TITLE

MIGRAINE COMORBIDITY IN BIPOLAR DISORDER

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ABSTRACT

Introduction: Bipolar Disorder (BD) is a chronic mental illness associated with functional decline, mortality, and significant health care costs; furthermore, specific general medical conditions have been found to occur disproportionately within BD patient populations, among them, migraine is one of the most studied. Migraine has a global prevalence of 10%, and it is a disorder with elevated direct and indirect costs, the later mostly derived from its association with mood and anxiety disorders. Specifically, the reported prevalence of migraine in the BD population ranges from 24.8% to 39.8%, rates that are considerable higher than those found in the general population.

Objective: To explore the prevalence and clinical characteristics of BD patients with and without migraine (Study 1), and to examine the psychiatric comorbidity in patients suffering from migraine (Study 2).

Methods: 323 BD patients were studied, using SADS-L and SCID as diagnostic interviews, and ID-Migraine questionnaire to assess the presence of migraine. Statistical analyses were conducted using parametric analysis and the development of log-linear models. Additionally, 102 migraine patients were interviewed using SADS-L, and the descriptive characteristics of the sample were analyzed.

Results: For Study 1, we found that 24.5% of BD patients suffer from migraine, and it is significantly associated with BD 2, suicidal behaviour, and a variety of anxiety disorders. As well, over 70% of migraine patients showed a lifetime psychiatric diagnosis, mainly within the spheres of mood and anxiety disorders; specifically, the prevalence of BD among migraine patients was 12.7%.

Conclusions: Our study highlights the high prevalence of migraine among BD patients, and the elevated prevalence of psychiatric comorbidity among migraine sufferers. The study of this comorbidity will deepen our understanding of the mechanisms that underlie both disorders and provide a better framework for the developing of molecular techniques to further analyze the molecular physiopathology of Bipolar Disorder.

ABSTRACT (FRENCH)

Introduction : Le Désordre Bipolaire (BD) est une maladie mentale chronique associée avec le déclin fonctionnel, la mortalité, et les coûts de services de santé significatifs ; de plus, les conditions médicales, générales et spécifiques ont été trouvées pour arriver d'une façon disproportionnée dans les personnes atteintes, parmi eux, la migraine est un des plus étudié. La migraine a une prédominance globale de 10%, et c'est un désordre avec les coûts élevés, directs et indirects, surtout dérivé de son association avec les désordres d'humeur et anxiété. En particulier, la prédominance rapportée de migraine dans les malades bipolaires est de 24,8% à 39,8%, considérable plus haut que ces trouvé dans la population générale.

Objectif : Explorer la prédominance et les caractéristiques cliniques de BD avec et sans la migraine (Etudie 1), et examiner la présence de désordres psychiatriques dans les malades souffrant de la migraine (Etudie 2).

Méthodes : 323 malades de BD ont été étudiés, utilisant SADS-L et SCID comme diagnostic entrevue, et le questionnaire ID-MIGRAINE pour évaluer la présence de migraine. Statistique analyse a été dirigé l'utilisation de l'analyse paramétrique et le développement de log-linear modèles. En plus, 102 malades de migraine ont été entrevues avec SADS-L, et ceux caractéristiques descriptives ont été analysés.

Résultats : Pour l'Etude 1, nous avons trouvé que 24.5% de malades de BD souffre de la migraine, et il est significativement associé avec BD 2, le comportement suicidaire, et désordres d'anxiété. Aussi, plus de 70% de malades de migraine a montré un diagnostic psychiatrique à vie, principalement dans les sphères de désordres d'humeur et anxiété ; en particulier, la prédominance de BD parmi les malades de migraine était 12.7%.

Conclusion : Notre étude souligne la prédominance de migraine parmi les malades de BD, et la prédominance élevée des désordres psychiatriques dans migraneurs. L'étude de cette relation approfondira notre compréhension des mécanismes moléculaires impliqués dans le Désordre Bipolaire.

CHAPTER 1: INTRODUCTION

More than three decades ago, Feinstein coined the term *comorbidity* to refer to the "greater than coincidental association of two conditions in the same individual" [1]. The original concept has undergone a historical evolution: comorbidity should be regarded today as a non-casual association of clinical entities; and, as accepted in modern practice, the concept refers to the statistical association of two distinct diseases in the same individual at a rate higher than expected by chance [2].

More recently, the study of comorbidity has begun to emerge as an important task itself, with the recognition that understanding how comorbidity arises may extend our understanding of the development of psychopathology, and as well function as a tool for improving nosology.

If properly assessed, a comorbidity link may indicate that a condition is causally involved with other. Alternatively, it may suggest the existence of a shared physiopathological mechanism independently promoting the development of both diseases in the same individual. The shared mechanisms can be genetically determined (ion channel dysfunctions can lead to brain hyperexcitability states that promote both migraine an epilepsy) or acquired (head trauma can lead to both migraine and epilepsy) [3].

An existing problem with the term "comorbidity" is that it has been used to include a multitude of different temporal relationships amongst disorders. For instance, *concurrent comorbidity* refers to the comorbidity between current disorders at the time of assessment, although their times of onset and offset may not be coterminous. *Successive comorbidity* applies then when two disorders do not overlap in time, and may have never been present simultaneously [4]. These characteristics can explain the different rates between current and lifetime comorbidity for some, but not for all, disorders. Another problem is that in association studies, the selection bias can overestimate comorbidity of diseases presenting a symptomatologic overlap and therefore carrying a partial sharing of diagnostic criteria sets.

There is a growing body of evidence relevant to understanding the causes of comorbidity, which can be addressed as different questions [4]:

a) Is comorbidity a methodological artefact?

The possibilities here include effects of referral bias, rater expectancy, or halo effects, and effects of current information collection strategies, such as the use of multiple informants. However, the available information suggests that comorbidity seen in clinical samples is not simply the results of Berkson's or clinical referral biases, but represents a psychopathological phenomenon in relation to DSM-IV diagnoses. In the second case, the use of structured assessments for research, and the demonstration that comorbidity is seen with self-report questionnaires, respondent-based interviews, and interviewer-based interviews, rule out clinician bias or interviewer expectancies as possible explanations of the observed rates of comorbidity.

b) Is comorbidity an artefact of current diagnostic systems?

Several authors have pointes out that comorbidity could not be generated by the fact that individual 'nonspecific' symptoms are shared by separate diagnosis, with the result that certain amount of overlap is built into the diagnostic system. Because this raises the question of the degree to which the current DSM and ICD nosologies really suffer from this problem, we should examine the criteria for the different disorders and determine the degree of overlap. There is also comorbidity between the non-overlapping symptoms of such syndromes, suggesting again that comorbidity is not just an artefact of our flawed diagnostic system in psychiatry.

c) Epiphenomenal comorbidity

When three conditions are all associated with one another, it is possible that one of pairwise associations is nothing other than the mathematical product of the other two. By providing a large enough sample to test for this possibility, and controlling each pairwise comparison for the effects of other comorbidities, one of the major achievements of research on comorbidity over the last decade has been its

demonstration has been that comorbidity is not the product of two related disorder, but a real phenomenon per se.

Timing is a key component for understanding comorbidity. Most studies have relied on a single-wave of cross-sectional data, or relied on recall of disorders over the whole life course. Both of these approaches are incapable of providing descriptions of the interplay of shared and specific risk factors over time and their effects on diagnostic status over time. There is still quite abundant conceptual confusion and conflicts to be sorted out if we are to have a set of coherent explanations of comorbidity and nosological responses to them, but there is also a much better appreciation of what the problems are, and of the need to use multiple approaches to overcoming them.

Migraine, a disorder that has been widely study in this sense, is a condition with both recurrent and paroxysmal manifestations of disturbed brain function, specifically, a condition caused by an altered cortical excitability. Over the years, several studies have shown that various psychiatric conditions are particularly associated with migraine, among them, major depressive disorder [5-9], bipolar disorder [6, 10-12], and anxiety disorders [6, 13, 14].

In this sense, Bipolar Disorder (BD) is a chronic mental illness associated with functional decline, mortality, and significant health care costs [15]; furthermore, specific general medical conditions have been found to occur disproportionately within BD patient populations. Several studies have reported that there is a strong correlation between medical comorbidities in BD and the duration of depressive lifetime episodes, as well as a poor prognosis for the disorder [16]. In different studies [11, 17], it has been shown that BD patients exhibit a higher prevalence of medical comorbidities, such as gastric disorders, hyperlipidemia, chronic fatigue syndrome, hepatitis C, COPD, asthma, dementia, and migraine.

The comorbidity between migraine and BD is relevant because patients with both conditions use health resources in an extended way, when compared with patients suffering from only one of these conditions; and because the recognition and treatment of comorbid conditions improves in general the prognosis of the both disorders [18].

Many similarities are found between migraine and BD, including the episodic course of both illnesses, the possible mechanism of kindling, the efficacy of antiepileptic drugs (AED) in their treatment, their increased vulnerability to stress, and the positive family history of migraine and affective disorders, all of these conditions that might point to a common underlying pathophysiology.

In this context, the targets that AED share with lithium, the gold-standard for the treatment of BD, include inositol depletion, inhibition of glycogen synthase kinase 3β (GSK3β) and increased activity of the extracelullar signal-regulated kinase (ERK) pathway [19]. In despite of their similarities, the mechanisms of comorbidity between migraine and BD remain elusive. They may include shared genetic and/or environmental underlying risk factors that produce a brain state that gives rise to both conditions. Another approach that may serve in the understanding of how migraine and BD are associated, is an observation of their phenomenology over time [20], understanding that migraine and BD are paroxysmal dysregulations of the central nervous system. They both have an increased vulnerability to stress, an early onset of the disorder and they can be worsened by common conditions (e.g., menstrual). Finally, the strong connection between BD 2 and migraine supports the contention that BD I and BD II represent two different nosological conditions. Therefore, it follows a review of the mechanisms implicated in neurotransmission, brain imaging and genetics in both disorders, to obtain a deeper understanding of the shared physiopathological processes in BD and migraine.

CHAPTER 2: MIGRAINE

Introduction

Migraine is defined as a recurrent headache disorder manifested in attacks lasting 4 to 72 hours; the typical characteristics of the headache include an unilateral location, its aggravation by routine physical activity, and its association with nausea and/or photophobia and phonophobia [21]. The classification includes different subtypes of migraine, being the most frequent addressed: migraine with aura (MA) and migraine without aura (MO).

Diagnostic criteria for migraine without aura (ICHD-II) [22]

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
    a. Unilateral location
    b. Pulsating quality
    c. Moderate or severe pain intensity
    d. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
    a. Nausea and/or vomiting
    b. Photophobia and phonophobia
E. Not attributed to another disorder

Diagnostic criteria for migraine with aura (ICDH-II) [22]

At least two attacks fulfilling criterion B

A. Migraine aura fulfilling criteria B and C for one of the subforms
B. Not attributed to another disorder

Diagnostic criteria for typical aura with migraine headache [22]

A. At least two attacks fulfilling criteria B-D
B. Aura consisting of at least one of the following, but no motor weakness:
    a. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
    b. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
    c. Fully reversible dysphasic speech disturbance
C. At least two of the following:
    a. Homonymous visual symptoms and/or unilateral sensory symptoms
    b. At least one aura symptom develops gradually over ≥ five minutes and/or different aura symptoms occur in succession over ≥ five minutes
    c. Each symptom lasts ≥ 5 and ≤ 60 minutes
D. Headache fulfilling criteria B-D for migraine without aura. Migraine without aura begins during the aura or follows aura within 60 minutes.
E. Not attributed to other disorder

According to the Second edition of the International Headache Society [22], migraine with aura is now subdivided into migraine with typical aura, basilar migraine, and hemiplegic migraine. Migraine with typical aura, the most common subtype, is characterized by visual, sensory or dysphasic aura (being a visual aura the most frequent type), and it is subtyped according to the characteristics of the headache following the aura: typical aura with migraine headache, typical aura with nonmigraine headache and typical aura without headache. Nevertheless, co-occurring attacks of basilar-type migraine seem to occur in up to 10% of patients with migraine with typical aura [23]. Moreover, to further operationalize the diagnosis of MA, there has been recently developed a Visual Aura Rating Scale (VARS), which score is the weighted sum of the presence of five visual symptom characteristics, including: duration 5-60 minutes, gradual development $\geq$ 5minutes, scotoma, zigzag lines and unilaterality [24], providing clinical evidence that support that MA and MO are different disorders, as well as enabling the differentiation among MA and other non-specific visual disturbances.

Although migraine has been considered as a benign disorder, recent studies have shown that it can be complicated by serious adverse events, such as migranous stroke, the induction of seizures, and a persistent aura without infarcts [25]. The relationship between migraine, aura, and stroke; as well as the relationship between migraine and epilepsy is a complex one, and mechanisms different from cause-effect could be involved.

In this sense, some studies have suggested that migraine, particularly MA [26], is also associated with an unfavourable cardiovascular risk profile, reporting, for example, that the odds for having a clinically relevant Framingham risk score were higher for migraine patients (OR = 1.51) when compared to the control group (OR = 1.0); and the difference was even more striking when migraine was classified according to subtypes: for MA, OR = 2.05; and for MO, OR = 1.26, as reported in the cross-sectional study from Scher [27]. In a prospective study by Kurth and colleagues [28], that included 27840 women aged 45 years or older, it was found that any history of migraine was associated with an increased risk of major cardiovascular disorder; and the risk was different according to the presence of aura status: the presence of active MA was associated with an increased risk of major cardiovascular disease, myocardial infarction, ischemic stroke and death due to ischemic cardiovascular disease; all these risks remained after adjusting for a number of

cardiovascular risk factors. Some of the hypothesis proposed to explain the comorbidity of MA and cardiovascular disorders include endothelial dysfunction [28], the presence of patent foramen oval [29], hyperhomocysteinemia, and vasospasm and prothrombotic factors [27].

Migraine has also been associated with other co-morbid conditions, such as asthma [30], eczema, rhinitis, COPD and epilepsy [21]. For instance, the prevalence of epilepsy in migraine patients varies from 1% to 17%, substantially higher than the population prevalence of epilepsy [31]; and, given their shared symptom profile and treatment, some authors have proposed that this crossover can add valuable information for the treatment and pathophysiology of both neural excitability disorders. Some authors have also reported that a mutation in factor V Leyden, a common risk factor for venous thromboembolism, was more frequent among those survivors of brain or heart stroke that also had migraine. The ensuing studies, however, gave conflicting results [32].

Pathophysiology of migraine

Migraine results from episodic changes in central nervous system physiologic function in a hyperexcitable brain. There are several mechanisms which converge in the pathway represented by neuronal membrane hyperexcitability, and the triggers might been genetically determined, environment-related, or both. Additionally, and due to the relationship between migraine and epilepsy, there are some authors that consider migraine as "a long lasting epileptic phenomenon, in certain cases, even as a pure autonomic status epilepticus" [33].

Migraine has been conceptualized also as a form of sensory processing disturbance, with several implications within the central nervous system [34]. There are multiple studies supporting interictal and ictal hyperexcitability in migraine brain, as showed by exaggerated CO_2 reactivity with transcranial Doppler, abnormal cerebrovascular reactivity, enhanced photic drive responses, abnormal energy metabolism and membrane instability [35]. A variety of causes for hyperexcitability of the brain in migraine have been suggested, including low magnesium levels, mitochondrial dysfunction and dysregulation

of the calcium channels, that could result in disinhibited NO synthase activity or membrane instability, resulting in abnormal ion fluxes, elevated external potassium concentrations and initiation of a phenomenon named cortical spreading depression (CSD). CSD is a slowly propagating wave of neuronal and glial depolarization that spreads across the cortex with a speed of 3-5 mm/min. It is accompanied by a short-lasting dramatic increase in regional cerebral blood flow (CBF) followed by a long-lasting regional CBF hypoperfusion [36]. Enhanced neuron excitation, coupled with firing in a localized region of the cortex, is known to result in the local build-up of extracellular K+, which depolarizes adjacent neurons and thus causes the phenomenon to spread. If diffusion, re-uptake and transport processes cannot contain the glutamate release and change in ionic concentrations, a wave of spreading depression is generated [37].

Evidence that CSD is linked to migraine with aura has been strengthened recently by the availability of non-invasive brain imaging. In the study from Choudhuri [38], the approach to identify altered gene expression in the immediate aftermath of CSD was performed by DNA arrays and RT-PCR analysis in the mouse brain. They found, of the over 1180 genes examined, that only a small number were consistently regulated by CSD, clustered in functional groups: vasoactive peptides (Atrial natriuretic peptide was induced by CSD, while the vasoconstrictor neuropeptide Y was downregulated), genes involved in responses to oxidative stress (major prion protein precursor, PRP, glutathione-S-transferase-5, GST-5, and apo E) and the L-type calcium-channel. In summary, genes that are intrinsic to its propagation, that identify accompanying vascular responses as a potential source of pain, and that protect against its potential pathological consequences.

Bolay et al., in 2002, demonstrated that CSD is able to activate the ipsilateral trigeminal nerve system as demonstrated by c-fos expression in the trigeminal nucleus caudalis and meningeal plasma protein extravasation. In addition, delayed meningeal blood flow increase is mediated by a trigeminal-parasympathetic brain stem connection. This way, intrinsic brain events are able to activate extracerebral meningeal nociceptors [39]. This data point to CSD as a critical event in the mechanism of migraine with aura, and support the notion of CSD as a therapeutic target in this disorder [40], as shown by studies using a CSD inhibitor (Tonaberstat: SB-220453) in some clinical trials of migraine [34]; as well as topiramate, which also inhibits CSD in cats and rats, and it is a useful agent for the

treatment of epilepsy; although, in despite of its use for the treatment of BD, it has not fulfilled the expectations for the treatment of this psychiatric disorder.

All or some of this peripheral pathology stimulates trigeminal sensory afferents, which in turn, transduce this nociceptive information centrally. This arc is referred to as the trigeminovascular system (TGVS). The TGVS consists of the meningeal and superficial cortical blood vessels that are innervated by the trigeminal nerve, which projects into the trigeminal nucleus caudalis in the brainstem, which in turn, projects into higher-order pain centers. Evidence in animals (not yet in humans) suggests that CSD might activate the TGVS, potentially linking the mechanism for aura and headache. Indeed, an interesting current hypothesis includes CSD not only as the primary cause of aura, but as the factor that could initiate the headache per se [41]. This hypothesis is based on the models related to Ca^{++} channels and their expression in the cerebral cortex, trigeminal ganglia, periaqueductal gray, and brainstem nuclei, all regions related involved in nociception.

An important component of migraine pathophysiology is sensitisation. It has been shown that almost 60% of migraine patients complain of allodyinia [42], defined as the perception of pain arising from non-noxious stimuli, in the upper limbs, that are ipsilateral and contralateral to the pain in migraine. This finding is consistent with a third-order neuronal sensitisation, or central sensitisation, or a form of disinhibitory sensitisation, with dysfunction of descending modulatory pathways [34] in migraine pathophysiology.

Neurotransmission in migraine

The introduction of the several tryptan compounds for headache and migraine treatment, acting at 5-hydroxytriptamine (5-HT) receptors, made these serotonin receptors the ideal candidate genes in the pathogenesis of migraine. However, linkage studies of the 5-HT2A, 5-HT2C, 5-HT1D, and 5-HT1B have been uniformly negative [43-45] , as well as studies related to the genes governing the metabolic enzymes in the serotonergic pathway (human tryptophan hydroxylase, amino acid decarboxylase, and monoamine oxidase A) [46] . Nevertheless, it is important to conceptualize that serotonine dysregulation may be present in migraine at a later stage of the disorder, as shown by studies involving 5-HT receptors and the antinociceptive efficacy of non-narcotic analgesics [47]; furthermore, negative genetic studies of the aforementioned candidate loci are not necessarily an argument against the implications of serotonergic mechanisms in migraine.

Nitric oxide (NO) is proposed to be an important mediator in the development of migraine headaches. Administration of nitroglycerin, the donor of NO, causes headache in nonheadache control patients and more pronounced headache in patients with migraine. It is known that an increase of intracellular calcium, secondary to 5-HT_{2A} receptor activation, leads to an increase in nitric oxide synthase (NOS) expression in various structures in the trigeminovascular pathway, an effect that resembles that observed after NTG infusion [48].

It has been also shown that monoamine depleters (e.g., reserpine) can further aggravate headaches among migraine sufferers; and the evidence from SSRI treatment for migraine is not encouraging either [49].

Dopaminergic transmission has also been a candidate implicated in the pathophysiology of migraine, starting with the notion of dopaminergic hypersensitivity underlying some symptoms during attacks, in particular, nausea and vomiting; and extending to the hypothesis that MA and MO do not share common pathophysiologic mechanisms [50]. Moreover, there have been reports regarding the use of antipsychotic medications (olanzapine) in the treatment of refractory migraine [51], with the underlying hypothesis that, aside of a serotonergic dysfunction among migraine sufferers, they may also have an

overly functioning dopaminergic system. Nevertheless, association studies have been showing conflicting results for dopamine receptors and their implications in migraine [32, 52].

Other peptides involved in migraine include:

a) **Calcitonin gene-related peptide (CGRP):** an important modulator of the TGVS released during acute migraine attacks. Specifically, there is a marked increase in the external jugular vein, but no change in peripheral blood during the migraine attack and return to its baseline after pain cessation [53]. Moreover, both migraine with aura and without aura result in substantial increases in venous CGRP levels at the same time as the patients exhibit pain [54]. Experimental CGRP receptor antagonists are being currently studied for migraine treatment in its acute phase [55, 56].

b) **Substance P (SP):** SP is an undecapeptide which belongs to the group of neurokinin peptides, and exerts its effect through the action of G-coupled receptors (neurokinin receptors, NK). SP is the most abundant neurokinin and it has been involved in the regulation of many physiological systems, as well as in the pathophyisiology of pain, including migraine, fibromyalgia, and asthma, among others [57]. The basic perception behind the development of neurogenic models for migraine is that migraine is due to a sterile neurogenic inflammation within the meninges, followed by the activation of trigeminal nerve terminals to release neuropeptides, such as substance P and CGRP [58]. However, different studies have reported that there are no changes in substance P concentration in the jugular vein or in the peripheral blood during a migraine attack [54], probably due to its lower level within the trigeminovascular system, compared to that of CGRP. So, although the role of SP in nociceptive signal transmission has been well characterized, NK1 receptor antagonists have shown little effect in the treatment of migraine [57, 58].

c) **Vasointestinal polypeptide (VIP):** VIP is a neurotransmitter in cerebral parasympathetic perivascular nerve fibres and cranial parasympathetic ganglia. Elevated VIP levels in the cranial circulation have been reported in a subgroup of migraine sufferers with pronounced autonomic symptoms [59], although some

studies have not found such an elevation in migraine sufferers without this particular characteristic [54]; moreover, other studies have shown that VIP does not trigger migraine attacks in patients with migraine [60], although it markedly increases intra- and extracranial arteries.

d) **Cytokines**: Adypocite-secreted cytokines, also known as adipocytokines, include adiponectin, resistin and leptin. They have an effect on central metabolic functions, inflammation and platelet aggregation; and it has been proposed that obesity could be seen as a proinflammatory and prothrombotic state [61]. Due to the finding that BMI is associated with the frequency of headache attacks (although not with the prevalence of migraine), some authors have proposed that obesity could be a risk factor for migraine [62].

e) **Orexines**: The orexinergic system has been implicated in a variety of functions, including feeding, sleep wake cycle, cardiovascular and endocrine functions. Their possible role in migraine has been recently acknowledged, in an animal model of trigeminovascular pain, showing that activation of OX_1R elicits an antinociceptive effect, whereas OX_2R activation elicits a pronociceptive effect [63].

Migraine Genetics

Considering the high prevalence of the disorder, a single gene is not likely to cause MA or MO, and in fact, migraine is now viewed as a polygenic multifactorial disease, having both environmental and genetic causative factors.

Genetic epidemiological studies of migraine show increased disease risk in relatives of migraine probands: compared to the general population, first-degree relatives of probands with MO have 1.9 times the risk of MO and 1.4 times the risk of MA; whereas first-degree relatives of MA probands have 3.8-fold increased risk for MA and no increased risk of MO [64], indicating that MA and MO are distinct disorders. Furthermore, the pairwise concordance rate has been shown to be significantly higher among MZ than DZ twin pairs (28% vs. 18% for MO and 34% vs 12% for MA) [65].

In 1996, it was recognized that familial hemiplegic migraine (FHM) was caused by mutations in the calcium channel gene CACNL1A4, located in chromosome 19p13 [66],

leading to an increase in Ca^{++} influx through CaV2.1 channels, and, as a result, an increase in glutamatergic neurotransmission. Altogether 15 different CACNA1A mutations resulting in FHM1 have been described so far; in addition, different types of CACNA1A mutations have been shown to cause episodic ataxia type 2 and spinocerebellar ataxia type 6 [67].

In 2003, the second gene responsible for FHM2 was discovered in chromosome 1q23 [68], affecting the α2 subunit of the Na/K pump gene, resulting in loss of its function, which could result in a reduced uptake of ions and neurotransmitters from the synaptic cleft, and, thus, an increased susceptibility for CSD. More recently, it was found that FHM3 mutations in the SCN1A gene, in chromosome 2q24, cause a more rapid recovery from fast inactivation of neuronal Nav1.1 sodium channels after depolarization, causing an increase in the frequency of neuronal firing and enhanced neurotransmitter release [69, 70]. Moreover, recent studies suggest that the presence of FHM in families without mutations or linkage to CACNA1A, ATP1A2, and SCN1A could account for the presence of a fourth gene [69] in FHM.

The unravelling of the genetics of FHM has led to the proposition that some of the genes involved in FHM might also be involved in the pathogenesis of the more common forms of migraine; however, this initial assumption has not been confirmed by recent studies, because, in contrast to FHM, the common forms of migraine are genetically complex disorders. Nevertheless, the striking advances made by molecular genetic studies of the periodic paralyses and episodic ataxias, amplified the concept of migraine as a channelopathy, representing migraine as a disease of neural excitability with a genetically-determined lowered threshold for the triggering of the attacks, a concept which may explain the comorbidity of migraine with epilepsy [32].

New loci for the common forms of migraine were reported on chromosomes 4q24, 5q21, 6p12.2-21.1 (MA and MO), 11q24 (MA), 14q21.1-q22.3 (MO), 18p11, 19p13 and Xq24-28 [67,71-73]. Some of these positive linkage findings have been confirmed in independent samples, but for all these loci no causative gene alterations have been identified.

In addition, some groups have proposed that the invidual components of migraine, i.e., traits, might independently contribute to its susceptibility. Conducting thus a trait-component analysis, Anttila and colleagues [74] identified several traits that showed linkage

to the previously reported MA locus on chromosome 4q24 (photophobia, phonophobia, and intensity); and identified one novel locus on 17p13, with significant evidence of linkage to the pulsation trait, as well as two another loci with suggestive evidence of linkage to IHS full criteria (18q12). Their findings support the hypothesis that specific gene variants in different loci contribute in different combinations to the individual susceptibility.

Because migraine with aura and migraine stroke are recognized features of the MELAS (Mitochondrial Encephalomyopathy, Lactic acidosis and Stroke-Like) syndrome, some authors have proposed migraine as a disorder of mitochondrial function, speculating that maternal DNA (mtDNA) mutations could contribute to the pathogenesis of migraine [32]. However, the degree of heteroplasmy, as well as methodological factors, have made difficult the study of mtDNA; leaving thus place for larger studies to achieve a conclusion in this issue.

Brain imaging abnormalities in migraine

Brain imaging studies in patients with migraine have demonstrated the presence of permanent interictal changes in brain areas involved with trigeminal pain processing, including ascending (trigeminocortical tract) and descending (periaqueductal gray, PAG) sensory pathways [75]. Moreover, brain imaging studies show the presence of changes during a migraine attack: in studies during migraine without aura, functional brain imaging with positron emission tomography (PET) has shown activation of the dorsal midbrain, including the PAG and the dorsal pons close to the nucleus coeruleus; and dorsolateral pontine activation is seen with PET in episodic and chronic migraine [34].

The rostral brainstem has been also implicated in the pathophysiology of migraine, and as shown in a recent PET study with patients suffering from chronic migraine, there were increased cerebral metabolism in areas of the brainstem compared to the global flow, as well as decreased areas of cerebral metabolism in the frontal and parietal cortex [76]. Diffusion tensor (DTI) magnetic resonance imaging has also reported the presence of

subtle grey matter damage in migraine patients [77], although further studies are needed to confirm these findings.

Among other putative mechanistic overlap between BD and migraine are vascular causes. It has been reported that migraine is associated with a higher prevalence of infarcts in the posterior circulation territory of the cerebellum; and that female patients with migraine have a higher risk for deep white matter lesions, when compared with controls, and this risk increased with the attack frequency [78]. Several hemodynamic features of migraine may contribute to the pathogenesis of both white matter lesions and infarcts in migraine, including repeated or prolonged reduced perfusion pressure, vasoconstriction, and activation of the coagulation cascade, that could be mediated or induced by endothelial perturbation [79, 80]. However, it is very difficult to distinguish between the vascular phenomena related to migraine and the observed behavioural and mood consequences of vascular events, mainly in elderly patients. Functional imaging studies in patients with cluster headache have demonstrated significant activations during acute attack in the hypothalamic gray matter, ipsilateral to the side of the headache [81] , although similar findings cannot be accounted for migraine. Cluster headache is a strictly one-sided syndrome with a relapsing-remitting course, seasonal variation and clock-like regularity. The activation of the hypothalamus is specific to the disease and explains the profoundly periodic features of the syndrome, and a recent study has shown that there is a correlation between structural and functional changes in the inferior posterior hypothalamus [82] . However, even if patients with migraine also present a fluctuating course and seasonal variation at some degree, these are different types of headache. Nonetheless, gaining access to the brain imaging abnormalities reported in cluster headache may offer some insight into the brain imaging abnormalities that may be shared by BD and migraine patients [83, 84].

CHAPTER 3: BIPOLAR DISORDER

Introduction

Bipolar Disorder (BD) is a mood disorder characterized by manic and depressive episodes, with a fluctuating course and substantial relapse rates. Traditionally, BD has been subdivided mainly in two subtypes: BD type 1 and type 2. BD 1 is characterized by the alternating episodes of depression and mania; while the second one is characterized by depressive episodes alternated with hypomanic episodes. Estimates of BD 1 prevalence have ranged from 2% (12-month) and 3.3% (lifetime prevalence) of the population [85]; whereas for BD 2 (regarded as a disorder with depressive periods that alternate with hypomanic episodes) the lifetime prevalence rate has been about 0.5% [86].

Epidemiologic and clinical data indicate that there is a substantial rate of psychiatric co-morbidity with BD, such as anxiety disorders, personality disorders, and substance use; and that Axis I or II co-morbidity has been associated with an increased severity and a poorer outcome of the disorder [15, 85, 87], aside from the medical conditions that are found increasingly associated with the disorder, such as cardiovascular disorders and metabolic abnormalities.

A considerable number of studies support abnormalities in the regulation of cellular plasticity cascades as integral to the underlying neurobiology of BD, as well as neuroanatomical and neurochemical abnormalities, that arise within the milieu provided by a genetic predisposition for the disorder. The phenotypic expression of the disorder includes not only mood disturbances, but also a constellation of cognitive, motor, autonomic, and endocrine abnormalities.

With respect to the study of mood disorders, the monoaminergic neurotransmitter systems have received the greatest attention in neurobiological studies, due to the fact that these systems are extensively distributed throughout the network of limbic, striatal and prefrontal cortical neuronal circuits [88]. Indeed, pharmacological evidence is also consistent with the presence of neurotransmitter disturbances in the central nervous system function in BD, in the serotonergic, dopaminergic and glutamatergic systems [89-91].

Nevertheless, the neurotransmission hypothesis in BD have not greatly advanced our understanding of the neurobiology of the disorder, and new assumptions have been held that can be fit into a more cohesive bioenergetic and neurochemical model [92] that involves mitochondrial dysfunction, among others.

Consequently, some of the most recent advances regarding the neurobiology of the disorder will be discussed in the next section.

Biological correlates in Bipolar Disorder

a) Structural neuroimaging findings

For BD, magnetic resonance (MR) studies have reported several changes, such as: decreased cortical and laminar thickness in the dorsolateral prefrontal cortex (without changes in the overall neuronal density); enlarged locus coeruleus, larger thalamic volumes, greater grey/white ratios, increased gyral complexity and enlarged amygdala [93]. Due to the potential confound effect that mood stabilizers exert on neuronal plasticity, significant volumetric differences have not been consistently reported in the hippocampus [94].

MR techniques have also consistently identified periventricular and deep hyperintensities in the subcortical white matter (white matter hyperintensities, WMH) of BD patients, particularly in the frontal lobes [94], and appear to be associated with poor treatment response [95]. Also, brain imaging using DTI has also reported the presence of microstructural changes in the white matter of the orbital frontal areas [83].

These results support the contention that patients with BD have an impairment of cellular resilience, leading to hypoxic-like changes, even in the face of normal cerebrovascular flow.

b) Magnetic Resonance Spectroscopy (MRS)

High-resolution 1H-MRS imaging studies have found decreased levels of N-acethyl-aspartate (NAA), a neurochemical compound that is localized to mature neurons and is used as a marker of neuronal integrity, in BD, specifically in hippocampus, dorsolateral prefrontal cortex, orbitofrontal cortex, and basal ganglia [94].

Studies that used phosphorus-31 (^{31}P MRS) showed a decrease in phosphocreatinine and ATP levels in mood disorder patients, as well as low pH levels in the whole brain of BD patients, observations that led to the hypothesis of mitochondrial dysfunction in BD and an altered cellular metabolism [96].

c) Post-mortem brain findings

In addition to the previous results from imaging studies, the analysis of post-mortem tissue from BD patients has revealed several abnormalities, such as reduced cortical thickness in layers III, V, and VI in subgenual anterior cingulate cortex, reduced volume of subgenual prefrontal cortex, and of nucleus accumbens and basal ganglia [94, 97]. A reduced neuronal size or density has as well been reported in the dorsolateral prefrontal cortex and in the subgenual anterior cingulate cortex; and a reduced glia has been as well reported in the dorsolateral prefrontal cortex [93, 94].

d) Signal transduction

As a result of lithium's proposed mechanism of action on second-messenger systems and on the expression of a number of genes, several studies regarding signal transduction in BD have been conducted. Among them, some are particularly relevant:

1. **cAMP responsive element binding protein (CREB):** A transcription factor that increases the expression of key growth factors involved in synaptogenesis and neurogenesis, has been proposed as a target in the study of BD, due to its role in gene expression. The study from Mamdani [98] reported an association between lithium response and CREB1-1H SNP (G/A change) and the CREB1-7H SNP (T/C change).
2. **X-box binding protein 1 (XBP-1):** The transcription factor X-box binding protein (XBP-1) was first identified by its ability to bind to the x-box, a conserved transcriptional element in the human leukocyte antigen (HLA) DR alpha promoter. XBP-1 is upregulated as part of the endoplasmic reticulum (ER) stress response. It has been found recently that the 116C→G polymorphism causes an impairment of the ER stress response and increases the risk of BD [99]; while there have been reports regarding the association between the -116C/G SNP pf the XBP1 gene and lithium prophylaxis in BD [100].

3. **Inositol polyphosphate-1-phosphatase (INNP1):** INPP1 encodes the enzyme inositol polyphosphate-1-phosphatase, one of the enzymes involved in phosphatidylinositol signalling pathways, which has been studied with respect to the therapeutic action of lithium. In fact, the study from Steen [101] in a Norwegian sample showed that 67% of lithium responders showed the C937A polymorphism, compared with 11% of non-responders, although some other studies have not replicated these findings [102].
4. **Brain Derived Neurotrophic Factor (BDNF):** BDNF is a neurotrophic factor that is implicated in neuronal proliferation and synaptic plasticity. Conflicting results regarding an association between BD and BDNF have been reported [103, 104], although in other studies rapid cycling has been associated with Val66met polymorphism of BDNF [105].
5. **Phospholipase γ-1(PLCγ-1)**: Lithium is thought to stabilize mood by acting at the phosphoinositide cycle, and the γ-1 isozyme of phospholipase C plays an important role in the phosphoinositide second messenger system. Therefore, polymorphisms in the PLCγ-1 gene have been investigated in lithium responders. The study from Turecki [106] involved over 130 patients, and found an association between lithium response and the PLC γ-1/5 polymorphism; his findings have as well been replicated by other groups [107], however, other studies have failed to replicate the initial findings [108].
6. **Inositol monophosphatase (IMPA):** The activity of IMPA, the target enzyme of lithium in the phosphatidilinositol (PI) signal transduction system, has been another candidate for the study of BD, and studies have shown a lower activity of IMPA in cells lines from lithium-responsive patients [109]. Two genes coding for IMPA, *IMPA1* and *IMPA2*, have been identified; the first is localized to chromosome 8q21.13-21.3 [110]; and the second in the chromosomal region 18p11.2. Whereas no linkage or association studies so far have provided evidence for a role of IMPA1 in BD, there have been many reports suggesting the role of 18p11.2 as a susceptibility locus for the disorder [111-114].

Genetics of Bipolar Disorder

Methodological improvements have been the consequence of the increased awareness of uncertainties and complexities in the analysis of complex psychiatric disorders. However, conflicting results are still the dominant figure in this sense. Some of the most used techniques are linkage studies and association studies. Linkage studies use a "reverse-genetics" strategy; they are mainly concerned with the testing of anonymous DNA markers (generally in the context of a genome-wide scan) for co-segregation with the disease in families. "Significant" or "suggestive" (under parametric analysis, it corresponds to LOD scores of 3.3 and 1.9, respectively) evidence of linkage has been reported in several chromosomal regions: 1q31-32, 4p16, 6pter-p24, 10p14, 10q25-26, 12q23-24, 13q31-32, 18p11, 18q21-23, 21q22, 22q11-13, and Xq24-28 [115, 116]. Conversely, association studies involve candidate genes, dynamic mutations, mitochondrial mutations, and chromosomal aberrations. The candidate genes strategy employs "forward-genetics": testing gene markers with presumed functional relevance for the disease. These studies examine the co-occurrence of a marker and disease using either a case-control design or a family-based design. Most association studies have involved genes implicated in serotonergic, dopaminergic, and noradrenergic systems, and it follows a concise review of the findings regarding areas throughout the genome that have been implicated in BD.

a) Serotonin-related genes: One of the most widely investigated genes in BD is the serotonin transporter (SLC6A4), located in 17q11.1-q.12; positive results have been obtained with respect to a 48 bp promoter polymorphism (SERTPR), and four meta-analyses confirmed the finding. Another candidate gene that has been constantly associated with BD is neuronal tryptophan hydroxylase (TPH2), which codes for the rate-limiting enzyme in the biosynthesis of serotonin in the central nervous system; and, although this gene is not located in a region found in positive linkage with BD, single-nucleotide polymorphisms (SNPs) within the gene have been associated with BD in five independent studies. HTR1A, HTR2A and HTR2C seem to be promising candidates as well[117].

b) Dopaminergic genes: Studies support the involvement of DRD4 and in the dopamine transporter gene (SLC6A3) in BD. DRD4 is located in a region found in positive linkage with BD: 11p15.5; and some polymorphisms in the SLC6A3, have as well been associated with BD [117].

c) γ amino butyric acid (GABA) genes: Although GABAergic genes have not provided strong evidence in BD, GABRA1 and GABRA5 can be considered promising genes [117].

d) Glutamate-related genes [117]

   a. D-amino acid oxidase activator (DAOA) is located in a region in positive linkage with BD (13q33.2), and it plays a role in the activation of N-methyl-D-aspartate (NMDA) receptors, implicated in the pathophysiology of both BD and schizophrenia. A number of SNPs within this gene have been associated with BD in six independent studies.

   b. N-methyl-D-aspartate 2B (GRIN2B) encodes for a NMDA receptor, and it is involved in long-term potentiation and in activity-dependent increase in the efficiency of synaptic transmission. In BD, two studies have reported positive findings, particularly in association with psychotic symptoms.

   c. Dystrobrevin-binding protein 1 (DTNBP1): a gene expressed in neuronal populations in the hippocampus, located in presynaptic axon terminals of the glutamatergic neurons. Five independent studies have confirmed the association of SNPs within DTNBP1 and BD.

e) Other amines' metabolism-related genes [117]

   a. Monoamine oxidase A (MAOA) is located in the region Xp11.3, and it has been widely investigated for over two decades. Three independent studies have confirmed the association between CA repeat microsatellite in intron 2 and BD.

   b. Catechol-O-methyltransferase (COMT): the results obtained by the study of this gene have been controversial.

f) Signal transduction related-genes [117]

   a. Inositol monophosphatase (IMPA-2): Located in 18p11.12, a region associated with BD, has been an interesting candidate due to the crucial

role of myoinositol in the phosphatidilinositol signalling pathway, a pathway that is thought could be modified by lithium. Two studies have found a positive involvement of SNPs -416 C > T and -207 T > C in BD.

b. Phospholipase C γ 1 isoform A (PLCG1): It encodes an enzyme that mediates the production of second messenger molecules. Two studies have studied an intronic dinucleotide repeat polymorphism, and have found positive associations in lithium responders.

c. Transient receptor potential cation channel (TRPM2): located in region 21q22, its activity is related to the regulation of calcium influx into the cells. However, the results obtained regarding to an association with BD have been controversial.

d. Synaptobrevin-like 1 (SYBL1): located in region Xq28. Synaptobrevin is an intrinsic membrane protein of small synaptic vesicles, with a role in neurotransmitter release and vesicle recycling. An SNP G → C in intron 5 was reported associated with BD in two independent studies.

g) Cell growth-related genes [117]

a. Glycogen synthase kinase 3-β gene (GSK3β): Involved in energy metabolism and neuronal cell development. Recent reports have involved the presence of duplication in copy number variations in BD, probably affecting 3'-coding elements.

b. Brain derived neurotrophic factor (BDNF): Located in 11p13, BDNF is a gene that seems to be constantly associated with BD, particularly a G > A SNP, which has been associated with BD in nine independent studies. However, six other independent studies have failed to replicate the association.

c. Neuroregulin 1 gene (NRG1): A gene that is expressed predominantly in embryogenesis, and whose product promotes the proliferation and survival of the oligodendrocyte and the myelinating cell of the central nervous system. Three different studies have found an association between BD and a number of SNPs within NRG1.

d. DISC1 gene (Disrupted in schizophrenia 1): located in 1q42.1, encodes a protein that interacts with a variety of cytoeskeletal proteins, some of them associated with cortical development. Four independent studies have associated a number of SNPs within the gene with BD.
e. Cell adhesion molecule, neural 1 (NCAM1): It encodes a protein related to brain development, and as well with cell signalling and neuroplasticity in the adult brain. Two independent studies have reported an association between polymorphisms within the gene and BD.

h) Circadian rhythm-related genes [117]
   a. Period homolog 3 (PER3): located in 1p36.33, a region linked with BD, is involved in the regulation of circadian rhythms. Two different studies reported positive findings in association with BD.
   b. Aryl hydrocarbon receptor nuclear translocator-like (ARNTL): It encodes a protein (Arntl) that dimerizes with the circadian locomotor output cycles kaput (CLOCK) protein. Two studies have reported a positive association with SNPs within the gene and BD.

The genome-wide association (GWA) studies represent an important step beyond both candidate gene studies and linkage studies, although they also have important limitations, such as their potential for false-positive and false-negative results. GWA studies rely on the "common disease, common variant" hypothesis, which suggests that genetic influences on many common diseases will be at least partially attributable to a limited number of allelic variants present in more than 1% to 5% of the population [118].

Recently, a GWA study in which over 550 000 SNPs were genotyped in 1233 BD 1 patients and 1439 matched controls, reported 88 SNPs near 80 distinct genes that met replication criteria in both samples. In this study, the most significant result was observed for the diacylglycerol kinase eta (DGKH) SNP, rs 1012053 ($p = 1.5 \times 10^{-8}$, OR = 1.59 in combined samples) [119].

The study from the Wellcome Trust Case Control Consortium [120] individually genotyped 1838 BD cases and 2938 controls, and reported 14 SNPs associated with BD at $p < 10^{-5}$.

The strongest signal was with rs420259 at chromosome 16p12, and the best fitting model was recessive. However, this signal was not additionally supported by the expanded reference group analysis.

A meta-analysis of the previously mentioned GWA revealed that the SNPs that showed consistency across both studies at the allelic level lied closest to genes with known roles in synaptic transmission (the Zn^{2+} transporter ZIP3, SLC39A3) and cell-cell adhesion in the brail (junctional adhesion molecule 3, JAM3) [121]. The meta-analysis also identified strongly associated SNPs near the gene DFNB31, and thus reveals several points of agreement between the two GWAS.

Other approaches to study the genetics of BD include the identification of phenotypic subtypes of BD, as performed in the study from Cheng [122] : psychosis, suicidal behaviour and panic disorder were simultaneously analyzed in a genome-wide linkage scan. Their results, using linkage signals and standard diagnostic models, showed that regions 10q25, 10p12, 16q24, 16p13, and 16p12 provided the strongest signals; and regions 6q25, 7q21, and 16p12, using phenotypic subtyping, showed association with suicidal behaviour, panic disorder and psychosis, respectively. As well, the genome-wide linkage study from Zandi and colleagues [123], that involved 98 BD pedigrees as the primary sample, and 64 pedigrees as the independent sample, used the clinical variables of age at onset (AAO), psychotic symptoms and co-morbidity with anxiety disorders to identify susceptibility loci for BD. Although there were no genome-wide significant loci found in the analyses, their results showed that for the variable AAO an association was identified on 3q28 for AAO, 11p11 with psychosis, 17q25 with co-morbid anxiety disorders.

The prospects of imminent gene discovery, thus, become complex in light of several factors, including small sample size with limited power, large linkage intervals, absence of a full complement of potential candidate genes and polymorphisms, as well as analytical tools with methodological deficiencies [115].

CHAPTER 4: MIGRAINE AND BIPOLAR DISORDER

Migraine and mood disorders

Migraine is a highly prevalent disorder: for adult population, the estimates of migraine prevalence range from 3.3% to 21.9% for women, and from 0.7% to 16.1% for men [124-126]. It is also a disease with elevated direct and indirect costs, the later mostly derived from its association with mood and anxiety disorders, co-morbidities that exert an even greater economic impact.

As a matter of fact, an association between migraine and affective disorders has been widely addressed [10]. In the 90's decade, Merikangas [7, 9, 127] reported an elevated one-year prevalence rates for a wide range of psychiatric disorders in people with migraine, compared with subjects without the disorder, and reported odds ratios (OR) of 2.2 (95% CI 1.1-4.8) for major depressive disorder (MDD), 2.9 (95% CI 1.1-8.6) for bipolar spectrum disorders (BD), 5.3 (95% CI 1.8-15.8) for generalized anxiety disorder (GAD), and 3.3 (95% CI 0.8-13.8) for panic disorder. Breslau, in 1991, [128] found that lifetime prevalence rates of dysthymia, MDD, BD, GAD and phobia were also significantly elevated in patients with migraine, compared with those without migraine. The results from these studies gave notion to the concept that migraine was strongly associated with anxiety and affective disorders, ruling out major sources of artifactual associations.

The initial research has been followed by studies regarding other interesting features of the association, such as the presence of a linear trend association between the frequency of migraine attacks and the OR for depression [1]; an increased suicide risk in patients with migraine (even when depression is controlled for) [6, 129]; as well as the existence of a bidirectional chronology between migraine and depression [130].

It is important to mention that the study of pain and affective disorders brought the concept of limbically augmented pain disorders, set forward by Rome and Rome [131], defined as the process through which limbic activation may lead to the progression of chronic pain and affective disorders overtime. Other authors [132] have applied this concept

to headache disorders, suggesting that neuroplastic phenomena could be implicated in this intertwined relationship in susceptible individuals.

Migraine and Bipolar Disorder

The reported prevalence of migraine in the BD population varies from 24.8% to 39.8% in different studies, being also higher in females [12, 133, 134], rates that are considerable higher than those found in the general population.

Furthermore, a variety of studies discuss the presence of clinical differences among BD patients with and without migraine. In the study from Low [133], BD patients with migraine had fewer hospitalizations when compared to patients without it (2.7 vs 4.4) and an initial presentation of antidepressant-associated switch into mania was more common in the migraine group (14%), compared to those without migraine (1.5%). A study from Mahmood [134] also showed that BD patients who suffered from migraine tended to have an earlier onset of BD, and to have a poorer psychosocial functioning, compared to those patients without migraine.

Consonant with these findings, in 2006, McIntyre and colleagues [12] studied the prevalence of migraine in BD, and their data were derived from respondents (n=36984) to the Canadian Community Health Survey (CCHS). Respondents reporting a lifetime WHO-CIDI defined manic episode and physician-diagnosed migraine (lifetime also) were compared to respondents without migraine. Their results also showed that there is a higher prevalence of migraine among people with BD (24.8%: 14.9% for males and 34.7% for females); and that BD male patients with migraine were significantly more likely to report an earlier average age of onset of BD, as well as a lifetime co-morbid anxiety disorder and to be receiving a higher number of medications.

Particularly regarding the subtype of BD, studies have shown that the prevalence of migraine was the highest among patients with BD 2 (up to 77%), significantly different from the prevalence among BD 1 (14%) and from unipolar disorder (46%) [133-135].

Important clinical differences between unipolar depressed patients with and without comorbid migraine have been found [136], showing that the clinical features of unipolar depressed patients with comorbid migraine resemble those from BD 2 patients. This

study reports that unipolar patients with migraine, when compared to those without it, had a higher total number of depressive episodes (4.5 vs 2.5), had significantly more often an affective temperament (46% vs. 16%), irritability (70% vs. 45%) and seasonal variation of depressions (22% vs. 3%). The characteristics of BD 2 patients with migraine resemble those found in the unipolar patients with migraine, concerning both number of depressive episodes (4.9), affective temperament (49%), irritability (77%) and seasonality (33%), whereas the BD I patients seem to have more depressive episodes (6.6), affective temperaments (58%), and less irritability (56%).

A previous study from the same author has also shown that BD patients with migraine have an increased number of anxiety disorders, particularly panic disorders and agoraphobia [137].

RATIONALE

Given these lines of evidence, we hypothesized that migraine diagnosis will show a higher prevalence between patients with Bipolar Disorder (BD), particularly type 2, and that there will be differences in terms of the clinical picture of the disorder between BD patients with and without migraine.

Furthermore, in order to analyze the cross-prevalence of migraine and Bipolar Disorder, we designed a second separate study, devoted to the analysis of the psychiatric co-morbidity in a sample of migraine patients.

CHAPTER 5:
STUDY 1: MIGRAINE COMORBIDITY IN BIPOLAR DISORDER

Methods

The sample is composed of two populations: the Maritime Bipolar Registry (MBR), and the Bipolar Disorder Database from the McGill University Health Center (MUHC).

The MBR (n=390) is a community-based project in the Maritime Provinces of Canada [138]. It includes 228 subjects with BD 1 and 99 subjects with BD 2 diagnoses. The rest of the sample is composed of patients with the following diagnosis: Not otherwise specified disorder (NOS), schizoaffective disorder and deferred diagnosis. Patients are informed about the possibility to participate through their treating clinicians, typically family doctors or community psychiatrists. Patients who had given consent to participate in the project were interviewed by an experienced research nurse, a psychiatrist or clinical research fellow. The diagnostic interviews are performed by pairs of clinicians, and diagnostic information is then reviewed in blind fashion in consensus meetings of the research team. The diagnostic interviews follow the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) format [139]. The diagnoses are based on both Research Diagnostic Criteria [140] and DSM-IV criteria. Medical comorbidity was ascertained based on previous diagnosis and treatment for each selected medical condition. All subjects were assessed during their stabilization treatment, not during an acute episode of the illness. The diagnosis of migraine follows the guidelines of the International Headache Society (HIS) [141] and was corroborated by a standard questionnaire (ID-Migraine) [142], with a sensitivity of 0.81 (95% CI, 0.77, 0.85) and a specificity of 0.75 (95% CI, 0.64, 0.84), relative to an IHS-based migraine diagnosis assigned by a headache specialist. This questionnaire was mailed to the participants and we obtained a response close to 60% (n= 214).

The MUHC group comprises 109 patients with a diagnosis of BD 1 (n= 78) and BD 2 (n= 31). The patients were interviewed by an experienced clinician, using the Structured

Clinical Interview for DSM-IV disorders (SCID) [143] as the screening instrument and diagnosed according to the DSM-IV criteria. For this group, the diagnosis of migraine was made according to the International Headache Society criteria – I [144].

The groups were compared using two methods: a parametric analysis (chi-square analysis), and log-linear modeling, by the BMDP Statistical Software (BMDP Statistical Software, Inc. 8.1).

Results

Descriptive characteristics of the sample

The MBR sample size included 214 BD patients, with a mean age of 47.3 ± 10.7 years, with a female preponderance: 140 (65.4%) females, versus 74 (34.6%) males. 53 (24.8%) patients had comorbid migraine; and 161 (75.2%) did not. Regarding the diagnostic subtype, 126 (58.9%) had a BD 1 diagnosis and 61 (28.5%) a BD 2 diagnosis. The mean (SD) Body Mass Index (BMI) was 30.6(6.9).

The MUHC database included 109 patients, with a mean age of 46.3 ± 13.4 years, with a slight female preponderance: 59 (54.1%), versus 50 (45.9%). 26 subjects (23.9%) had comorbid migraine, whereas 83 (76.1%) did not. For the diagnostic subtype, 78 (71.6%) had a BD 1, and 31 (28.4%) had BD 2 diagnosis. The mean BMI was 26.5 ± 4.0.

Total sample characteristics

The total sample size was 323 BD patients. Of them, 124 (38.4%) were males, and 199 (61.6%) females, with a mean age of 46.4 ± 12.3 (95% CI: 45.1, 47.8), and a mean BMI of 29.1 ± 6.2 (95% CI: 28.3, 29.9). 79 (24.5%) patients had comorbid migraine, while 244 (75.5%) did not. 204 (63.1%) were BD 1 patients, whereas 92 (28.5%) had a BD 2 diagnosis, and 27 (8.2%) had other diagnoses. Regarding statistical differences between both samples, the only difference was that the MBR sample showed a higher BMI, when compared to the MUHC sample ($t=2.85$, $p<0.01$). The rest of the variables did not differ between sites.

Parametric analysis

Table 1 depicts the results from patients with and without migraine, regarding demographic characteristics and clinical characteristics. A χ^2 performed on the data showed that migraine status is significantly associated with suicidal behaviour [χ^2 (1) = 4.51, $p < 0.05$], diagnostic subtype [χ^2 (1) = 8.53, $p < 0.005$], body mass index (BMI) [Kruskal-Wallis statistic = 4.5, $p<0.05$], social phobia [χ^2 (1) = 17.33, $p < 0.005$], panic disorder [χ^2 (1) = 24.79, $p < 0.005$], obsessive-compulsive disorder [χ^2 (1) = 3.78, p =

0.05], and generalized anxiety disorder (GAD) [χ^2 (1) = 6.64, p < 0.01]. The rest of the variables did not show statistical significance (p>0.05).

1. Suicidal behaviour

A higher proportion of BD subjects with migraine showed a history of suicidal behaviour (39.7%), compared to those without migraine (27.0%), being this difference statistically significant: χ^2 (1) = 4.51, p < 0.05.

2. Diagnostic subtype

Overall, 63.1% (n=204) of the sample was diagnosed as BD 1, and 28.5% (n=92) as BD 2. Among BD 1 patients, 19.1% showed comorbid migraine, whereas in the BD 2 subgroup, 34.8% patients had comorbid migraine (χ^2 (1) = 8.53, p = 0.003).

3. BMI

We divided BMI according to the WHO classification [145] in three subgroups: ≤ 24.9, 25-29.9 and ≥ 29.9. Among the patients with migraine, the highest prevalence was found in the first subgroup (≤ 24.9) with 45.8%; followed by 28.8% in the third subgroup (≥ 29.9); and by 25.4% in the second one (25-29.9). On the other hand, among those patients without migraine, the highest prevalence was found in the third subgroup (41.2%), followed by the second subgroup (37.3%); and 21.5% of the subjects without migraine belong to the first group. We found that these differences were statistically significant, according to non-parametric tests (Kruskal-Wallis) (KW = 9.4, p<0.01). Specifically, between the first and second subgroup (Z=2.51, p<0.05) and between the first and last subgroup (Z=2.89, p<0.05).

4. **Anxiety disorders**

We found statistically significant differences for three different anxiety disorders:

a) **Social phobia**: Over 30% (30.1%) of BD patients with co-morbid migraine had as well a diagnosis of social phobia, compared with 10.1% of BD patients without migraine. This difference was statistically significant: χ^2 (1) = 17.33, p < 0.005.

b) **Panic disorder**: A statistically significant difference was found with respect to the comorbid diagnosis with panic disorder in patients with and without migraine (χ^2 (1) = 24.79, p < 0.005): 40% of migraine patients showed a comorbid diagnosis with panic disorder, compared to 13.4% of those who did not suffer from migraine. On the other hand, 60% of migraine patients did not show

comorbid panic disorder, and 86.6% of patients without migraine did not have comorbid panic disorder.

c) **Generalized anxiety disorder (GAD)**: 37.1% of patients with migraine showed a comorbid diagnosis with GAD, compared to 21.8% of those who did not. Among those patients without GAD comorbid disorder, 62.9% had migraine, whereas 78.2% did not. This difference was also found to be statistically significant, χ^2 (1) = 6.64, $p < 0.01$.

d) **Obsessive-compulsive disorder (OCD):** We found that comorbid OCD diagnosis was associated with migraine in BD patients (χ^2 (1) = 3.78, p = 0.05): 15.6% of migraine patients showed comorbid OCD; compared to 7.9% of patients without migraine. On those patients without comorbid OCD, the highest proportion was found among those patients without co-morbid migraine (92.1%), compared to 84.4% of patients with migraine.

Log-linear model (LLM)

LLM convert classical analysis from a multiplicative to a linear model by taking the natural logarithm of the expected frequencies. They are used in a manner analogous to that employed when an analysis of variance (ANOVA) is accomplished by a regression approach. A given model is fitted and a goodness-of-fit measure for the expected and observed frequencies (a residual measure) is obtained. A second model having an additional term(s) is then used to estimate the cell frequencies. A residual goodness-of-fit measure for this augmented model is obtained and the difference in the two goodness-of-fit measures is found. This difference in fit (a component measure) is ascribed to the additional term(s) in the model.

Under the classical approach to the analysis of a contingency table, only hypothesis of independence of the classificatory factors can be tested. The LLM approach increases the amount of information that can be obtained from the data. Each of the models provides information as to the structure of the data, and the model(s) fitting the data can be determined through the residual $\chi 2$ statistics.

The main question I wanted to answer by applying LLM to the data was: is migraine, in fact, correlated to (clinical characteristic, i.e., panic disorder), and not only to the site (MBR/MUHC)?

The results are as follow:

1. Diagnostic subtype: The best model found was MD, S. ($G^2 = 0.58$, $p = 0.90$; difference due to adding MD = $G^2 = 8.19$, $p = 0.004$). The fit improved with the additional term, which represented the effect of migraine on the model (which would correspond to a treatment main effect in the ANOVA terms). The model states that there is an interaction between migraine and diagnostic subtype, but that both are independent of the site.

2. Generalized Anxiety Disorder (GAD): The best model found was MG, GS. ($G^2 = 0.63$, $p = 0.72$; difference due to adding MG = $G^2 = 6.30$, $p = 0.01$). The fit improved with the additional term, which represented the effect of migraine on the model. This model states that there is an interaction between migraine and GAD, and between GAD and the site.

3. Obsessive compulsive Disorder (OCD): The best found model was MO, S. ($G^2 = 1.49$, $p = 0.68$; difference due to adding MO = $G^2 = 3.47$, $p = 0.06$). This fit also improved with the additional term, which represented the effect of migraine. The model states that there is an interaction between migraine and OCD, and both are independent of the site.

4. Panic Disorder (PD): The best model found was MP, S. ($G^2 = 1.68$, $p = 0.64$). The model states that there is an interaction between migraine and panic disorder, both are independent of the site.

5. Social Phobia (SP): The best model found was MA_1, S. ($G^2 = 6.38$, $p = 0.09$). The model states that there is an interaction between migraine and social phobia, both are independent of the site.

6. Attention-Deficit Disorder (ADD): The best model found was M, A_2S. ($G^2 = 5.63$, $p = 0.13$). The model states that there is an interaction between ADD and site, but both are independent of migraine.

7. Substance abuse: The best found model was M, A_3S. ($G^2 = 2.12$, $p = 0.54$). The model states that there is an interaction between substance abuse and site, but both are independent of migraine.

8. Body Mass Index (BMI): The best model found was BS, MB. ($G^2 = 0.48$, $p = 0.92$). The model states that there is an interaction between BMI and site, and as well, an interaction between migraine and BMI.

9. Diabetes Mellitus (DM): The best model found was MD, DS. ($G^2 = 0.16$, $p = 0.92$; difference due to adding MD = $G^2 = 1.36$, $p = 0.24$). The model states that there is an interaction between migraine and DM, and as well, an interaction between DM and site.

10. Thyroid abnormalities: The best model found was M, TS. ($G^2 = 0.39$, $p = 0.94$; difference due to adding MT = $G^2 = 0.02$, $p = 0.89$). The model states that there is an interaction between thyroid abnormalities and site, but both are independent of migraine.

11. Systemic hypertension: The best model found was M, HS. ($G^2 = 0.18$, $p = 0.98$; difference due to adding HS = $G^2 = 0.62$, $p = 0.043$). The model states that there is an interaction between systemic hypertension and site, but both are independent of migraine.

12. Gender: The best model found was M, G_2S. ($G^2 = 2.41$, $p = 0.49$; difference due to adding GS = $G^2 = 3.86$, $p = 0.04$). The model states that there is an interaction between gender and site, but both are independent of migraine.

13. Marital Status: The best model found was M, WS. ($G^2 = 4.24$, $p = 0.75$). The model states that there is an interaction between marital status and site, but both are independent of migraine.

14. Social status: The best model found was MY, YS. ($G^2 = 4.69$, $p = 0.32$). The model states that there is an interaction between social status and migraine, and as well, between migraine and site.

Discussion

In this study, we examined the clinical data of 323 BD patients, in order to examine the prevalence and clinical characteristics associated with migraine. Our results confirmed the higher prevalence of migraine in patients with BD (24.5%), particularly among those with BD 2 (45.1%); and showed as well higher rates of suicidal behaviour, panic disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, and social phobia, among BD patients with migraine.

An association between migraine and affective disorders has been widely addressed, as several reports have shown that the lifetime prevalence rates of major depression, Bipolar Disorder (BD), and anxiety disorders are significantly elevated in patients with migraine. In addition, diverse authors have reported that migraine occurs disproportionately within the BD population.

Recent characterizations of psychopathology and headache have implicated shared neuropathic mechanisms between migraine and affective disorders. Some authors [146] have suggested a co-sensitization of the sensory and affective components of head pain as a possible phenomenon underlying observed comorbid relationships. Both concepts refer to neuroplastic processes in the corticolimbic structures, where an expanding corticolimbic field becomes activated by both nociceptors and psychological stimuli over a period of time, resulting in an integrated relationship between migraine and psychiatric abnormalities in susceptible individuals [147, 148].

Even if the complex mechanisms underlying this comorbidity have not been fully studied and/or explored, the clinical implications of this relationship are important. Our results agree with those from other authors, with respect to the higher prevalence of migraine in patients with a BD 2 diagnosis, as shown by Fasmer [135], even when we account for the differences in the diagnosis of BD 2 in their study in which is reported that 14% of the bipolar I patients had a migraine diagnosis, compared to 77% of the bipolar 2 group, being this difference statistically significant. There was also a significant difference regarding the frequency of migraine attacks, which was significantly higher in patients with bipolar 2 disorder than in patients with unipolar disorder. The authors also found a non-significant association for panic disorders in patients with migraine.

Other studies have reported as well higher prevalence of migraine in BD 2 [149], with similar characteristics to those included in the study from Fasmer, although the inclusion criteria for both migraine and BD did not follow the guidelines that we are familiar with nowadays. This study included 400 patients with major affective disorders, and his findings include a higher prevalence of migraine in BD 2 patients (51%), compared with a 22% prevalence in BD I patients.

In our study, among BD 1 patients, only 19.1% showed comorbid migraine, whereas in the BD 2 subgroup, 34.8% patients had comorbid migraine, findings that further support the evidence regarding migraine comorbidity as more prevalent among BD 2 patients. This relationship, however, may be undertwined with other Axis I comorbidity that are also more prevalent conditions among BD II, such as anxiety disorders.

As a matter of fact, recent research suggests that anxiety disorders may be the most prevalent psychiatric comorbid condition among patients with BD [150]. In our study, we found that BD patients with migraine show higher rates of panic disorder (40%), generalized anxiety disorder (37.1%), obsessive-compulsive disorder (15.6%), and social phobia (30.1%), when compared to bipolar patients without migraine (13.4%, 21.8%, 7.9%, and 10.1%, respectively), as previously reported by other authors [137]. The ubiquity of anxiety in BD has been taken for some researchers as the conception that anxiety may be a core dimension of BD, rather than a comorbidity [87], and particularly for panic disorder, several studies have suggested that it may be genetically related to BD [151-153]; in fact, in the study from Gonda et al [154], a significant association between the s allele of the 5HTTLPR and the high anxiety level in migraine patients is described. Specifically for social phobia, several studies have acknowledged its association with BD, particularly among BD 2 patients [155], whereas others have suggested that patients with social anxiety may belong to a different subcategory [156]. More important, a recent study has reported the association between social phobia and suicidal attempt in BD [157].

Regarding the prevalence of anxiety disorders according to diagnostic subgroups, the findings have been contradictory. A study from Rihmer [158] and colleagues reported that the prevalence of generalized anxiety disorder, agoraphobia and simple phobia was the highest among BD 2 patients (20.8%, 37.5% and 16.7%, respectively), when compared to unipolar patients and bipolar I patients. Our results may indeed be in concordance with

their findings, because the comorbid anxiety diagnosis found in our sample may be a result of the higher prevalence of migraine among BD 2 patients. However, some other studies have reported no significant differences in anxiety disorders comorbidity between patients with BD 1 and BD 2 [159]; or that the prevalence of anxiety disorders is higher among BD I patients (51.2%), when compared to BD 2 (30.5%) [160].

Given the strong association between suicide and BD, various studies have attempted to give a clearer definition of its picture. Reports suggest that 25%-60% of all bipolar patients will have attempted suicide at least once in their lifetime, and they also revealed that bipolar patients, compared with all other DSM-III defined patients, were the most likely to have a history of previous suicide attempts [161]. A recent review also concluded that bipolar patients in general, and bipolar II patients in particular, are over-represented among both committed and attempted suicides [162]. However, some other studies reported a lack of association of suicide with clinical characteristics of the disorder, including the bipolar II subtype [163]. In our study, almost 40% of patients with migraine showed a positive history of suicidal attempts, compared to 27% of migraine patients that did not. This is in accordance with the study from Breslau [6], in which she conducted more than 1000 structured interviews to evaluate the lifetime psychiatric disorder prevalence in patients with and without migraine, finding that patients with migraine (with or without aura) had higher rates of attempted suicide than those without migraine, even when major depression was controlled for.

Our findings showed as well that almost half of migraine patients have a normal BMI (45.8%), whereas those without migraine showed a BMI ≥29.9. It has been described that the prevalence of migraine does not vary significantly with BMI [164]; however, among migraine patients, a high BMI was associated with more frequent headache attacks [165]. However, we lack information regarding attack frequency in this sample.

In summary, we found that migraine is an important and common comorbid condition in BD, and that its prevalence is higher among patients with BD 2. Specifically for BD 2, gathering data regarding headaches and migraine history may be beneficial for the treatment of both conditions. BD patients with migraine showed as well higher comorbidity with various subtypes of anxiety disorder, namely, panic disorder, social

phobia, OCD, and GAD; being this comorbidity probably particularly deleterious for the overall prognosis of the disorder. If the treatment involves all the comorbid conditions, although complicated to achieve, the clinical course of the disorder and prognosis in general will be improved.

History of suicidal behaviour was another important clinical characteristic with a higher prevalence among BD patients with migraine. Particularly interesting, it has been described that comorbidity with panic disorder is also a factor that may contribute to the risk of suicidal behaviour in bipolar patients. Again, as clinicians, our efforts should be directed to the diagnosis of all comorbid conditions and to the treatment of most –if not all- of them. An evidently out-of- proportion enterprise, although with outstanding benefits for the treatment of the disorder and the quality of life of BD patients.

CHAPTER 6: STUDY 2: PSYCHIATRIC CO-MORBIDITY IN MIGRAINE PATIENTS

Methods

The sample is composed of 102 patients, interviewed at a private clinic in Montreal, specialized in migraine, where the migraine diagnosis is based on the International Headache Society criteria [141]. Patients were randomly chosen among the complete population of the Migraine Clinic, and were informed about the possibility to participate through their treating neurologist. Written informed consent was obtained from all participating individuals.

Participants were interviewed by the same investigator (AO) using a semi-structured research interview: the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) format [139], and case note information was obtained. Current and lifetime best estimate psychiatric diagnoses were made according to both Research Diagnosis Criteria [140] and DSM-IV criteria. Diagnostic information was then reviewed in blind fashion using clinical data from ten randomly chosen cases in consensus meetings of the research team. Each case ascertainment was then compared to obtain a consensus diagnosis.

Descriptive data analysis was conducted using the BMDP Statistical Software (BMDP Statistical Software, Inc. 8.1).

Results

Table 3 shows the descriptive characteristics of the sample. 102 migraine patients were included in the second part of the study: 25 (24.5%) males and 77 females (75.5%), with a mean age of 45.7 ± 11.7 years (CI 95%:43.3, 47.9). The reported age at onset of migraine was at 20.7 ± 10.7 years (CI 95%: 18.4, 22.9); and the age at onset of any psychiatric disorder about 10 years later [31.7 ± 12.4 years (CI 95%: 28.5, 35.1)]. The most prevalent migraine subtype was migraine without aura, with 85 patients (83.3%), followed by migraine with aura, with 17 patients (16.7%) in the sample. Regarding demographic variables, almost 70% of the patients were married, and most of the patients in the sample (59.8%) were employed.

Sixty-six patients (64.7%) had one or more first-degree relative(s) also with migraine; and 57 patients (55.9%) had one or more first-degree relative(s) with any psychiatric diagnosis. Table 4 depicts current and lifetime psychiatric diagnosis in migraine patients. In fact, over 40% of the sample (41.2%) had a current psychiatric diagnosis, and over 70% (73.5%) had a lifetime psychiatric diagnosis, as it follows:

a) Mood disorders: The most prevalent disorder among patients with migraine was Major Depressive Disorder (29.4%), followed by Major Depressive Episode (19.6%), and finally by Bipolar Disorder (12.7%). Subtyping BD, most of the patients had a BD 2 diagnosis (7.8%), compared to a BD 1 diagnosis (4.9%).

b) Anxiety disorders: 47.1% of the patients had had an anxiety disorder. Of them, the most prevalent was generalized anxiety disorder (23.5%), followed by panic disorder (10.8%) and phobic disorder (8.8%). Furthermore, 42.2% of the sample presented both a mood disorder diagnosis and an anxiety disorder diagnosis across their lifespan.

c) Psychotic disorders: Only 5 patients (4.9%) presented psychotic symptomatology. Of them, two patients (2.0%) presented psychotic symptoms only during a mood episode, and three patients had a diagnosis of schizoaffective disorder (2.9%).

d) Other disorders in Axis I or II: 27.5% of the patients presented an associated diagnosis in Axis I or II. Among Axis I, the most frequently observed diagnosis was somatization disorder (44.4%), followed by seasonal affective disorder (SAD) by 22.2%, and finally

by eating disorders (16.6%), and adjustment disorders (16.6%). Regarding Axis II, 35.7% of the patients presented a personality disorder.

e) Axis III comorbidity: 33.3% of the patients presented an Axis III comorbid disorder. Of them, the most prevalent were asthma (17.7%), cardiovascular disorders (17.7%), and hypothyroidism (17.7%), followed by fybromyalgia (11.7%), peptic-ulcer disease (8.9%), and cancer (8.9%).

f) Drug abuse: 11.8% of the migraine patients had presented drug abuse at some point in their lives, compared to 88.2% who did not.

g) Associated features

1. Suicidal behaviour: 11 migraine patients (10.8%) presented suicidal ideation or a suicidal attempt at some point in their lives, compared to 89.2% that did not.

2. Use of psychiatric medications: 36.3% of migraine patients had received a prescription for the use of antidepressants or benzodiazepines, by their treating neurologist or psychiatrist, related to the treatment of other conditions than those associated with their use in migraine.

3. Psychiatric hospitalizations: 7 migraine patients (6.9%) showed previous psychiatric hospitalizations, compared to 93.1% who did not.

Discussion

Several studies have demonstrated the cross-sectional relation between psychopathologic features and migraine headache in community samples. While the association between psychiatric disorders and migraine may or may not reflect a causal one, a greater understanding of these specific relations may ultimately contribute to our understanding of the underlying aetiologies of both conditions.

Our results show the demographic and clinical variables associated with psychopathology in a migraine population. These results agree to a great extent with respect to those supporting the higher prevalence of migraine among those patients between 25 to 55 years old, and among the female gender [125], contributing to over 75% of the sample size in the study. Our results also confirm that migraine without aura has a higher prevalence (83.3%) than migraine with aura (16.7%), and that there are few conditions that are not associated with migraine, among them, psychotic symptoms and drug abuse, as shown by previous studies [166].

The familial association among headache syndromes and psychiatric disorders has been widely studied. One of the most interesting studies conducted 15 years ago [127] suggested that both migraine and affective/anxiety disorders are familial, with an increased risk of migraine in the relatives of probands with migraine (OR = 3.2), and an increase of anxiety/depression in the relatives of probands with anxiety/depression (OR = 2.1). Moreover, there was a significant association between anxiety/depression and migraine among the relatives (OR = 2.3). This suggests that migraine and anxiety/depression share a syndromic relationship, rather than representing manifestations of the same underlying etiologic factors. Our results as well confirm these observations, in view of the high prevalence for both migraine (64.7%) and psychiatric disorders (55.9%) among the relatives of migraine patients.

The prevalence of psychopathology among patients with migraine has also been extensively studied. Merikangas [9] reported a prevalence of 39.3% psychiatric disorders (anxiety disorders, depressive disorder, and anxiety and depressive disorders) among patients with migraine, an estimate that is very close to the prevalence of psychiatric disorders that we found in our study: 41.2%. In her study, generalized anxiety disorder

and social phobia showed the greatest associations with migraine, with OR of 5.3 and 3.4, respectively. As well, our study shows a higher prevalence of these conditions among migraine sufferers (23.5% and 8.8%, respectively). Particularly regarding mood disorders, Merikangas' study reports as well that bipolar spectrum disorders had a nearly threefold greater prevalence among migraine sufferers, with a prevalence of over 10% in the population studied. Other studies have also confirmed this association, reporting a prevalence of the migraine – BD comorbidity being particularly high, specially in patients with migraine with aura, with OR = 7.3 [6, 128]. Our results also confirm the high prevalence of mood disorders among migraine sufferers, and portray that 12.7% of the migraine sufferers had a diagnosis of BD.

In this sense, it has been shown that medical comorbidites associated with BD could influence its outcome through several factors, including quality of life, functioning, and psychological well-being; and as well, as suggested by Thompson [16], some aspects of the psychiatric disorder, such as age at onset, could also be a significant predictor of future comorbidites. Particularly, his study describes that for each year of later onset of depression, there was a 2% decrease in the number of active baseline comorbidities.

Migraine, for instance, may disrupt circadian rhythms and sleep, contributing to mood dysregulation in BD; conversely, particularly during the depressive episodes, BD patients may increase the risk of medical illness, through an extensive reinforcement of negative health behaviours, such as smoking, overeating, poor dieting, and sedentary life style.

Several papers as well have studied the theme of quality of life and comorbidities in migraine, due to the noted comorbidity of migraine with a variety of illness, among them, stroke, hypertension, hypothyroidism, asthma, and allergies are well-recognized comorbidities [1], although migraine has also been associated with fybromyalgia, chronic fatigue syndrome, and irritable bowel syndrome [6]. In an effort to clarify the complex array of symptoms and comorbidities within migraine, a recent paper published a proposed series of constellations of comorbid disorders [167]. After a retrospective chart analysis of over 200 patients, the authors suggest that they may be three different groups in this regard: the first one would be defined by the comorbidity with hypertension, hyperlipidemia, diabetes mellitus, and hypothyroidism; the second one would be characterized by the presence of depression, anxiety, and fybromyalgia; and the third one

would be characterized by the absence of comorbidities. They also suggest that the quality of life and disability would be related to these comorbidities, having reported that patients in the second group showed the highest disability and the lowest quality of life, when compared to the rest of the sample.

Our findings regarding Axis III comorbidity in patients suffering from migraine agree with previous reports regarding the higher risk of cardiovascular risk disease in migraine patients, particularly in those with migraine with aura [28], and the role of the pulmonary pathology on the disorder. In this sense, it appears that migraine patients, particularly those with aura, have again an increased risk of decompression illness, a higher prevalence of persistent foramen oval (PFO), and a high prevalence of pulmonary shunts [29]. Our results show that patients suffering from migraine have a higher rate of comorbid asthma (17.7%), cardiovascular disorders, such as systemic hypertension and arrhythmias (17.7%), and endocrine abnormalities, such as hypothyroidism (17.7%).

As well, personality disorders are important components within the migraine psychopathology constellation, and may be capable of affecting its course by also influencing the response to the treatment. Our findings show that over 35% of the patients suffering from migraine present an associated Axis II disorder diagnosis, which can influence the treatment and prognosis of both disorders, as showed by a recent study regarding high baseline scores in the Minnesota Multiphasic Personality Inventory (MMPI) subscales of Hypochondriasis, Depression, Hysteria, and Schizophrenia and its association with an unfavourable prognosis, independently of the level of baseline disability, according to the Migraine Disability Assessment Questionnaire (MIDAS) questionnaire in chronic migraine patients [168].

Suicidal behaviour among general medical conditions has been studied as well, in relation to the number of factors unrelated to psychopathology and independently associated with suicidal ideation and/or completed suicide; however, understanding the role of general medical illnesses as potential risk factors for suicidality is complex because of their high comorbidity with depression [169]. The study from Druss and Pincus [170] showed that the presence of a general medical illness is associated with lifetime suicidal ideation in over 25% of individuals with a general medical condition, and having

more than one illness conferred a higher risk (35%); moreover, this relationship persists after controlling for depression and alcohol use. Regarding suicidal attempts, the same study showed that 8.9% of those with a general medical condition, and 16.2% of those with two or more medical conditions had attempted suicide. More specifically, pulmonary diseases, such as asthma or bronchitis, were associated with two thirds increase in the odds of lifetime suicidal ideation; as well, asthma and cancer were each associated with a more than four-fold increase in the likelihood of a suicide attempt. This interesting association with suicidal ideation and pulmonary disease was confirmed by a recent study [171], and some studies have proposed the role of the neurotoxic effects of hypoxia on neurological and neuropsychological measures as a plausible explanation for these findings [172]. Particularly regarding suicide and migraine, we found that almost 11% migraine sufferers in our sample had presented suicidal behaviour (suicidal ideation and/or suicidal attempt). Several studies have showed that migraine is an independent risk factors for an increased suicidal risk [128, 129, 173]. In the study from Wang [174], the frequencies of high risk of suicide were 50% for subjects with migraine with aura, 21% for migraine without aura, and 7.5% for those without migraine; and after controlling for depressive and anxiety disorders, the association for migraine with aura remained, with an OR = 7.8.

CHAPTER 7: CONCLUSIONS

Migraine is remarkably common, with a global prevalence of 10% [175]. Its prevalence exceeds that of osteoarthritis, diabetes mellitus, and asthma, and is greater than the combined prevalence of epilepsy, multiple sclerosis, stroke, and Parkinson's disease [176]. In Canada, the migraine lifetime prevalence in females has been increasing, from 23% in 1992 to 26% in 2006, whereas for males, although not recent studies have been conducted, its prevalence ranges from 7.8% to 10% [177]. Other studies have shown that approximately 60% migraine sufferers have one or more headache attacks per month, and 25% of migraine sufferers have attacks at least once a week [178]. Migraine is generally under diagnosed: up to 48% of women with migraine had never consulted a physician for their headaches [179].

The World Health Report published in 2001 by WHO [180] demonstrated that a number of psychiatric and neurological disorders are amongst the most disabling, accounting for 12.3% of the total DALYs (Disability-adjusted life years), and the trend analysis shows that this burden will increase in the future, with projections indicating 15% by the year 2020 [181]; and although migraine entails no increase mortality, it was ranked 19th with regard to the years lived with disability for both sexes [182]. Moreover, its comorbidity with psychiatric disorders is particularly relevant, in the sense that it is also a psychiatric disorder (major depressive disorder, or unipolar depression) the leading cause of years lived with disability. In this sense, we consider that the study of the relationship among both disorders deserves further consideration.

Overall, our results from Study 1 show that migraine is a common disorder among BD patients (with a prevalence of 24.5%), specially among BD 2 patients, and that migraine status is significantly associated with the presence of suicidal behaviour, and a diversity of anxiety disorders, such as social phobia, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder in BD patients.

The results from the second study show as well that migraine patients show a broad range of comorbidity with psychiatric conditions. Among them, mood disorders and anxiety disorders are the most frequent; particularly, 12.7% of migraine sufferers had

a diagnosis of BD, being again more frequent the BD 2 subtype. Other comorbidities in Axis I in this sample of migraine sufferers include somatization disorder, seasonal affective disorder, and eating disorders. In Axis II, 35.7% of the patients showed an associated diagnosis; and in Axis III, several comorbidites were found, among them, asthma, cardiovascular disorders, hypothyroidism, and fybromyalgia were the most prevalent. 10.8% of migraine patients also presented suicidal behaviour at some point during their lives, and 6.9% of migraine sufferers had been psychiatric inpatients.

One of the limitations for the first study include that our results represent migraine diagnoses made by a self-assessment questionnaire (ID-Migraine), which has therefore recall bias associated with questionnaire-based surveys, although the data regarding its validation shows that is a valid and reliable screening instrument. Another limitation regarding Study 1 concerns the use of different structured interviews for diagnosing psychiatric disorders, i.e., SADS-L for the Maritime Bipolar Registry (Halifax, NS) and SCID for the Bipolar Disorder Database (Montreal, QC); however, the development of a log-linear model contributed to the clarification of the relationship among the variables. Regarding the second study, the Migraine Clinic is a super-specialized clinic in migraine headaches; therefore, is probable that patients in this clinic could have been referred by a specialist due to the severity of their migraines, raising the possibility that the patients seen in this setting have a chronic or more severe form of the disorder. The absence of comparison groups in both studies is a limitation as well. Finally, and although the temporal relationship between onset of migraine and different psychiatric disorders is of outmost interest, it is not possible to address it, since the age of onset of any psychiatric disorder was not classified accordingly to different diagnoses.

Our study highlights the importance of inquiring information for both disorders, either in the general practice or within the psychiatric population, due to the high prevalence of migraine among BD patients, and to the elevated prevalence of psychiatric comorbidity among migraine sufferers.

The approach can be beneficial in the sense that it will provide the means to appropriately treat both conditions, to improve the patients' quality of life, to ameliorate the outcome in BD patients; and to diminish the rate of chronification of headaches associated to psychological distress.

Eventually, as well, the study of this comorbidity will deepen our understanding of the mechanisms that underlie both disorders and provide a better framework for the developing of molecular techniques to further analyze the molecular physiopathology of Bipolar Disorder.

Table 1

Clinical and demographic characteristics of BD patients with and without migraine

Variable		Migraine + (%)	Migraine – (%)	Total (%)	X^2	df	p
Gender	Masculine	25 (31.6)	99 (40.6)	124 (38.4)			
	Femenine	54 (69.4)	145 (59.4)	199 (61.6)			
	Total	79 (100)	244 (100)	323 (100)	2.01	1	0.15
Marital status	Single	23 (29.1)	59 (24.7)	82 (25.8)			
	Married	38 (48.1)	123 (51.5)	161 (50.6)			
	Divorced	17 (21.5)	49 (20.5)	66 (20.8)			
	Widow	1 (1.3)	8 (3.3)	9 (2.8)			
	Total	79 (100)	239 (100)	318 (100)	1.52	3	0.67
Social status	Employed	30 (38.0)	97 (40.7)	127 (40.0)			
	Unemployed	18 (22.8)	36 (15.1)	54 (17.0)			
	Disabled	19 (24.1)	57 (23.9)	76 (23.9)			
	Other	6 (7.6)	14 (5.8)	20 (6.3)			
	Retired	2 (2.5)	24 (10.1)	26 (8.2)			
	Student	4 (5.1)	10 (4.2)	14 (4.4)			
	Total	79 (100)	238 (100)	317 (100)	7.34	5	0.28
Suicidal behaviour	Yes	31 (39.7)	62 (27.0)	93 (30.2)			
	No	47 (60.3)	168 (73.0)	215 (69.8)			
	Total	78 (100)	230 (100)	308 (100)	4.51	1	0.03
Diabetes Mellitus	Yes	6 (7.7)	30 (12.3)	36 (11.2)			
	No	72 (92.3)	214 (87.7)	286 (88.8)			
	Total	78 (100)	244 (100)	322 (100)	1.26	1	0.26
Systemic hypertension	Yes	13 (16.5)	36 (14.8)	49 (15.2)			
	No	66 (83.5)	207 (85.2)	273 (84.8)			
	Total	79 (100)	243 (100)	322 (100)	0.12	1	0.72
Thyroid abnormalities	Yes	21 (26.9)	67 (27.7)	88 (27.5)			
	No	57 (73.1)	175 (72.3)	232 (72.5)			
	Total	78 (100)	242 (100)	320 (100)	0.01	1	0.89
Body Mass Index (BMI)	≤ 24.9	27 (45.8)	34 (21.5)	61 (28.1)			
	25-29.9	15 (25.4)	59 (37.3)	74 (34.1)			
	≥ 29.9	17 (28.8)	65 (41.2)	82 (37.8)			
	Total	59 (100)	158 (100)	217 (100)	12.6	2	0.005
Substance abuse	Yes	19 (28.4)	50 (23.8)	69 (24.9)			
	No	48 (71.6)	160 (76.2)	208 (75.1)			
	Total	67 (100)	210 (100)	277 (100)	0.56	1	0.45
Diagnosis subtype	BD 1	39 (54.9)	165 (73.3)	204 (68.9)			
	BD 2	32 (45.1)	60 (26.7)	92 (31.1)			
	Total	71 (100)	225 (100)	296 (100)	8.53	1	0.003
Social phobia	Yes	22 (30.1)	23 (10.1)	45 (15.0)			
	No	51 (69.9)	204 (89.9)	255 (85.0)			
	Total	73 (100)	227 (100)	300 (100)	17.33	1	0.000
Panic disorder	Yes	30 (40.0)	30 (13.4)	60 (20.1)			
	No	45 (60.0)	194 (86.6)	239 (79.9)			
	Total	75 (100)	224 (100)	299 (100)	24.79	1	0.000
Obsessive Compulsive Disorder (OCD)	Yes	12 (15.6)	18 (7.9)	30 (9.9)			
	No	65 (84.4)	209 (92.1)	274 (90.1)			
	Total	77 (100)	227 (100)	304 (100)	3.78	1	0.05
Generalized Anxiety Disorder (GAD)	Yes	26 (37.1)	49 (21.8)	75 (25.4)			
	No	44 (62.9)	176 (78.2)	220 (74.6)			
	Total	70 (100)	225 (100)	295 (100)	6.64	1	0.009
Attention Deficit Disorder (ADD)	Yes	6 (8.3)	8 (4.2)	14 (5.3)			
	No	66 (91.7)	183 (95.8)	249 (94.7)			
	Total	72 (100)	191 (100)	263 (100)	1.78	1	0.18

Table 2

Migraine in BD patients: Log-linear modeling

Diagnostic subtype

SITE	DIAGNOSTIC SUBTYPE	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	BD1	24 (53.3)	102 (71.8)	126 (67.4)
	BD2	21 (46.7)	40 (28.2)	61 (32.6)
	TOTAL	45 (100)	142 (100)	187 (100)
MUHC	BD 1	15 (57.7)	63 (75.9)	78 (71.5)
	BD 2	11 (42.3)	20 (24.1)	31 (28.5)
	TOTAL	26 (100)	83 (100)	109 (100)

a) Simplest non-significant model: M, D, S. (M=Migraine, D = Diagnosis, S = Site)

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
4.	8.77	0.06	9.10	0.06

b) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MD, S.

Model	D.F.	G^2	Probability	X^2	Probability
MD, S	3	0.58	0.90	0.57	0.90
Difference due to adding MD	1	8.19	0.004		

Generalized Anxiety Disorder

SITE	GAD	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	19 (43.2)	39 (26.7)	58 (30.5)
	NO	25 (56.8)	107 (73.3)	132 (69.5)
	TOTAL	44 (100)	146 (100)	190 (100)
MUHC	YES	7 (26.9)	10 (12.7)	17 (16.2)
	NO	19 (73.1)	69 (87.3)	88 (83.8)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: M, GS (M= Migraine, G = GAD, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	6.93	0.07	7.37	0.06

b) Stepwise modeling by deleting effects: No difference with respect to original model.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MG, GS.

Model	D.F.	G^2	Probability	X^2	Probability
MG, GS	2	0.63	0.72	0.64	0.72
Difference due to adding MG	1	6.30	0.01		

Obsessive-Compulsive Disorder (OCD)

SITE	OCD	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	8 (15.7)	14 (9.5)	22 (11.1)
	NO	43 (84.3)	134 (90.5)	177 (88.9)
	TOTAL	51 (100)	148 (100)	199 (100)
MUHC	YES	4(15.4)	4 (5.1)	8 (7.6)
	NO	22 (84.6)	75 (94.9)	97 (92.4)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: M, O, S (M = Migraine, O = OCD, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
4	4.96	0.29	4.95	0.29

b) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MO, S.

Model	D.F.	G^2	Probability	X^2	Probability
MO, S	3	1.49	0.68	1.40	0.70
Difference due to adding MO	1	3.47	0.06		

Panic Disorder (PD)

SITE	PD	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	17 (34.7)	19 (13.1)	36 (18.6)
	NO	32 (65.3)	126 (86.9)	158 (81.4)
	TOTAL	49 (100)	145 (100)	194 (100)
MUHC	YES	13 (50.0)	11 (13.9)	24 (22.9)
	NO	13 (50.0)	68 (86.1)	81 (77.1)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: S, MP (S = Site, M = Migraine, P = Panic disorder)

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	1.68	0.64	1.69	0.63

b) Stepwise modeling by deleting effects: The best model found was no different from the original.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was PS, MP.

Model	D.F.	G^2	Probability	X^2	Probability
PS, MP	2	0.91	0.63	0.90	0.63
Difference due to adding PS	1	0.77	0.37		

Social Phobia (SP)

SITE	SP	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	15 (31.9)	20 (13.5)	35 (17.9)
	NO	32 (68.1)	128 (86.5)	160 (82.1)
	TOTAL	47 (100)	148 (100)	195 (100)
MUHC	YES	7 (26.9)	3 (3.8)	10 (9.5)
	NO	19 (73.1)	76 (96.2)	95 (90.5)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: S, MA (S= Site, M = Migraine, A = Social phobia)

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	6.38	0.09	5.54	0.13

b) Stepwise modeling by deleting effects: The best model found was no different from the original.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was AS, MA.

Model	D.F.	G^2	Probability	X^2	Probability
AS, MA	2	2.34	0.31	2.29	0.31
Difference due to adding AS	1	4.04	0.04		

Attention-Deficit Disorder (ADD)

SITE	ADD	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	3 (6.1)	1 (0.7)	4 (2.1)
	NO	46 (93.9)	142 (99.3)	188 (97.9)
	TOTAL	49 (100)	143 (100)	192 (100)
MUHC	YES	3 (13.0)	7 (14.6)	10 (14.1)
	NO	20 (87.0)	41 (85.4)	61 (85.9)
	TOTAL	23 (100)	48 (100)	71 (100)

a) Simplest non-significant model: M, AS (M=Migraine, A = ADD, S = Site)

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	5.63	0.13	6.30	0.09

b) Stepwise modeling by deleting effects: The best model found was again M, AS.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was: MA, AS.

Model	D.F.	G^2	Probability	X^2	Probability
MA, AS	2	3.99	0.13	4.0	0.13
Difference due to adding MA	1	1.64	0.20		

Substance Abuse

SITE	SUBSTANCE	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	8 (19.5)	14 (10.7)	22 (12.8)
	NO	33 (80.5)	117 (89.3)	150 (87.2)
	TOTAL	41 (100)	131 (100)	172 (100)
MUHC	YES	11 (42.3)	36 (45.6)	47 (44.8)
	NO	15 (57.7)	43 (54.4)	58 (55.2)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: M, AS. (M=Migraine, A= Substance abuse, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	2.12	0.54	2.27	0.51

b) Stepwise modeling by deleting effects: The best model found was no different from the original model.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MA, AS.

Model	D.F.	G^2	Probability	X^2	Probability
MA, AS	2	1.57	0.45	1.61	0.44
Difference due to adding MA	1	0.55	0.45		

Body Mass Index (BMI)

SITE	BMI	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	≤ 25	19 (40.4)	26 (20.0)	45 (25.4)
	26 – 30	13 (27.7)	49 (37.7)	62 (35.0)
	31 – 35	8 (17.0)	32 (24.6)	40 (22.6)
	≥ 35	7 (14.9)	23 (17.7)	30 (16.9)
	TOTAL	47 (100)	130 (100)	177 (100)
MUHC	≤ 25	8 (66.7)	8 (28.6)	16 (40.0)
	26 – 30	2 (16.7)	10 (35.7)	12 (30.0)
	31 – 35	2 (16.7)	10 (35.7)	12 (30.0)
	≥ 35	0 (0.0)	0(0.0)	0(0.0)
	TOTAL	12 (100)	28 (100)	40 (100)

a) Simplest non-significant model: BS, MB (B= BMI, M= Migraine, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	0.48	0.92	0.47	0.92

b) Stepwise modeling by deleting effects: The best model found was BS, M.

Model	D.F.	G^2	Probability	X^2	Probability
BS, M	6	12.54	0.0509	13.17	0.040
Difference due to deleting MB	3	12.07	0.0072		

c) Stepwise modeling by adding effects (simple method): the best model found was MS, BS, MB:

Model	D.F.	G^2	Probability	X^2	Probability
MS, BS, MB	2	0.47	0.79	0.46	0.79
Difference due to adding MS	1	0.01	0.94		

d) Stepwise modeling by adding effects (multiple method): the best model found was MBS.

Model	D.F.	G^2	Probability	X^2	Probability
MBS	0	0.0	1.0	0.0	1.0
Difference due to adding MBS	3	0.48	0.92		

Diabetes Mellitus

SITE	DM	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	5 (9.6)	26 (16.1)	31 (14.6)
	NO	47 (90.4)	135 (83.9)	182 (85.4)
	TOTAL	52 (100)	161 (100)	213 (100)
MUHC	YES	1 (3.8)	4 (4.8)	5 (4.6)
	NO	25 (96.2)	79 (95.2)	104 (9.4)
	TOTAL	26 (100)	83 (100)	109 (100)

a) Simplest non-significant model: M, DS (M= Migraine, D = DM, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
3	1.51	0.67	1.41	0.70

b) Stepwise modeling by deleting effects: No differences from original model.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MD, DS.

Model	D.F.	G^2	Probability	X^2	Probability
MD, DS	2	0.16	0.92	0.16	0.92
Difference due to adding MD	1	1.36	0.24		

Thyroid abnormalities

SITE	THYROID	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	14 (26.9)	46 (28.9)	60 (28.4)
	NO	38 (73.1)	113 (71.1)	151 (71.6)
	TOTAL	52 (100)	159 (100)	211 (100)
MUHC	YES	7 (26.9)	21 (25.3)	28 (25.7)
	NO	19 (73.1)	62 (74.7)	81 (74.3)
	TOTAL	26 (100)	83 (100)	109 (100)

a) Simplest non-significant model: M, T, S. (M= Migraine, T= Thyroid, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
4	0.40	0.98	0.40	0.98

b) Stepwise modeling by adding effects (simple and multiple methods): the best model found was M, TS.

Model	D.F.	G^2	Probability	X^2	Probability
M, TS	3	0.39	0.94	0.38	0.94
Difference due to adding MT	1	0.02	0.89		

Systemic Hypertension (HBP)

SITE	HBP	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	YES	8 (15.1)	22 (13.8)	30 (14.1)
	NO	45 (84.9)	138 (86.2)	183 (85.9)
	TOTAL	53 (100)	160 (100)	213 (100)
MUHC	YES	5 (19.2)	14 (16.9)	19 (17.4)
	NO	21 (80.8)	69 (83.1)	90 (82.6)
	TOTAL	26 (100)	83 (100)	109 (100)

a) Simplest non-significant model: M, H, S (M= Migraine, H = Systemic Hypertension, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
4	0.79	0.93	0.80	0.93

b) Stepwise modeling by adding effects (simple and multiple methods): the best model found was M, HS.

Model	D.F.	G^2	Probability	X^2	Probability
M, HS	3	0.18	0.98	0.18	0.98
Difference due to adding HS	1	0.62	0.43		

Gender

SITE	GENDER	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	MASCULINE	16 (30.2)	58 (36.0)	74 (34.6)
	FEMININE	37 (69.8)	103 (64.0)	140 (65.4)
	TOTAL	53 (100)	161 (100)	214 (100)
MUHC	MASCULINE	9 (34.6)	41 (49.4)	50 (45.9)
	FEMININE	17 (65.4)	42 (50.6)	59 (54.1)
	TOTAL	26 (100)	83 (100)	109 (100)

a) Simplest non-significant model: M, G, S (M= Migraine, G = Gender, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
4	6.27	0.17	6.38	0.17

b) Stepwise modeling by adding effects (simple and multiple methods): the best model found was M, GS.

Model	D.F.	G^2	Probability	X^2	Probability
M, GS	3	2.41	0.49	2.35	0.50
Difference due to adding GS	1	3.86	0.04		

Marital Status (MS)

SITE	MS	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	SINGLE	11 (20.8)	31 (19.5)	42 (19.8)
	MARRIED	31 (58.5)	95 (59.7)	126 (59.4)
	DIVORCED	11 (20.8)	28 (17.6)	39 (18.4)
	WIDOW	0 (0.0)	5 (3.1)	5 (2.4)
	TOTAL	53 (100)	159 (100)	212 (100)
MUHC	SINGLE	12 (46.2)	28 (35.0)	40 (37.7)
	MARRIED	7 (26.9)	28 (35.0)	35 (33.0)
	DIVORCED	6 (23.1)	21 (26.3)	27 (25.5)
	WIDOW	1 (23.1)	3 (3.7)	4 (3.8)
	TOTAL	26 (100)	80 (100)	106 (100)

a) Simplest non-significant model: M, WS (M= Migraine, W= Marital status, S= Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
7	4.24	0.75	3.04	0.88

b) Stepwise modeling by deleting effects: The best model found was no different from the original.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MW, WS.

Model	D.F.	G^2	Probability	X^2	Probability
MS, WS	4	2.56	0.63	2.17	0.70
Difference due to adding MW	3	1.68	0.64		

Social Status

SITE	Social Status	MIGRAINE		
		YES (%)	NO (%)	TOTAL (%)
MBR	Work full-time	11 (20.8)	42 (26.1)	53 (24.8)
	Work part-time	9 (17.0)	16 (9.9)	25 (11.7)
	Unemployed	2 (3.8)	5 (3.1)	7 (3.3)
	Social assistance	4 (7.5)	2 (1.2)	6 (2.8)
	Disabled	19 (35.8)	57 (35.4)	76 (35.5)
	Other	6 (11.3)	14 (8.7)	20 (9.3)
	Retired	0 (0.0)	17 (10.6)	17 (7.9)
	Student	2 (3.8)	6 (3.7)	8 (3.7)
	Unknown	0 (0.0)	2 (1.2)	2 (0.9)
	TOTAL	53 (100)	161 (100)	214 (100)
MUHC				
	Work full-time	10 (38.5)	39 (49.4)	49 (46.7)
	Work part-time	0 (0.0)	0 (0.0)	0 (0.0)
	Unemployed	12 (46.2)	29 (36.7)	41 (39.0)
	Social assistance	0(0.0)	0(0.0)	0 (0.0)
	Disabled	0(0.0)	0(0.0)	0 (0.0)
	Other	0(0.0)	0(0.0)	0 (0.0)
	Retired	2 (7.7)	7 (8.9)	9 (8.6)
	Student	2 (7.7)	4 (5.1)	6 (5.7)
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)
	TOTAL	26 (100)	79 (100)	105 (100)

a) Simplest non-significant model: M, YS (M=Migraine, Y = Social status, S = Site).

D.F.	Likelihood-ratio Chi-square (G^2)	Probability	Pearson Chi-square (X^2)	Probability
12	19.05	0.08	15.62	0.20

b) Stepwise modeling by deleting effects: The best model found was no different from the original model.

c) Stepwise modeling by adding effects (simple and multiple methods): the best model found was MY, YS.

Model	D.F.	G^2	Probability	X^2	Probability
MY, YS	4	4.69	0.32	4.21	0.37
Difference due to adding MY	8	14.37	0.07		

Table 3

Psychiatric comorbidity in migraine patients: Descriptive characteristics

Variable		n	%
Sex	Masculine	25	24.5
	Feminine	77	75.5
	Total	102	100
Marital status	Single	20	19.6
	Married	70	68.6
	Divorced	10	9.8
	Widow	2	2.0
	Total	102	100
Social status	Work full-time	61	59.8
	Work part-time	8	7.8
	Unemployed	4	4.0
	Disabled	4	3.9
	Other	12	11.8
	Retired	8	7.8
	Student	5	4.9
	Total	102	100
First-degree relatives with migraine diagnosis	Yes	66	64.7
	No	34	33.3
	Unknown	2	2.0
	Total	102	100
First-degree relatives with any mood disorder diagnosis	Yes	57	55.9
	No	30	29.4
	Unknown	15	14.7
	Total	102	100
Current psychiatric diagnoses	Yes	42	41.2
	No	60	58.8
	Total	102	100
Lifetime psychiatric diagnoses	Yes	75	73.5
	No	27	26.5
	Total	102	100
Drug abuse	Yes	12	11.8
	No	90	88.2
	Total	102	100
Other disorders in Axis I or II	Yes	28	27.5
	No	74	72.5
	Total	102	100
Type of disorder	Somatization disorder	*8*	*28.6*
	Personality disorders	*10*	*35.7*
	Eating disorders	*3*	*10.7*
	SAD	*4*	*14.3*
	Adjustment disorders	*3*	*10.7*
Use of psychiatric medications	Yes	37	36.3
	No	62	60.8
	Unknown	3	2.9
	Total	102	100
Axis III co-morbidity	Yes	34	33.3
	No	67	65.7
	Unknown	1	1.0
	Total	102	100

Type of co-morbidity	Asthma	6	17.7
	Cardiovascular	6	17.7
	Hypothyroidism	6	17.7
	DM	1	2.9
	Fybromyalgia	4	11.7
	Cancer	3	8.9
	Neurological	1	1.9
	Gastric	3	8.9
	Other	4	11.7
Suicidal behaviour	Yes	11	10.8
	No	91	89.2
	Total	102	100
Migraine subtype	Migraine with aura	17	16.7
	Migraine without aura	85	83.3
	Total	102	100
Psychiatric hospitalizations	Yes	7	6.9
	No	95	93.1
	Total	102	100

TABLE 4

CURRENT AND LIFETIME PSYCHIATRIC COMORBIDITY IN MIGRAINE PATIENTS

Variable		Current (%) n = 42	Lifetime (%) n = 78
Mood Disorders			
	Major Depressive Episode	5 (11.9)	19 (24.4)
	Major Depressive Disorder	17 (40.5)	31 (39.8)
	Dysthymia	3 (7.1)	4 (5.1)
	Bipolar Disorder 1	5 (11.9)	5 (6.4)
	Bipolar Disorder 2	8 (19.0)	8 (10.3)
	Other	1 (2.4)	2 (2.6)
	None	3 (7.2)	9 (11.4)
Anxiety Disorders			
	GAD	13 (31.0)	24 (30.8)
	Panic Disorder	4 (9.5)	11 (14.1)
	PTSD	1 (2.4)	1 (1.3)
	OCD	3 (7.1)	3 (3.8)
	Phobic Disorder	6 (14.3)	9 (11.5)
	None	15 (35.7)	30 (38.5)
Psychotic Disorders			
	Psychotic symptoms only during affective episodes	0	2 (2.6)
	Schizoaffective disorder	3 (7.1)	3 (3.8)
	None	39 (92.8)	73 (93.6)
More than one mood disorder		9 (21.4)	9 (11.5)
More than one anxiety disorder		10 (23.8)	13 (16.7)
Both mood and anxiety disorders		26 (61.9)	43 (55.1)

ADDENDUM 2: ID-Migraine

Do you have headaches that limit your ability to work, study, or enjoy life?
Do you want to talk to your health professional about your headaches?

Please answer these questions and give your answers to your healthcare professional.

During the last three months, did you have the following with your headaches? :

	YES	NO
1. Pain is worse on just one side		
2. Pain is pounding, pulsing, or throbbing		
3. Pain is moderate or severe		
4. Pain is made worse by activities such as walking or climbing stairs		
5. You feel nauseated or sick to your stomach		
6. You see spots, stars, zigzags, lines, or grey areas for several minutes or more before or during your headaches (aura symptoms)		
7. Light bothers you (a lot more than when you don't have headaches)		
8. Sound bothers you (a lot more than when you don't have headaches)		
9. Your headaches limited your ability to work, study or do what you needed to do for at least one day		

ADDENDUM 3

LIST OF ABBREVIATIONS

BD	Bipolar Disorder
COPD	Chronic Obstructive Pulmonary Disease
AED	Antiepileptic drugs
HIS	International Headache Society
ICHD- I/II	International Classification of Headache Disorders (First or second edition)
MA	Migraine with aura
MO	Migraine without aura
OR	Odds ratio
CO_2	Carbon dioxide
NO	Nitric oxide
NOS	Nitric oxide synthase (page 17)
CSD	Cortical spreading depression
CBF	Cerebral blood flow
TGVS	Trigeminovascular system
5-HT	5-Hydroxytriptamine
NTG	Nitroglycerine
SSRI	Selective serotonin reuptake inhibitors
CGRP	Calcitonin gene-related peptide
SP	Substance P
NK	Neurokinin receptors
VIP	Vasointestinal polypeptide
BMI	Body Mass Index
OX	Orexine
MZ	Monozygotic
DZ	Dizygotic
FHM	Familial Hemiplegic Migraine
MELAS Syndrome	Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like
mtDNA	Mitochondrial DNA
PAG	Periacueductal gray
PET	Positron emisión tomography
DTI	Difusión tensor magnetic resonance imaging
MR	Magnetic resonance
WMH	White matter hyperintensities
NAA	N-acethyl-aspartate
CREB	cAMP responsive element binding protein
XBP-1	X-box binding protein 1
ER	Endoplasmic reticulum
INNP1	Inositol polyphosphate-1-phosphatase
BDNF	Brain derived neurotrophic factor
PLCγ1	Phospholipase γ1
IMPA	Inositol monophosphatase

SNP	Single nucleotide polymorphism
TPH2	Tryptophan hydroxylase 2
GABA	Gamma amino butyric acid
DAOA	D-amino acid oxidase activator
NMDA	N-methyl-D-aspartate
DTNBP1	Dystrobrevin-binding protein 1
MAO	Monoamine oxidase A
COMT	Cathecol-O-methyltransferase
IMPA-2	Inositol monophosphatase 2
PLCG1	Phospholipase Cγ1
TRPM2	Transient receptor potential cation channel
SYBL1	Synaptobrevin-like 1
GSK3β	Glycogen synthase kinase 3- β
NRG	Neuroregulin
DISC1	Disrupted in schizophrenia gene
NCAM	Cell adhesion molecule, neural 1
PER3	Period homolog 3 gene
ARNTL	Aryl hydrocarbon receptor nuclear translocato-like gene
CLOCK	Circadian locomotor output cycle kaput
GWA	Genome-wide association studies
DGKH	Diacylglycerol kinase eta
AAO	Age at onset
MDD	Major depressive disorder
GAD	Generalized anxiety disorder
OCD	Obsessive compulsive disorder
ADHD	Attention Deficit and Hyperactivity Disorder
DM	Diabetes mellitus
MBR	Maritime Bipolar Registry
MUHC	McGill University Health Center
SADS-L	Schedule for Affective Disorders and Schizophrenia, Lifetime version
RDC	Research Diagnostic Criteria
SCID	Structured Clinical Interview for DSM-IV Disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ANOVA	Analysis of Variance
LLM	Log-linear model
5HTTPLR	Serotonin transporter gene promoter polymorphism
PFO	Persistent foramen oval
MMPI	Minnesota Multiphasic Personality Inventory
MIDAS	Migraine Disability Assessment Questionnaire
WHO	World Health Organization
DALYs	Disability-adjusted life years

LLM only-used abbreviations

M	Migraine
S	Site
D	Diagnostic subtype
G	GAD
O	OCD
P	Panic Disorder
A1	Social phobia
A2	Attention Deficit Disorder
A3	Substance abuse
B	BMI
D	DM
T	Thyroid abnormalities
H	Systemic hypertension
G2	Gender
W	Marital status
Y	Social status

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