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Primary headache and comorbidity with mood and anxiety disorders: an example of the psycho-neuro-biological loop

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Abstract Although an association between primary headache and psychiatric disorders has been recognised for over 100 years, this association has been investigated systematically only recently. The nature of this association has also been examined in recent studies. Real comorbidity implies that primary headache and psychiatric disorders are indipendent phenomena, i.e. a casual co-presence, while the frequency of their association suggests different and deeper links. Literature data show that psychiatric comorbidity in migraine and tension-type headache is very similar (88% and 85% respectively). Anxiety disorders is the most frequent association (54.9% and 52.5% respectively) followed by mood disorders (34.4% and 36.4% respectively). We discuss the available evidence on the psycho-neuro-biological cascade of events possibly linking primary headache to mood and anxiety disorders.

Key words Psychiatric comorbidity • Primary headache • Mood disorders • Anxiety disorders • Psychiatric disorders

Introduction

Edward Leiving described the psychiatric symptoms of migraine, depressed mood, irritability, anxiety, fatigue and impaired memory concentration over 100 years ago [1, 2]. Although this pioneer observation has been confirmed in successive studies conducted over decades in both psychiatric and neurological settings, it is only recently that the psychiatric comorbidity with primary headache [3] has been systematically examined. A review of the most important studies suggests that an association exists between either tension-type headache or migraine and psychiatric disorders, mood disorders and anxiety disorders, giving rise to a gross body of studies on the nature of their relationship.

One of the first contributions on this matter came from Stewart et al. [4] who found evidence for a strong association between migraine and anxiety, and described a higher incidence of migraine in male subjects with panic disorder, compared to normal controls. A prevalence of 2.5% anxiety and mood disorder has been shown in a sample of 162 young subjects suffering from migraine compared to subjects with no history of migraine [5]. Moreover, Breslau et al. [6] reported psychiatric disorders in 88% of migraine subjects, anxiety disorders in 54%, major depression in 34% and a higher lifetime rate of suicide attempts.

A few years later, Merikangas et al. [7] reported an increased frequency of psychiatric comorbidity in migraine patients with aura; this included elevated rates of mood disorders (e.g. hypomania, dysthymia, major depression, recurrent brief depression), and anxiety disorders (e.g. generalized anxiety disorder, panic disorder, simple phobia, social phobia and agoraphobia). Evidence clarifying the relation-

ship among these disorders also came from follow-up studies which provide information about the course or sequence of disorders and indicated that the age at onset of anxiety disorders generally preceded that of migraine and that in the majority of comorbid subjects studied the onset of mood disorder followed that of migraine [7].

Supporting these findings, Breslau and Davis [8] found a 4-fold increased risk for new onset mood disorder and/or anxiety disorder in patients with migraine compared with subjects without migraine during the 12 months after a migraine attack.

Thus, migraine has been commonly accepted to be tightly associated with anxiety and mood disorders as well as with isolated psychopathological phenomena, such as insomnia or demoralization which may not lead to a nosographically classified syndrome, but indicate that many subjects with migraine have at least hidden and isolated psychopathological features. Likewise, the ubiquity of psychiatric comorbidity related to tension-type headache has been widely accepted, with the important exception of a group of researchers who found that the frequency of psychiatric disorders in this type of headache is not higher than that expected in the general population [7].

The Italian contribution in the field of the cephalalgic pathology has been a great support. The Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headaches carried out a multicenter study in 10 Italian headache centers, in order to investigate the prevalence of psychiatric disorders in a wide sample of patients suffering from tension-type headache [9, 10]. This study found a psychiatric comorbidity, which sometimes was multiple, in 85% of patients with tension-type headache. The authors observed that dividing the sample of patients into three main clusters on the basis of their psychiatric disorder (anxiety, depression and somatoform disorder), the most recurrent cluster was anxiety (52%), followed by depression (36%) and to a less degree somatoform disorder (21%). Generalized anxiety disorder (83%), dysthymia (46%) and somatoform pain disorder (36%) were the most frequent disorders within their respective psychiatric clusters. This study concluded that psychiatric comorbidity was more frequent in the chronic than in the episodic form of tension-type headache, without any correlation with sex or with the other variables examined [9].

In daily chronic headache, the comorbidity with an anxiety or mood disorder was even higher, reaching even 90% of the cases [11].

In addition to studies on the association with psychiatric disorder, studies on personality features of patients with headache are also important and even more interesting because they may provide more insight into the nature of this association, which is something that the concept of comorbidity does not consent to determine. When Merikangas et al. [7] examined the personality profile of patients with tension-type headache, using both the Freinburg Personality Inventory and the Symptom Checklist-90 Scale, they did not find any relevant difference compared to the profile of a control sample of subjects. On the other hand, Schaefer [12] emphasized the presence of the "typhus melancolicus" personality trait in migraine subjects who showed high levels of neuroticism, overly strict standards of behaving, low levels of tolerance to frustrations and extroversion. Breslau and Andresky [13] substantially confirmed these findings and reported that migraine subjects in their study had a higher score on the Eyseneck Personality Questionnaire's Neuroticism Scale compared with healthy controls. Moreover, some authors sustained that the "hysteric" personality trait may represent a condition of vulnerability to migraine [14].

Causal association or mutual facilitation

This brief review of the literature on psychiatric comorbidity with primary headache reveals that their co-existence is still open to several interpretations that range from the hypothesis of a casual association, unlikely for the high rate of concordance observed, to the hypothesis of mutual facilitation. Recent progress in studying cerebral function and its pathophysiology more likely supports this last issue.

Psychiatrists have always accepted this co-existence as a natural outcome within the concept of psychosomatic medicine, which considers primary headache to be a symptom or even a factor that "masks" a psychiatric condition. This is the meaning of the concept of "depressive equivalent" and "masked depression" for which the headache as a somatic symptom hides the real expression of the underlying affective disorder and replaces it [15].

In a similar way, the North American Psychometric System included headache among the items of some standardized rating scales for anxiety and depression [16, 17]. In the DSM-IV, primary headache is among the diagnostic criteria of some syndromes [18].

Regarding tension-type headache, the position of the International Headache Society (IHS) is similar. In 1988, in addition to the usual diagnostic criteria, they included seven new, probable "causal" factors. Five of these factors are associated either directly or indirectly with psychopathology, ranging from anxiety to depression, and from hallucination to delusion and to psychosocial stress [3]. Thus, the IHS classification also recognizes at least the intervention of psychogenetic factors in the pathogenesis of tension-type headache, which remains a strictly somatic pathology.

All the knowledge gained in the last few years on the neurobiological effects of experience as well as on the neu-

rochemical correlates of life allows us to consider the possibility of a mutual interaction, so that we can assume either that anxiety or depression induces headache or, on the other hand, that cephalalgic suffering makes the subject vulnerable to psychopathological experiences. The basis of this model, within the neuronal plasticity theory, lies in the fact that every psychological condition and every life event, through the activation of a complex chain of events that involves both neuroendocrine and immunological systems, modify the psychobiological balance of the organism. This may cause homeostasis alterations in the attempt to re-establish balance [19, 20]. The way of reacting is greatly individual but it is influenced by numerous factors, either accidental (impact with the environment) or pre-established (genetic set), which concur to model the personality, the behavior and the ability to face the events of life [21]. Every stressing life event is followed by a sequence of mechanisms of either psychological or biological nature which can affect the onset and the course of somatic pathologies and which increase vulnerability to psychopathological events [22]. In this model, psychosocial stress, anxiety disorder, mood disorders and the different forms of primary headache may constitute links in the same chain in which psycho-neuro-biochemical events can modify or even facilitate the course of the disorder with repercussions on the psychological or somatic side, through the neurohumoral and neuroendocrine effects of stressors, and through the organism's ability to adapt [22].

Headache comorbidity with anxiety and mood disorders and, conversely, the frequent finding of cephalalgic pain in subjects suffering from anxiety and depression suggest again the existence of a circular vulnerability between psychiatric conditions of the affective spectrum and chronic somatic pathologies. Therefore, differences in the results reported by the differents authors may be due to the time at which the patients' histories were recorded rather than to real differences in psychiatric comorbidity.

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