

Maria Nicolodi
Federigo Sicuteri

Planet pain: focus on chronic migraine

M. Nicolodi (✉) • F. Sicuteri
Interuniversity Centre of Neurochemistry
and Clinical Pharmacology of Primary
Headache,
Florence University Unit,
Viale Pieraccini 18, I-50139 Florence, Italy
Tel.: +39-055-599186
Fax: +39-055-597500

Abstract Chronic headache is often described but poorly understood regarding its mechanisms. We discuss the clinical presentation, differential diagnosis of chronic headache syndromes and treatment options. Patients presenting these pain syndromes are best assessed using a multidisciplinary approach. Our purpose was to investigate these types of chronic primary pain by using an internal medicine, neurological as well as a pain-specialist approach. We developed a model for estimating the entity of central sensitization, which seems to be the pivotal feature in these painful syndromes. Our approach allowed us to gain further insight into the mechanism of central

sensitization and neuronal changes in the central nervous system. The findings run counter to the possibility that these primary pain syndromes, especially chronic migraine, are refractory to specific treatments.

Key words Visceral sensory innervation • Somatic sensory innervation • Hyperalgesia • Genetic hyperalgesia • Chronic migraine • NMDA receptor

A method to ascertain the nature of a chronic headache

In our practice we observed that many chronic daily headache sufferers receive more than one diagnosis. Indeed, the diagnosis varies with each physician consulted. Contrasting diagnoses are given in a period of a few months while the patient's pain diary indicates no change in pain pattern or features nor in behavior regarding the consumption of analgesic drugs. Thus, it is obvious that there is something in the current classification which is unclear and can lead to misdiagnoses which play a crucial role when proposing a therapeutic approach. As a general rule, simplifying is a way to catch the core of the topic under research. That led us to propose a method for distinguishing tension-type headache from chronic migraine. The method is strictly based on pain semiotics,

derived from the anatomical sensory innervation [1]. Table 1 presents our method for diagnosing chronic headaches; it directly derives from a method for distinguishing tension-type headache from migraine which we first published in 1989 [2] and successively up-dated and republished [3, 4]. This simple and clear method is characterized by the following:

- As shown by 3 physicians and 3 nurses, it can be used by every medical or paramedical operator after a 2-h training. Noteworthy, the diagnoses given by the authors, the nurses as well as by the physicians were absolutely overlapping in all 128 cases evaluated.
- This classification method is a suitable tool to avoid diagnostic traps. Thus, the diagnosis is absolutely clear. In a population of 167 chronic headache sufferers, only 97 patients were able to reach a self-diagnosis. We observed that the mistakes were linked to prejudices the patients had

Table 1 Method for distinguishing chronic somatogenic (alias tension-type) headache from chronic viscerogenic (alias migraine) headache

	Clinical features	Headache-inducing substances	Overuse of analgesics	Personal history of episodic migraine	Type of hyperalgesia
Chronic viscerogenic headache	Daily headache often with superimposed migraine attacks Pain: pulsating and/or “wound-like” often inhibiting daily activities Frequent autonomic disturbances such as shivering vomiting, irritable colon and sensation of severe malaise [6]	Nitroglycerin Histamine Morphine [22]	Frequent	Always present	Visceral hyperalgesia sometimes associated with mild somatic hyperalgesia
Chronic tension-type headache	Daily headache with infradian changes in severity Pain: continuous, burning, or icy sensation, or pins and needles With few exceptions, pain does not inhibit daily activities Autonomic disturbances: absent	None	Absent	Never present	Somatic hyperalgesia never visceral hyperalgesia

on their headache because of decision of previous physicians or because of information from the media. The last-mentioned items were capable of leading the subject under observation to conclude for a diagnosis which did not fit with the data given by the same subject. A defect of our inquiry seemingly consists in indicating the final name of the chronic migraine, while it seems more correct to give a solution A or B and to adjoin trap questions to increase the reliability of the self-diagnosis. It remains possible that the patient allows prejudices to destroy an evidence-based diagnosis. So, it seems that, at the moment, general culture is not sufficient to reach a non-influenced, but only data-based diagnosis. Some puzzling questions remain about the difficulty to reach a diagnosis among specialists who know IHS criteria well. The reason seems to reside in several traps that severe headache pain involves. The main traps are herein listed:

- Muscle-cutaneous referred pain in migraine. The well known phenomena labelled “referred pain” [5] is here playing its misleading role and may lead to a wrong diagnosis of tension-type headache.
- Negative or weakly positive results in measuring vascular-visceral hyperalgesia, the stigmata of migraine (Table 1), are due to the previous use of specific or non-specific acute antimigraine drugs, particularly when in large doses. This represents a contamination of the evidence.

- Painful pulsation of the temporal artery can sometimes be reported by tension-type headache sufferers. This happens because the hyperalgesia affects somatic tissues immediately around the vessel. Therefore, a somatic sensory pathology can be interpreted as a migraine feature, which, conversely, is a viscerosensory problem in nature.
- Chronic somatogenic headache may have some clinical feature of chronic viscerogenic headache in case of a severe somatic hyperalgesia which makes the pulsation of vessels against somatic tissues (muscles, skin) painful. In this case, painful symptoms may resemble those of migraine (alias viscerogenic headache). Nonetheless, we can distinguish chronic migraine from somatic headache by asking the patient under observation to perform a marked head jolting. Only in case of migraine (viscerogenic headache) does jolting induce a succussion against dura mater that is viscerosensorily innervated and painful because of a clear visceral hyperalgesic state. The hyperalgesic state of the meninges is conversely absent in somatic headache where the jolting cannot worsen the headache pain nor markedly increase the sensation of a painful pulsation. In fact, in somatic headache tissues aching because of a somatic hyperalgesia does not induce beating against and stimulation of a somatic tissue.
- Chronic viscerogenic headache (alias migraine) can

have features of chronic somatogenic headache (alias tension-type headache), consisting in pain of the scalp muscles and skin. This is the expression of the well known phenomena of referred pain which, due to a convergence-projection mechanism, transfers visceral pain to somatic tissues [5]. The most cited example is that of heart angina manifesting itself as pain in the left arm.

In 1989, we substituted the old, archaic label migraine with the label viscerogenic headache [2–4, 6]. The adjective viscerogenic is composed of a prefix indicating the nature of the sensory innervation: the visceral one. The suffix “genic” indicates that the genesis of migraine is linked to an imbalance of pain transmission or inhibition along visceral sensory innervation pathways. Similarly, the new label “somatogenic headache” substituted that of tension-type headache and focused the attention on the fact that such a type of headache originates from an imbalance between pain inhibition and pain transmission regarding sensory pathways devoted to somatic tissue innervation. In Table 1 we use the above-mentioned taxonomy.

The relevance of chronic migraine in the planet of chronic daily headache

In different provinces of northern, middle and southern Italy, we evaluated the frequency of chronic tension-type headache and chronic migraine using the diagnostic criteria presented in the previous section and in Table 1. As a rule, with the label chronic migraine (alias chronic viscerogenic headache), we indicate a migraine characterized by episodic attacks and clear headache-free period which, in time becomes a daily chronic headache often associated with superimposed severe migraine attacks (Table 2).

The main outcome was that the frequency of chronic migraine was higher than that of chronic tension-type headache. In fact the mean prevalence of chronic migraine was 20-times greater than that of chronic tension-type headache. These data vary in different countries all over the world; nevertheless the frequency of the two chronic daily headache types may be actually known when a method allows to clearly distinguish and diagnose between these two painful diseases. At the moment our classification method seems to be sufficiently well based on anatomy and pain semiotics, sufficiently clear and well furnished of exhaustive parameters to allow a final, non-misleading diagnosis. Compared to chronic tension-type headache, chronic migraine has a dramatic social-economic cost, chiefly because it inhibits daily activities and implicates higher personal and social expenses for drugs.

The clearly higher frequency as well as the higher eco-

nomic cost of chronic migraine led us to investigate its mechanism, and to search for an adequate, possible solution for such a disabling painful syndrome.

From episodic migraine to chronic migraine: reasons for meeting the condition of chronic migraine

In 1991 we established that hyperalgesia-allodynia is the stigmata of all migraine sufferers [7–10]. This allowed us to establish, in 1994, that migraine cannot have an origin different from the central sensitization [11], i.e. hyperalgesia-allodynia. As a matter of fact, hyperalgesia-allodynia, even when initiated by a peripheral event, is caused, sustained and maintained by peculiar events in the central nervous system. These events chiefly consist in a hypersensitivity of second-order sensory neurons. We proposed that these phenomena result from a defect of analgesizing-modulator systems [12, 13]. The theory is supported by neurochemical and clinical pharmacological data [12, 13] as well as by observations of several operators in the field of primary pain research. Indeed, the hypothesis is clearly supported by obituary medical data [14–16]. In 1994 we definitively established that generalized visceral-vascular hyperalgesia is a common feature of migraine sufferers. The feature is specific to migraine (alias viscerogenic headache) and is not found in healthy subjects or in patients with tension-type headache. The feature is equally present in all patients without regard to age or gender [17].

Recently we introduced the concept that visceral-vascular hyperalgesia is the pivotal factor for meeting the condition of chronic migraine. The observation stems from a study showing that hyperalgesia-allodynia, consisting of an abnormal, non-physiological state of the central nervous system, is genetically transmitted according to mendelian law in first-degree consanguineous relatives of migraine sufferers [9, 10]. As already mentioned, such an abnormal state, neurophysiologically consisting in hypersensitivity of second-order amino acidergic sensory neurons [12, 13, 18, 19], results from a break-down of the protective alliance between pain transmitting and inhibiting systems. So, the failure of analgesic systems becomes a crucial event in the mechanism of hyperalgesia-allodynia characterizing primary pain as migraine. Stimuli physiologically known to activate analgesia are expected to provoke a different result in case of a non-physiological functioning of the pain modulator systems [20, 21]. Indeed, in migraine, as in other types of primary pain, adversative stresses, emotion and other stimuli physiologically evoking analgesia [22] have converse effects. Indeed, since 1947 [21] these stimuli have been known to induce pain in subjects suffering from primary pain with an abnormal function of analgesic systems.

Table 2 The spiral of worsening of migraine: the vicious circle of hyperalgesia set-up*Pre-clinical stage:*

The stage of third, genetic, inherited visceral hyperalgesia

The subject is consanguineous of migraine sufferers but personally exempt from any type of headache [10]

Visceral hyperalgesia is detectable by means of maneuvers suitable to evaluate a possible lowering of visceral pain threshold

Visceral pain threshold may manifest itself as abdominal pain ("abdominal migraine")

First clinical stage

The stage of primary and secondary hyperalgesia

During this period, as happens in all cases of iterative severe pain, migraine attacks, particularly if frequent, promote the well known, historic primary and secondary hyperalgesia. The first affects the aching area, while the second causes a generalized phenomenon of lowering of the pain threshold. Depending on the entity of a third, genetic hyperalgesia [10], the primary and secondary hyperalgesia give rise to a redundancy of hyperalgesia phenomena in the central nervous system

Episodic migraine attacks stem off following clearly headache-free periods

Second clinical stage

The start of a vicious circle between third, genetic hyperalgesia and primary as well as secondary hyperalgesia

Headache-free periods vanish and are substituted by a mild nearly daily headache. The vicious circle between third, inheritable hyperalgesia, and primary and secondary hyperalgesia states is already started and a subsequent worsening of pain can be predicted

Episodic migraine attacks stem off very often following headache-free periods

Third clinical stage

The stage of hyperalgesia state redundancy associated with a marked hypersensitization of second-order sensory neurons at the central nervous system level [9, 12, 13]

Chronic migraine often associated with overuse of analgesic drugs. Daily pain is associated with a variable number of migraine attacks (mean, 3.4 ± 1.9 per month, observed in 535 chronic migraine sufferers) and is often difficult to control using specific or non-specific acute, abortive antimigraine drugs

Fourth clinical stage

The stage of marked redundancy of hyperalgesia states associated with central hypersensitization of sensory pathways and possible neuroplastic changes, difficult to be reverted

Chronic migraine associated with primary fibromyalgia

A completely disabling condition

This peculiar pathological response to otherwise analgesizing stimuli [20] individuates subjects having a seriously compromised pain-analgesia homeostasis and makes them prone to a redundancy of hyperalgesia-allodynia mechanism at a neuronal receptor level. Indeed, any repetitive, severe painful signal is able to induce a central sensitization by sensitizing second-order amino acidergic neurons [23]. That results in a "pain memory" condition at intraneuronal and synaptic levels. This means that genetic and phenotypic factors co-operate in determining the sensitization of second-order sensory neurons which is sufficient to lead from a cryptic non-physiological central nervous system state to a clinically open condition of primary pain, namely migraine. Moreover, the redundancy of such a mechanism allows a definite central sensitization, which in turn meets the condition of chronic migraine. The pivotal role of hyperalgesia in chronic migraine sufferers expresses itself as a lowering of the visceral pain threshold, i.e. a visceral-vascular hyperalgesic state. We observed that the worsening of migraine syn-

drome is paralleled by an increase in the severity of visceral hyperalgesia [12, 13, 24] according to different methods. Briefly, in one method, sharp stretching of vein walls is induced by a noninvasive maneuver, while another method refers to the application of an osmotic stimulus to the wall of the vessels [17]. Both methods are based on the application of stimuli which are suited, in nature, to activate polymodal receptors of hollow viscera. Pain evoked by a stimulus which is adequate in its nature but not in its entity allows to evidence a hyperalgesic state. Allodynia, which is a painful response to inadequate or analgesizing stimuli, can be academically differentiated from hyperalgesia; nevertheless, most authors evidence the same mechanism as that acting in both the mentioned conditions.

Now we focus our attention on hyperalgesia since it is a noticeable clue in the road leading to chronic migraine. We previously said that a worsening of the visceral hyperalgesic state is parallel to a worsening of migraine up to the condition of chronic migraine associated with an overuse of drugs

for the acute, abortive treatment of migraine attacks [13, 19]. Our data allow us to underline that the escalation from episodic to chronic migraine is semeiologically characterized by a similar escalation in the severity of visceral hyperalgesia (Table 2). In its turn, the escalation of visceral hyperalgesia is mirrored by an increase in nitric oxide (NO) synthase activity as we showed by measuring in plasma L-citrulline, the equimolar, stable co-product of NO [13, 25, 26]. Because of the measurements in the plasma, we cannot indicate the observed increase in plasmatic NO production as a marker of the hypersensitization of amino acidergic neurons of the central nervous system. The finding only indicates that the increase of visceral hyperalgesia is associated with a generalized, peculiar state of the NO-NO synthase system. We only can say that it seems reasonable that this can happen in the entire body. Nevertheless, a clinical pharmacological approach gives the final proof testifying a role of hypersensitivity of amino acidergic system in the "crescendo" of hyperalgesic state. Indeed in 1995 we found that we can reverse the condition of chronic migraine as well as the increased severity of generalized visceral hyperalgesia by administering low, non-anesthetic, non-dissociative doses of ketamine, a specific, reversible antagonist at the ionotropic NMDA receptor. The treatment is also able to reverse the condition of analgesic drug overuse [19, 27]. The last result can be explained merely by saying that patients no longer needed analgesic, abortive drugs so often. Nonetheless, it cannot be denied that NMDA receptors play a fundamental role in drug abuse and abstinence [28]. So, by inhibiting the NMDA receptor we also gave a solution to the drug habituation. It seems noteworthy that the treated subjects, now over 400, were all non-responders to conventional prophylactic antimigraine therapies assumed daily for more than three months. It is also noteworthy that a comparison with

placebo, performed in the first phase of the study on a subgroup consisting of 89 chronic migraine sufferers, showed the absolute ineffectiveness of placebo itself. Since the first trial, we observed a significant, but non-dramatic, lowering of visceral hyperalgesia associated with a dramatic amelioration of both the painful syndrome and the analgesic drug overuse-abuse. This observation proved that in chronic migraine there is a genetically determined proneness to hyperalgesia, consisting in an abnormal state of the central nervous system [9, 10]. We can partly counteract such an inherited abnormality by means of neuroplasticity induced by agonists and antagonists active at the neurons involved in pain-analgesia homeostasis. Nonetheless, genetic imprinting can remain present even when the hyperalgesic condition returns to a cryptic state (Table 2).

Thereafter, we continued with an open study. Indeed we think that a large population is needed to assess the real effectiveness of a drug in a disease. In fact, placebo comparison in selected populations can also give misleading results. The treatment with ketamine, the only antagonist at the NMDA ionotropic receptors we can use in humans, gave relevant results at a relatively low expense. A further proof of the implication of excitatory amino acids in chronic migraine is represented by the outcomes of the studies we performed with gabapentin [27], an inhibitor of branched chain amino-transferase involved in the synthesis of glutamate. Also in this case we followed the plan used for ketamine. So, a double-blind cross-over study was followed by an open trial on over 300 patients suffering from chronic migraine refractory to conventional therapies. Following a 2-month administration, we obtained results similar to those for ketamine. The difference consisted in the fact that ketamine action was sharper and the level of benefit was higher. Obviously, both results are endowed with great social-economical importance.

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