated according to the secreted lineage-defining cytokines. Thus, Th17 secretes mainly interleukin 17 (IL-17) that is a pro-inflammatory cytokine, together with other proinflammatory cytokines such as IL-21 or IL-22. IL-17 and IL-23 have been associated with MS. These two cytokines are also involved in other chronic inflammatory diseases such as IBD [38] or RA [39]. Thus, looking for a common denominator between chronic inflammatory diseases and a relationship between these inflammatory diseases and migraine can be helpful to better understand potential factors common to such association. To date, no study has explored the level of CCL20, IL17 or IL23 in the serum of a large sample of patients with episodic or chronic migraine, compared with healthy controls. In addition, the impact of CCL20, IL17 or IL23 injection has not been tested in preclinical models to look for an increased sensitivity to migraine in animal models.

#### **3.2. Gut microbiome**

The terminology *gut-brain axis* points out a bidirectional relationship between the gastrointestinal system and the central nervous system [40]. To date, several studies have

shown that migraine is associated with some gastrointestinal disorders such as *Helicobacter pylori* infection, irritable bowel syndrome, and celiac disease. However, the mechanisms explaining how the gut and the brain may interact in patients with migraine are not entirely clear [41]. Studies suggest that this interaction seems to be influenced by multiple factors, notably inflammatory mediators (IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ ), gut microbiota profile, stress hormones or sexual hormones. Neuropeptides including calcitonin gene-related peptide (CGRP), substance P, vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) are thought to have antimicrobial impact on a variety of gut bacterial strains and thus speculated to be involved in the bidirectional relationship between the gut and the brain.

Concerning the gut microbiome, it has been shown that fusobacteria phyla are common features in IBD and CIRD patients [42]. Gut microbiome modifications have also been investigated in MS and various alteration have been described, disease modifying treatment also having an impact on the microbiota [43,44]. The link between such modification in the microbiome and potential impact on systemic inflammation peptides that could increase migraine risk has to be explored. One proposed biomarker is calprotectin, measured in daily practice in the feces of IBD patients for their follow-up, and that has been suggested to be used as a biomarker to monitor the risk of relapses in CIRDs when measured in the serum [45]. Serum calprotectin has also been shown to increase during MS relapses, and is also elevated in the cerebrospinal fluid [46,47]. To date, the impact of an increased in calprotectin has not been evaluated in preclinical models to look for an increased sensitivity to migraine.

#### **4. Conclusions**

It is clear from the studies reviewed here that migraine disorders are comorbid with various chronic inflammatory diseases such as MS, CIRDs or IBD. Nonetheless, the bidirectional mechanisms that are likely to underlie this extensive comorbidity between migraine and inflammatory diseases are not been found yet. Systemic inflammation biomarkers and gut microbiome modification are certainly avenues worth exploring.

#### **Disclosure of interest**

Xavier Moisset reports fees from Allergan, Biogen, Bristol Myers Squibb, Grünenthal, Lilly, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, TBWA, and Teva and non-financial support from SOS Oxygène, Boehringer, not related to the submitted work.

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Radhouane Dallel has no conflict of interests.

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