Psychiatric Comorbidities Associated with Headaches: the Experience of the Liaison Consultation

Comorbilidades Psiquiátricas Associadas às Cefaleias: a Experiência da Consulta de Ligação

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ABSTRACT

Introduction: The comorbidity between headaches and psychiatric disorders is common and may be explained by different mechanisms in terms of uni or bi-directional models, or sharing of genetic and environmental risk factors relating to development of both clinical conditions. The presence of this comorbidity has important implications for patients with headaches and for patients with psychiatric disorders, worsens the clinical situation, increases the risk of chronicity, the pain intensity and the rate of treatment failure.

Material and Methods: The authors performed a descriptive, retrospective study of prevalence, involving 250 patients seen in Psychiatry - Headaches liaison consultation, over a period of 3 years, from July 1, 2011 to July 1, 2013. The authors undertook the analysis of the clinical records, in respect to sociodemographic and clinical data, neurological and psychiatric diagnosis and prescribed therapy.

Results and Discussion: During this period were made 689 liaison consultations, with a prevalence of female patients (84%) and a mean age of 47 years. The tension type headache (60.8%), migraine (24.8%) and headache attributed to psychiatric disorders (7.2%) were the most prevalent types of headaches. Mood disorders (62%) and neurotic stress related disorders (39.2%) were the most frequent psychiatric diagnoses. The therapeutic intervention in these cases emphasizes the multidisciplinary approach with the collaboration of Neurologist and Psychiatrist, based in psychoeducation, cognitive-behavioral intervention and psychopharmacological treatment.

Conclusion: Given the complexity of the clinical picture in cases of comorbidity, the experience of psychiatry liaison consultation and multidisciplinary intervention has proved particularly valuable in treating these patients, configuring itself as the proper treatment of this comorbidity.

Keywords: Comorbidity; Headache; Mental Disorders; Psychiatry.
includes painful cranial neuropathies, other facial pains and other headache disorders.

Primary headache disorders are generally considered as chronic disorders and not just relapsing episodes of an acute headache. They are dynamic conditions that may progress or remit, with clearly identified structural and neuro-radiological markers. Despite the lack of pathognomonic biomarkers for migraine, several imaging studies have demonstrated changes in cerebral blood flow. A regional reduction in cerebral blood flow (cerebral oligemia), mainly in posterior cerebral regions, has been found during migraine crisis with the typical aura symptoms. In contrast, an increase in cerebral blood flow has been found in the medial brainstem, predominantly contralateral to the headache as well as in cingulate, auditory and visual association cortices, during migraine without aura. An increase in white matter lesions has been demonstrated by MRI (magnetic resonance imaging) studies in patients with migraine.²

Neuropsychiatric changes are not unexpected as these relate to neurobiological disorders. Comorbidity of headache and psychiatric disorders is frequent and may be explained by different mechanisms, using one or two-way models as well as sharing genetic and environmental risk factors. The presence of this psychiatric comorbidity has an impact on treatment of patients with migraine, imposing limitations and creating opportunities that allow for a study of the underlying pathophysiological mechanisms that are shared by both conditions.³

A high level of clinical suspicion is needed in a patient presenting with a headache disorder in order to diagnose psychiatric comorbidities, requiring the use of clinical scores aimed at screening these disorders, including several quick inventory depression or anxiety scales, examples of which are the Generalized Anxiety Scale (GAD-7) or the Patient's Health Questionnaire (PHQ-9).

Psychiatric comorbidities relate to headache progression and worsening, to adverse treatment results and more specifically it is known that depression is associated to the transformation of acute into chronic migraine episodes and to negative outcomes such as suicidal attempts.⁴ Psychiatric comorbidities diagnosis and treatment are of major importance as they have a known impact in terms of increased disability and a worse quality of life when compared to patients with headache and no psychiatric comorbidity.⁵

The depressive and anxiety disorders are clearly the psychiatric comorbidities most frequently associated to all types of primary headache disorders and different studies have shown their increased prevalence, namely at tertiary healthcare level.

Tension-type headaches are the most frequent primary headache disorders, with a 30 to 78% lifelong prevalence⁶ and its comorbidity with depressive and anxiety disorders is frequent due to a known association to stress factors.

However, migraine is the major neurological cause for seeking primary healthcare, due to associated clinical characteristics and disability.⁶ Approximately 1/3 of the patients attending primary healthcare present with criteria for migraine⁷ and a large percentage present with some comorbid psychiatric disorder, more so in patients with chronic migraine, which may be characterized by headache in 15 or more days per month, lasting over 3 months, with the clinical characteristics of migraine present in at least 8 days per month.¹

Some studies suggest that mood and anxiety disorders are approximately 2 to 10 times more prevalent in patients with migraine when compared to general population and that approximately 25% of these patients meet criteria for mood and anxiety disorders.⁵³

The prevalence of depressive disorders in patients with migraine is variable according to studies and methodology, between 4.3 and 47%, twice as frequent in patients with chronic vs. episodic migraine.¹⁰ Depression is one of the major risk factors for chronic migraine, beyond others, such as medication overuse, obesity, sleep disorders or other psychiatric comorbidities. This effect depends on symptom intensity and increased severity leads to a higher risk of chronicity. Despite a lack of correlation between depression improvement and conversion of chronic into acute episodes,¹¹ a reduction in the frequency of headache episodes may improve depressive and anxiety symptoms.

Breslau et al.¹² showed a two-way relationship between depression and migraine, in which depression anticipates a new migraine and migraine increases the incidence of major depression. However, only a one-way relationship has been shown for other types of primary headache disorders, in which headache increases the incidence of depression but depression does not predict other de novo headache disorders, except migraine. These evidences allow for the conclusion that the mechanisms of comorbidity are different according to the type of headache

Anxiety disorders, including Generalized Anxiety Disorder (GAD), Panic Disorder, Obsessive-Compulsive Disorder (OCD) and specific phobias are twice as prevalent in comorbidity with migraine than in general population. Approximately 50.7 to 57% of patients with migraine present with anxiety disorders, when compared to 27% in general population without migraine.⁸ The prevalence of comorbid GAD with migraine varies between two to five times higher than in the general population and panic disorder may be three times more prevalent in patients with migraine.⁸ Anxiety disorders are also considered as a risk factor for chronic migraine and are considered to aggravate
The presence of episodes of aggressive and agitated behaviour is common during cluster headache crisis. Some neuroimaging studies show their relationship with brain structures as the posterior hypothalamus, suggesting that neuro-stimulation therapy of this area may contribute to an improvement in behavioural changes that have been correlated to depressive symptoms and disability.

Death thoughts and suicidal ideation may occur in patients with headache disorders, namely in chronic cluster headache, corresponding to 22% of the patients and to 4% of the patients with migraine.17

Underlying mechanisms to comorbidity

Headache disorders involve the entire brain, namely the hypothalamus, a structure involved in the development of anxious and depressive symptoms.

Depression has been correlated to glucose metabolic changes within the insular cortex in studies involving neuroimaging in patients with cluster headache and disability associated to pain has been correlated to changes within the amygdala, both structures associated to the pathogenesis of anxiety and depression.16

There are common genetic and behavioural risk factors involved in both conditions, beyond the accepted two-way model for the comorbidity of psychiatric and headache disorders. A significant family expression was found both in headache disorders and in some comorbid psychiatric disorders, allowing for a syndromic relationship to be established between both conditions, shown in genetic studies.19

Genetic and behavioural risk factors produce latent brain conditions that induce both headache and psychiatric disorders, as shown by neuroimaging evidences. Different areas are activated during a headache crisis, such as the hypothalamus, the limbic region or the cortex. Secondary signs of pain are driven through trigeminal-vascular nerve endings to areas of the brain involved in the production of headache or depressive disorders.18

In line with this hypothesis, some authors propose that a serotonergic and dopaminergic dysfunction may explain comorbidity of depression and headache disorders. Abnormal levels of serotonin, a decrease in cortisol levels and an increase in prolactin are found during crisis of headache and frequently treated with triptans that are selective agonists of serotonin receptors. Experimental studies suggest that patients with anxiety disorders and patients with headache disorders, namely with migraine, show common polymorphisms in the 5-HT transporter gene. The receptors of serotonin are involved in the generation of circadian rhythm at the hypothalamus and may be a target for pharmacological treatment of patients with headache disorders. It follows that antagonists of 5-HT receptors have been suggested as rapid-action antidepressants. The relationship between depression, anxiety and serotonergic dysfunction is well known and therefore it is reasonable to...
establish that the biologic liaison between headache, mood and anxiety disorders is due to an aberrant activation of neurons in the brain, more specifically in the serotoninergic system.

Migraine usually presents with dopaminergic symptoms such as nausea and vomiting and different studies have shown high levels of dopaminergic receptors in circulating lymphocytes of patients with migraine, suggesting the presence of a hypo-dopaminergic status in these patients. The connection between dopamine deficiency and depression is well known and it is possible that the dopamine decrease may contribute to comorbidity of depression and headache disorders. Researchers believe that migraine and depression may be mediated through a neuronal cascade of events leading to central sensitization, from which cutaneous allodynia is a marker, corresponding to a status where neurons are abnormally excited, leading to a reduction of pain threshold and to hypersensitivity to harmful and harmless triggers. The patients with migraine and depression present with a more severe cutaneous allodynia than patients with migraine but without depression, confirming the hypothesis of a latent brain state underlying the development of these two conditions.

The production of inflammatory cytokines may also underlie the relationship between migraine and psychiatric disorders, namely BAP. In the latter, high levels of several interleukins and interleukin receptors are thought to be repeatedly released during a headache crisis and these disorders may have an impact on the development of depressive symptomatology.

Behavioural risk factors such as the consumption of substances, brain injuries, sleep disorder and the coexistence of migraine, increase the risk of development of a cluster headache crisis. Sleep disorders, namely sleep deprivation or extended sleep, may promote the crisis of headache disorders, namely migraine; it should be pointed out that sleep may be crucial towards the resolution of a crisis of headache. A history of childhood abuse has been shown to be a risk factor for this comorbidity, as well as the frequent use or overuse of medication.

**MATERIAL AND METHODS**

The authors carried out a prevalence descriptive and retrospective study involving 250 patients attending a headache outpatient clinic in liaison with Psychiatry Department over a three-year period, between 1st July 2011 and 1st July 2013 and including the analysis of clinical records as regards clinical and demographic data, the presence of a psychiatric and neurological diagnosis, as well as therapy.

**RESULTS**

In total, 84% (n = 210) of the 250 patients followed at the outpatient clinic were female.

The average age was 47, with a higher prevalence of patients between 41 and 50 years of age, from a minimum of 24 up to a maximum age of 73 years of age (Table 1).

According to the International Classification of Headache Disorders, 3rd edition, published by the International Headache Society (ICHD-3 beta), tension-type headache was the most prevalent, corresponding to 60.8% of our group of patients (n = 152) (Fig. 1). Migraine corresponded to 24.8% (n = 62) and headaches attributed to psychiatric disorders occurred in 18 patients (7.2%). Other secondary headaches (such as cluster headache and trigeminal neuralgia) were also observed in lower percentages.

Depressed mood (n = 195; 78%), asthenia (n = 130; 52%), insomnia (n = 120; 48%), anxiety and irritability were the psychiatric symptoms most frequently described by patients (Fig. 2). As regards psychiatric diagnosis ranked according to the ICD-10, mood disorders (F30-F39) were present in 62% of the patients (n = 187) and stress-related neurotic disorders (F40-F48) in 39.2% (n = 98) were the most prevalent. Among mood disorders, the most prevalent were major depressive disorders, recurrent and single episodes (Fig. 3).

Somatoform disorders and personality disorders were also among the most prevalent in patients with headache disorders.

Figure 1 - Types of headache disorders diagnosed in our group of patients

Figure 2 - Psychiatric symptoms more prevalent in our group of patients

Figure 3 - Psychiatric diagnosis, according to the ICD-10, found in our group of patients
The therapeutic approach was mainly oriented to depression symptoms, to normalisation of the circadian rhythm and to solving anxious paroxysms. Several therapeutic strategies were useful, namely psycho-education, psychotherapy and psychopharmacology. Antidepressants, mainly SSRI, namely sertraline and fluoxetine, antiepileptic drugs (topiramate) and anxiolytic drugs, namely benzodiazepine were the most frequently used, which often were already part of patient’s medication and difficult to be stopped (Fig. 4). Approximately 45 patients were on a tricyclic antidepressant such as amitriptyline and 65 patients were on other antidepressants, including trazodone.

DISCUSSION
In total, 689 medical visits were carried out over a three-year time period, with an increasing number of first medical visits, mostly referred through the Neurology Outpatient Clinic.

In our group of patients, we found that most were female (84%), with an average age of 47, mostly in the 41-50 age group (38%), from 24 to 73 years of age. Tension-type headaches were the most prevalent (60.8%) followed by migraine (24.8%) and headaches attributed to psychiatric disorders (7.2%), in line with previous reports.

Most patients presented with comorbid psychiatric symptoms, namely a depressed mood (78%), insomnia (48%) and anxiety (42.8%), although physical symptoms such as asthenia were also described (52%). The mostly diagnosed psychiatric disorders were mood disorders (F30-F39) in 62% of the patients (n = 187), stress-related neurotic disorders (F40-F48) in 39.2% (n = 98), recurrent major depressive disorders and dysthymia. Most of the times, the presence of psychiatric disorders aggravate the clinical presentation, increasing the risk of headache chronicity, pain intensity and the rate of therapeutic failure. These contribute to headache disorders featuring as one of the major causes for attending healthcare settings.

Therapy should mainly involve a multidisciplinary Neurology/Psychiatry approach. A psycho-educational and psychological, mainly involving a cognitive-behavioural approach, are crucial in these patients. However, psychoactive medications have a therapeutic role in prophylactic terms and in the treatment of depressive events underlying the somatic symptoms related to headache disorders. Antidepressants, namely SSRI were the most used (76%), as well as benzodiazepines (35%). Anti-epileptic agents showed their efficacy mainly in prophylactic terms and were used in 57% of the patients. Other classes of antidepressant agents, namely trazodone (a SSRI) and venlafaxine (a SNRI [Serotonin and Noradrenalin Reuptake Inhibitor]) were also used.

CONCLUSION
The association of headache with comorbid psychiatric disorders has a major influence on the clinical progression and treatment of patients presenting with both clinical conditions, contributing to a worse outcome and quality of life. After three years of experience within an Outpatient Headache Liaison Clinic with Psychiatry, the authors support a multidisciplinary approach, with early intervention and awareness regarding the presence of such comorbidity as a better option for the follow-up of these patients, aimed at reducing complexity and chronicity of underlying clinical conditions.

Figure 4 - Pharmacological treatment prescribed to our group of patients (SSRI: Selective Serotonin Re-uptake Inhibitors).
CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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