Introduction

About 40% of patients referring to headache centers suffer from chronic daily headache [1]. Chronic headache usually develops in patients with a history of episodic headache, but headache can occur on a daily or near daily basis from its onset. The lack of a specific set of diagnostic criteria for chronic headache is a weakness of the current International Headache Society (IHS) classification [2]. The identification of possible individual or environmental factors responsible for a chronic evolution of headache has represented a critical issue in recent years.

Medication overuse is believed to play an important role in transforming an episodic headache into a chronic type.Drug overuse has been found in 87.2% of patients with transformed migraine, in 67% of those with chronic tension-type headache and 66% with new daily persistent headache [1]. However, an appropriate diagnosis of drug overuse according to IHS criteria seems to shuffle these data [3]. According to Silberstein et al. [4], excessive use of analgesics is so strong to deserve a subclassification in the proposed classification of chronic daily headache.

The chronic use of analgesics is believed to induce a chronic evolution of headache by two actions: lowering the pain threshold and inactivating prophylactic treatment.
Therefore, it is noteworthy that no prophylactic therapy can relieve chronic head pain if the patient is overusing analgesics [5]. According to Pini et al. [6], chronic daily headache in patients who take analgesics daily is sustained by the chronic use of these drugs, and stopping the symptomatic medication results in headache improvement [6].

The most used drugs are the ergot alkaloids in the United Kingdom, the simple or combined analgesics, and the barbiturates in Germany, Austria, Switzerland and Italy. Narcotics and psychotropic drugs, such as calcium-channel blockers, beta-blockers, carbamazepine, and antiserotonin agents, are less used on a daily basis.

Recently, an Italian study of 20 chronic daily headache sufferers showed that the most overused drugs were the analgesics (40% of patients overused asialoacetac acid, and 10% overused non-steroid anti-inflammatory drugs), followed by the ergots in 30% of patients [7]. The combined analgesics usually overused were indomethacin in combination with caffeine and prochlorperazine (40% of patients), propyphenazone in combination with caffeine and butalbital (30% of patients), or propyphenazone with allobarbital (20% of patients) [7].

Personality pattern may also contribute to the chronic evolution of headache. In a recent neuropsychological investigation, Puca et al. [8] studied 181 chronic daily headache patients using a computerized version of the Minnesota Multiphasic Personality Inventory (MMPI). They found an impairment in the scales representing neuroticism: hysteria, depression and hypochondria. The patients exhibited lifestyles characterized by a tendency to somatization, depressive reactions to psychosocial stressors, poor self esteem, and the disposition to take advantage of headache in order to solve their own problems or to avoid any responsibility (primary gain) [8].

The continuous exposure to stress events may represent another causative factor of the transformation of episodic headache. To determine the most likely causative factors of chronic headache, the Italian Collaborative Group for the Study of Psychopathological Factors in Primary Headaches performed a multicenter study on the psychopathological aspects of drug use in chronic daily headache sufferers. The group was co-ordinated by Francomichele Puca (Bari) and was composed of 9 Italian headache centers.

### Subjects and methods

The goal of the research was to enroll adult chronic daily headache sufferers and to seek for possible transformation factors related to life events or to psychopathological factors by means of a complex neuropsychological investigation. The study enrolled 124 patients, 103 women and 21 men between 18 and 65 years of age, suffering from a primary headache for at least 15 days per month for at least 6 months. Exclusion criteria were: (1) diagnosis of chronic cluster headache, chronic paroxysmal hemicrania, hemicrania continua or chronic post-traumatic headache and (2) schizophrenia or cognitive deficit which could impair the co-operation of the patient. The psychiatric evaluation was performed using the Structured Clinical Interview (SCID), designed in the aim of obtaining a psychiatric according to the DSM-IV criteria. The characteristics of the population are summarized in Table 1. The statistical analysis was performed by means of Fisher’s exact test.

### Results

According to the IHS classification and diagnostic criteria of headache disorders, the study population presented the following types of headache: migraine (37 patients, 29.8%), chronic tension-type headache (32 patients, 25.8%), and chronic coexisting migraine and tension-type headache (55 patients, 44.4%). The type of onset headache was: migraine without aura (73 patients, 58.9%), migraine with aura (3 patients, 2.4%), episodic tension-type headache (25 patients, 20.2%), coexisting migraine and tension-type headache (3 patients, 2.4%), and new daily persistent daily headache (10 patients, 8.1%); 9 patients (7.2%) could not be classified according IHS criteria, and one case (0.8%) was not diagnosed. Eighty-nine patients fulfilled the IHS diag-

### Table 1 Demographic characteristics of the sample. Values in parentheses are standard deviations

|                   | Women (n = 103) | Men (n = 21) | Total (n = 124) |
|-------------------|----------------|-------------|-----------------|
| Mean age, years   | 44.0 (12.4)    | 43.3 (14.4) | 43.8 (12.7)     |
| Education, years  | 10.1 (4.2)     | 10.0 (3.0)  | 10.1 (3.8)      |
| Mean age at headache onset, years | 19.6 (9.7) | 25.4 (13.5) | 20.6 (10.5)     |
| Mean age at chronic headache onset, years | 36.7 (11.5) | 37.5 (14.5) | 36.9 (12.0)     |
| Mean headache duration, years | 24.4 (13.5) | 17.8 (14.7) | 23.3 (13.9)     |
| Mean chronic headache duration, years | 7.7 (8.8) | 6.1 (8.9) | 7.4 (8.8)       |
nostic criteria for analgesics-abuse headache (71.8% of the whole sample).

The overall prevalence of psychiatric disorders according to DSM-IV criteria was 66.1% (82 patients). The occurrence of anxiety disorders was 33.9%, that of depressive disorders was 14.5%, drug abuse disorders 12.1%, somatoform disorders 0.8%, and the remaining proportion was the sum of various combinations of them (Table 2). Altogether, an anxiety disorder was found in 57 cases (45.9%), a depressive disorder in 41 cases (33.1%), a somatoform disorder in 5 patients (4.0%) and an analgesic abuse disorder in 23 cases (18.6%) (Table 3). The apparent discrepancy between the data on analgesic abuse obtained with the clinical interview (64.1%) and those derived from the SCID interview (18.6%) is easily explained: the latter are based on DSM-IV criteria that are more rigorous than the former and involve 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 57.1% in non-abusers (the difference was not statistically significant). Comparing the three subtypes of CDH, a psychiatric disorder was found in 50.0% of chronic tension-type headache patients, in 72.2% of those with chronic coexisting migraine and tension-type headache (CTTH vs. CCMTTH, p < 0.01) and in 70.3% of patients with chronic migraine.

### Table 2 Distribution of psychiatric disorders diagnosed by SCID-IV in the 124 chronic daily headache patients

| Psychiatric disorder | Patients, n (%) |
|----------------------|-----------------|
| No psychiatric disorder | 42 (33.9) |
| Anxiety disorder | 18 (14.5) |
| Depressive disorder | 9 (7.3) |
| Somatoform disorder | 1 (0.8) |
| Drug overuse disorder | 15 (12.1) |
| Anxiety and drug overuse disorders | 3 (2.4) |
| Anxiety and depressive disorders | 27 (21.8) |
| Anxiety, depressive and drug overuse disorders | 5 (4.0) |
| Anxiety, depressive and somatoform disorders | 1 (0.8) |
| Anxiety and somatoform disorders | 3 (2.4) |

### Table 3 Overall prevalence of psychiatric disorders independently from their possible association with others, diagnosed by means of SCID interview in compliance with DSM-IV in 124 patients affected by chronic daily headache

| Psychiatric disorder | Patients, n (%) |
|----------------------|-----------------|
| No psychiatric disorder | 42 (33.9) |
| Anxiety disorder | 57 (45.9) |
| Depressive disorder | 41 (33.1) |
| Somatoform disorder | 5 (4.0) |
| Drug overuse disorder | 23 (18.6) |

\*The sum of the single percentages exceeds 100 because more than one psychiatric disorder was found in 39 individuals\*

### Discussion

The high prevalence of psychiatric disorders or symptoms in chronic daily headache sufferers states once again the much debated issue about the role of a psychological impairment: does it represent the cause of episodic pain transformation into a chronic pain or the effect of a chronic pain?

The mechanisms of chronic daily headache have rarely been studied and remain to be assessed. It is well known that a continuative descending inhibitory control from various supraspinal sources acts on neurons in the dorsal horn and in the nucleus caudalis of the brainstem. Thus, supraspinal mechanisms may very well exert a net inhibiting influence on nociception. It is noteworthy that the main sources of this effect are two serotoninergic areas, i.e. the raphe magnus nucleus and the periaqueductal gray matter in the pontomedullary reticular formation. In sufferers of transformed migraine, an upregulation of serotonin receptors has been found and has been regarded to be an adaptive response to repeated suppression of an already abnormal antinociceptive system (the serotoninergic hypofunction theory of migraine pathogenesis) [9]. In chronic tension-type headache sufferers, the uptake of serotonin by platelets was much lower than in controls, and abnormalities of serotonin uptake by platelets and factors which cause release of this neurotransmitter have been suggested [10]. Moreover, Schoenen [11] found a decrease of the late temporalis exteroceptive suppression period which represents a typical finding of patients with major depression. Considering the data on the anatomofunctional organization of masticatory reflexes, Schoenen postulated that temporalis exteroceptive suppression period was a marker of the excitability of interneuronal nets in the pontomedullary reticular formation. In chronic tension-type headache, excitability of these neurons is decreased because of an inadequate control by the serotoninergic raphe magnus nucleus and the periaqueductal gray matter [11].

Then, taking into account these findings, the pathogenesis of chronic daily headache may be explained by severe serotoninergic hypofunction. A deficit in serotoninergic activity results in defective pain modulation due to the supraspinal disinhibition of neurons in the nucleus caudalis and in a consequent exaggerated response to painful stimuli (central sensitization).
On the other hand, the important role of serotonin has also been demonstrated in several mental disorders, mainly in depression. Disorders in serotoninergic activity may contribute to many depressive symptoms, such as loss of appetite and insomnia. Interference with serotonin synthesis or storage may induce depression in some vulnerable individuals. Abnormality in serotoninergic activity may occur at one or more levels, for example synthesis, release or reuptake of the neurotransmitter or serotoninergic post-synaptic receptor abnormalities. The efficacy of antidepressant drugs may be partially due to an enhancement of serotoninergic activity [12]. Therefore, a common neurobiological basis consisting of an abnormality in serotoninergic pool, induced by genetic and/or environmental factors, may give rise to both chronic daily headache and type IV depression of comorbidity according to Lipton and Silberstein [13].

According to the present study, migraine is the most frequent type of onset headache in patients with chronic daily headache. For a specific subgroup of patients with migraine whose episodes progress from isolated and intermittent to chronic and daily, Post and Silberstein [14] hypothesized a pathophysiological mechanism similar to epilepsy: the amygdala kindling paradigm may be a useful, but not homologous, model. 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 capable of evoking episodes (middle or completed stage); if triggered episode occurs repeatedly, episodes begin to appear spontaneously (late or spontaneous stage)”. At last, “the interval between migraine attacks shortens with each successive recurrence”. This illness progression is underlied 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 [14]. Therefore, at least with regard to transformed migraine, a similar mechanism can also be hypothesized in humans. The recurrent exposure to stressful events may promote on the one hand the onset of migraine as a behavioral answer and on the other hand the onset of an adaption disorder 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. In the kindling model, it is interesting to observe that some of the neurobiological changes represent secondary or compensatory adaptations which attempt 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 to receive nociception inputs, so as to exert presynaptic control on pain [15]. 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 [16]. However, a GABAAergic hypofunction may contribute to the pathogenesis of the anxiety disorders associated with chronic daily headache. So, once again, abnormality of one neurotransmitter may explain both progression of headache and psychological disorders. The possible explanations for the chronic evolution of headache and for its frequent association with psychological disturbances must not dishearten the clinician. The evolution to chronic daily headache must not be regarded as an unavoidable course of “migraine”. In fact, early and adequate treatment, by reducing the frequency of migraine episodes, can certainly inhibit mechanisms of illness progression.

M. Guazzelli
Psychiatric Clinic,
University of Pisa, Pisa, Italy

V. Sciruicchio • G. Libro
Neurological Clinic I,
University of Bari, Bari, Italy

P. Sarchielli • S. Russo • A. Alberti
Neurological Clinic,
University of Perugia, Perugia, Italy

G. Zanchin
Neurological Clinic,
University of Padua, Padua, Italy

C. Schianchi
Institute of Neurology,
University of Parma, Parma, Italy

A.P. Verri • G. Nappi
IRCCS Mondino,
University of Pavia, Pavia, Italy

R. Cerbo • T. Catarci
Department of Neurological Sciences
University of Rome La Sapienza, Rome, Italy

G. Nider • G. Relja
Ospedale Maggiore, Trieste, Italy
References

1. Mathew NT (1993) Chronic refractory headache. Neurology 43[Suppl 3]:26–33
2. Headache Classification Committee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
3. Manzoni GC, Granella F, Sandrini G, Cavallini A, Zanferrari C, Nappi G (1995) Classification of chronic daily headache by international headache criteria: limits and new proposal. Cephalalgia 15:37–43
4. Silberstein SD, Lipton RB, Solomon S, Mathew N (1994) Classification of daily and near daily headaches: proposed revision to the IHS classification. Headache 34:17
5. Kudrow L (1982) Paradoxical effects of frequent analgesic use. Adv Neurol 33:335–341
6. Pini LA, Bigarelli M, Vitale G, Sternieri E (1996) Headaches associated with chronic use of analgesics: a therapeutical approach. Headache 36:433–439
7. Bonuccelli U, Nuti A, Lucetti C, Pavese N, Dell’Agnello G, Muratorio A (1996) Amitriptyline and dexamethasone combined treatment in drug-induced headache. Cephalalgia 16:197–200
8. Puca F, Genco S, Prudenzano MP, Sciricchio V, Pastore B, Relja G, Nider G, Bussone G, Grazzi L, Libro G, Di Pietro E, Tramontano A, Marzo A, Granella F, Schianchi C, De Fidio D (1997) Psychopathological aspects of chronic primary headache. A multicentric study by means of MMPI. Cephalalgia 17(3):285
9. Srikiatkhachorn A, Govitrapong P, Limthavon C (1994) Upregulation of 5-HT2 serotonin receptor: a possible mechanism of transformed migraine. Headache 34(1):8–11
10. Shimomura T, Takahashi K (1990) Alteration of platelet serotonin in patients with chronic tension-type headache during cold pressor test. Headache 30(9):581–583
11. Schoenen J (1993) Exteroceptive suppression of temporalis muscle activity in patients with chronic headache and in normal volunteers: methodology, clinical and pathophysiological relevance. Headache 33(1):3–17
12. Maers M, Meltzer HY (1995) The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: the fourth generation of progress. Raven, New York, pp 933–944
13. Lipton RB, Silberstein SD (1994) Why study the comorbidity of migraine? Neurology 44[Suppl 7]:S4–S5
14. Post RM, Silberstein SD (1994) Shared mechanisms in affective illness, epilepsy, and migraine. Neurology 44[Suppl 7]:S37–S47
15. Malcangio M, Bowery NG (1996) GABA and its receptors in the spinal cord. Trends Pharmacol Sci 17:457–462
16. Murphy DL, Mitchell PB, Potter WZ (1995) Novel pharmacological approaches to the treatment of depression. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: the fourth generation of progress. Raven, New York, pp 1143–1153