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## Psychopathological factors in chronic headache: an overview

### Introduction

The primary goal of this study conducted on chronic daily headache by the Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headache was to seek for factors able to influence the complex process of transformation of an episodic headache into a chronic one by the analysis of headache characteristics, analgesic abuse, life events occurrence, psychopathological traits and psychiatric symptoms and disorders. The first step was the choice of an objective method based on the utilization of a computerized survey tool planned for analyzing the clinical and neuropsychological characteristics of a broad sample of chronic primary headache patients.

The diagnostic controversies rising from the absence of a nosographic position for chronic daily headache in the current international headache classification [1] were solved by the use of a standard based on a frequency higher than 15 attacks for months and a duration more than 6 months. Data collected by means of the clinical interview allowed the further classification of chronic headache into three types: chronic migraine (CM), chronic tension-type headache (CTTH) and chronic coexisting migraine and tension-type headache (CCMTTH).

Data were analyzed according to daily chronic headache subtypes and analgesic abuse occurrence on a total sample of 245 subjects coming from nine Italian headache centers.

### Headache characteristics

The analysis of headache sample showed that in most cases the type of episodic headache preceding the chronic form was migraine without aura (182 cases, 75.20%). These results are in agreement with the report of Mathew [2] who found a prevalence of 77.91%.

The most frequent type of chronic daily headache in this study was chronic coexisting migraine and tension-type headache (114 cases, 46.5%), followed by chronic migraine

(74 cases, 30.2%) and chronic tension-type headache (57 cases, 23.3%). Women prevailed in all forms of CDH, more markedly in CCMTTH and CM. The age at onset of CDH was placed within the fourth decade for all the forms, even though CCMTTH tended to begin earlier.

The proportion of patients who showed a daily use of analgesics, independently from the dose, was 64.1%.

In CTTH the prevalence of analgesic abuse was 37%, significantly lower than in both CCMTTH (61%) and CM (89%).

### Memory impairment

The percentage of subjects with memory impairment varied in the range of 49%-69% in the different types of tests assessing visuospatial memory and in the range of 2%-52% in the field of verbal memory, without statistical differences between drug abusers and nonabusers. The visuospatial memory presented a whole impairment (short and long term), whereas the verbal memory showed a greater deterioration in long-term phase.

No difference was found in memory deficits among the various types of CDH. A higher prevalence of memory impairment was found within the patients with migraine as onset headache than in those with a new daily persistent headache (98% vs. 0:  $p < 0.05$ ). Patients with low performances on the delayed test of Buschke's procedure showed a longer mean duration of headache.

According to these results, memory function did not depend on drug overuse, nor on the current type of headache. A widespread impairment of memory functions in adult headache sufferers has already been reported in previous studies [3]. The longer duration of disease may explain why adults show poorer performances than juvenile patients [4]. Memory impairment in headache sufferers seems unlikely to be explained by a clear-cut neuro-anatomical damage since that assumed cerebral lesion should be quite small not to cause other neurological disorders than memo-

ry deficits but quite extended to result in an involvement of both short- and long-term memory. Memory impairment could be more reasonably caused by a neurotransmitter disorder involving both serotonin, the short memory neurotransmitter and glutamate, the long memory one [4].

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### **Anxiety and depression assessed with Zung's scores**

When administering Zung's anxiety and depression scales, higher scores than the cut-off values were found in 62.1% and 61.7% of the CDH patients, respectively. No statistical difference was revealed in anxiety and depression mean levels, either among the subtypes of CDH or among the various kind of onset headache. In the same way no difference was found between drug abusers and non abusers.

Women showed both anxiety and depression scores higher than males. This result is in agreement with a previous study by Mitsikostas and Thomas [5] who reported a prevalence of anxiety and depression, assessed with Hamilton's scales, twice as high in women than in men. A positive correlation was observed between age at chronic headache onset and anxiety score as well as depression score.

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### **Stress**

A total of 44 (9%) of CDH patients reported a deterioration of their chronic headache following a stressful event. Stress was moreover mentioned as a trigger of previous episodic headache in 36.4% of the cases of chronic headache resulting from the progression from an episodic form.

What is more important is that 44.8% of patients indicated that the passage from the episodic to the chronic form was correlated with a stress factor, thus suggesting the existence of a relation between stress and this transformation process. Stressful events were due to health problems in 35.6% of cases, family and social problems in 17% of cases, marriage in 13.6%, bereavement in 13.6%, and work-related issues in 11.4%. Less frequently, legal, education, courtship and cohabitation, financial and migration-related problems were mentioned. Of the patients in whom chronic headache had developed from episodic headache 154 (64.4%) reported a minor stressful event in coincidence with this change, while only 85 (35.6%) indicated a major event. These findings indicate that minor events (which we call daily hassles) play a greater role in transforming headache than major events (as we defined them), suggesting that patients with chronic headache are characterized not by greater exposure to major stressful events, but by a different way of reacting to stress.

### **SCL-90R**

When examining the Symptom Check List 90R (SCR-90R) profile of CDH patients, T-scores higher than 60 were found in all dimensions except for hostility and in all the three general indices. The comparison according to gender showed a percentage of patients with somatization T-score >60 statistically more elevated in women (71.9%) than in men (51.02%). No difference was found either between analgesic abusers and not, or among the three subtypes of CDH. A positive correlation emerged between somatization score and patients' age, between somatization score and chronic headache onset age, and between the index of positive symptoms distress and chronic headache duration. These results suggest that the way of living and expressing pain may change as age increases and that when chronic headache lasts too much, the patients tend to overestimate symptoms. This evidence demonstrates that SCL-90R is a useful tool for a complete evaluation of chronic headache subjects.

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### **Rorschach**

The mean number of responses given from the sample of chronic headache patients was lower than standard, indicating either a poor imaginative and intellectual productivity or a reduced affective participation in reality. The analysis of contents showed a high percent of animal themes (48.40%). These data suggest a psychological and clinical condition of inhibition beyond an affective and ideative uniformity. The high number of anatomic and radiographic contents of the responses configured a clear hypochondriac concern. The analysis of particular phenomenology revealed the high occurrence of anxiety and depression traits. The psychopathological features may play a major role in predisposing patients to chronic headache.

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### **SCID-IV**

The prevalence of psychiatric disorders according to DSM-IV criteria was 66.1% (33.9% anxiety disorders, 14.51% depression disorders, 12.1% drug abuse disorders, 0.8% somatoform disorders and in the remaining part various combinations of them). Altogether an anxious disorder was found in 57 cases (45.96%), a depressive disorder in 41 cases (33.06%), a somatoform disorder in 5 patients (4.03%) and an analgesic abuse disorder in 23 cases (18.54%). The apparent discrepancy between the data on

analgesic abuse obtained with the clinical interview (64.1%) and those derived from the SCID interview (18.54%) are easily explained by the latter being based on DSM-IV criteria that are more rigorous than the former and involving the social functioning impairment. No statistical difference was found in psychiatric comorbidity according to gender (women, 68.9%; men, 52.4%). The prevalence of psychiatric disorders was 69.7% in drug abusers (classified in accordance with clinical interview) and 57.14% in nonabusers (difference not statistically significant). Comparing the three subtypes of CDH, a psychiatric disorder was found in 50% of chronic tension-type headache patients, in 72.2% of those with chronic coexisting migraine and tension-type headache (CT vs. CCMTTH,  $p < 0.01$ ) and in 70.3% of chronic migraine patients.

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### SIP-IBQ

Summarizing the results of this study, it can be asserted that the patients with chronic headache showed a remarkable impairment in most of their daily activities and at the same time they seemed to live in a very bad way their illness. Such alterations increase with the patient's current age and age at chronic headache onset. The longer is chronic headache duration, the more disability is marked. Women have a more severe profile than men, both in SIP and in IBQ. Analgesic abusers showed some differences in comparison to nonabusers, consisting in a greater difficulty in communication and a more marked tendency to consider themselves as affected by a psychological disease. Abusers showed higher levels of irritability indicating feelings of anger and an awareness of interpersonal friction. Moreover their elevated scores in hypochondriasis index indicate their current fears and concerns about headache. Chronic migraineurs' profile was more impaired in irritability and social interaction than other chronic headache sufferers' one. This last result might be due to pain severity which is greater in migraine than in tension-type headache. These results suggest that the complaint of disability and of an abnormal way of living their illness should always be searched for and, where present, discussed as relevant elements both for diagnosis and treatment.

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### A possible interpretation

This study failed to demonstrate noticeable differences either in stress factor occurrence, or in memory deficit, psychopathological features and psychiatric comorbidity between analgesic abusers and nonabusers, thus suggesting

that drug abuse does not influence these kinds of comorbidity. The high prevalence of daily analgesic intake by chronic headache patients with a migraine component of pain may indicate a key role of drug abuse for chronic evolution of headache (though only for migraine), but may also simply be due to a greater severity of migraine than tension-type pain. An indirect confirmation of the minor role played by drug overuse in headache progression comes from the absence of reports concerning an increased headache incidence or a habit due to analgesic use in patients suffering from chronic arthritis. In contrast, analgesic intake is recommended in these patients and analgesic withdrawal is considered as non-compliance by physicians [7]. Moreover, several studies demonstrated that there is no evidence of addictive personality [8] or of sensation seeking behaviors in headache patients [9].

The most important result of this study is the evidence of high comorbidity between chronic headache and psychiatric disorders, especially frequent in the chronic coexisting migraine and tension-type headache and in chronic migraine, thus underlining the importance of the "migrainous component" of pain in the association with psychiatric pathology.

A possible interpretation of the results of chronic headache comorbidity with psychiatric disorders is furnished by recent advances in the knowledge of neurobiological effects of experience and of neurochemical correlates of life functions, which allow to consider the possibility of a mutual interaction between somatic and psychic fields. We can assume either that anxiety or depression induces headache or that head pain in its turn makes the subject vulnerable to the psychopathological experience. This model is based on the neuronal plasticity theory and lies in the fact that every psychological condition and life event modifies the psychobiological balance of the organism through the activation of a complex chain of events, which might involve both the neuro-endocrinological and immunological systems. The way to react is mostly 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 [10]. In this model of psychosocial stress, anxiety disorder, mood disorders and the different forms of primary headache constitute links of 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 organisms ability to adapt [11], so configuring a circular vulnerability between psychiatric condition of the affective spectrum and chronic somatic pathologies.

Among the biochemical changes correlated to chronic headache, an important role might be played by a neuro-

transmitter disorder involving serotonin pathways. As a deficit in serotonergic activity results in a defective pain modulation due to the supraspinal disinhibition of nucleus caudalis neurons and in a consequent exaggerated response to painful stimuli (central sensitization), consequently the pathogenesis of chronic daily headache might be underlined by a severe serotonergic hypofunction. Moreover, serotonin has been demonstrated to play an important role in several mental disorders, mainly in depression. Serotonergic hypoactivity might in fact induce depression in some vulnerable individuals. So a common neurobiological basis consisting of an abnormality in serotonergic pool, induced by genetic and/or environmental factors, might give rise to both chronic daily headache and depression.

The results of the present study show that migraine is the most frequent type of onset headache in patients with chronic daily headache. For patients with migraine whose episodes progress from isolated and intermittent to more chronic and daily, Post and Silberstein [12] hypothesized a pathophysiological mechanism similar to epilepsy, generated by the amygdala kindling. According to this model, in an early stage "stresses may not be enough to trigger a migraine attack (development stage), but, with repetition, may be able to evoke them (middle or completed stage); if triggered episode occurs repeatedly, they begin to appear spontaneously (late or spontaneous stage)". At last, "the interval between migraine attacks shortens with each successive recurrence". This illness progression is underlined by "apparent memory-like processes" which may be explained by the kindling model. Really, "transient synaptic events induced by external stimuli can exert longer-lasting effects on neuronal excitability and the microstructure of the brain via a cascade of effects involving alterations in gene transcription". In the early stages, "single stimulation may result in activation of second and third messenger systems, as well as a variety of immediate early genes (IEGs); repeated stimulation effects change in late effector genes (LEGs), such as increases in peptides or decreases in other peptide and receptor systems". Besides, c-Fos and other IEGs are not only induced by pain but also by conditioned stimuli associated with pain and stress: in rats, conditioned stimuli result in a marked and prolonged increase in the flexion withdrawal reflex [12]. So, at least with regard to transformed migraine, a similar mechanism might be hypothesized in human beings too. The recurrent exposure to stressful events could promote on the one hand the onset of migraine as a behavioral answer and on the other hand the onset of an adaption disorders or a real mental disorder. When both somatic (migraine) and mental disorders appear, they begin to support themselves to a chronic evolution of the symptoms.

Talking about the kindling model, it is interesting to observe that some of the neurobiological changes associated represent secondary or compensatory adaptations attempting to counteract the kindling mechanism. This is the case of the increase in GABA-A and benzodiazepine receptors. In fact, GABAergic neurons have been shown in the dorsal horn receiving nociception inputs, so as to exert a presynaptic control on pain [13]. Unfortunately, with the progression of the disorder, the typical attack-induced changes in GABA-A receptors fail to occur whereas a tolerance to previously effective prophylactic agents may develop [14].

A GABAergic hypofunction might contribute to the pathogenesis of the anxiety disorders associated with chronic daily headache. So, once again, an abnormality of one neurotransmitter might explain both progression of headache and psychological disorders.

Moreover, about the kindling model it must be stressed that a great importance is reserved to glutamate so if a decrease in serotonin activity and an abnormal NMDA receptor activation resulting in neuronal excitotoxicity are hypothesized to occur in memory pathways too, a common neurobiological dysfunction might underlie on one hand both short-term and long-term memory impairment, on the other hand the illness progression at least in those chronic daily headache sufferers who presented a migraine as their first onset headache.

Also the neurophysiological findings suggest that a common neuronal dysfunction could predispose to primary headache subtypes, whose chronicization may depend upon many factors, such as the influence of peripheral muscular factors and the dysfunction in central nociceptive modulation which may explain the large variability of clinical features.

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## Conclusions

The results of multiple comorbidity may suggest that chronic headache patients are characterized by a circular vulnerability between psychiatric condition of the affective spectrum and chronic somatic pathologies. This vulnerability derives from both genetic and environmental factors and configures some neurotransmitter dysfunction pattern that produce a certain clinical variability.

However, the possible explanations for the chronic evolution of head pain and for its frequent association with psychological disturbances must not dishearten the clinician. The evolution to a chronic daily headache must not be considered as an unavoidable course of migraine. A complete clinical and neuropsychological evaluation followed by adequate and early treatment, since the juvenile age when it is necessary, by reducing the frequency of migraine episodes, can certainly preserve from mechanisms of illness progression.

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