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When cluster headache was called histaminic cephalalgia (Horton's headache)

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Abstract The Author revives his experiences and reminiscences in the frontline research and everyday clinical practice dealing with what was then called "histaminic cephalalgia" (Horton's headache). In this context, the Author, one of the historical representatives of the School of Florence, reports an outline of the contribution of this pioneering period in order to promote research ideas concerning possible brain involvement in cluster headache (CH) pathogenesis, which is currently accepted worldwide. The recent history of CH has registered remarkable progress in revealing the mystery of this pathology and it is likely that, in the near future, through the development of better education and new treatments, the overall suffering of patients will be further minimised.

Key words Cluster headache • Histamine • Sumatriptan • Pupillary dysfunction • Central nervous system

At the end of the 1950s and the beginning of the 1960s, many desperate cluster headache (CH) patients came to the Headache Center of Florence, the only one in Europe at the time, to be examined. I was there…

Horton's headache era

More than 60 years ago Graham and Wolff [1, 2] proposed the vascular theory of migraine and related vascular headaches. At that time the clinical feature of the current CH syndrome was considered a migraine variant and therefore headache phase was attributed to painful dilatation and distension of the cephalic blood vessels. In 1939 Horton et al. [3] described cluster attack features, including increased temperature of the symptomatic side of the forehead and he reported the experience in treating this new vascular headache syndrome with histamine. But only in 1956, when Horton detailed the pain and its associated symptoms, did the syndrome become generally known [4]. However, Horton focused on the symptoms of episodes, omitting a description of the periodicity of occurrences. Therefore he considered this syndrome a vascular headache with chronic recurrent brief attacks similar to migraine. Horton used the term "histaminic cephalgia" [5] or "cephalalgia" [6], as he attributed this vascular painful syndrome to the potent vasodilator agent histamine. In many circles this form of headache has been called Horton's headache in his honour. Apart from acetylcholine, at that time histamine was the only known vasodilatative substance capable of explaining the vasodilatation phase of the so-called vascular headaches. Horton focused on the presumed role of histamine as an inducing factor of CH attacks as well as their prevention with histaminic desensitisation, and had

also observed that histamine subcutaneously provoked a cutaneous rash with increased temperature. Moreover, peptic ulcer was found to be a common affliction of these male patients and during the attacks gastric acid secretion increased. Although the pathogenetic implication of this term seems today rather small for progress in the field, Horton's definition raised our comprehension of this headache to a level able to promote a lot of enthusiastic research and well designed diagnostic and therapeutic procedures.

The disorder was attributed by Horton to a unique form of histamine sensitivity. The evidence for this was cited as follows "…a headache apparently identical with that of a spontaneous attack could be precipitated in some patients by the hypodermic administration of histamine in a small amounts, usually 0.35 mg histamine base. Gastric acidity was found to rise during an attack and attack subside after histamine desensitisation over an extended period of time" [4].

The pathophysiological role of vasoactive substances such as kinins and serotonin would be studied some years later.

Horton's headache era at the Headache Center of Florence

According to the accurate description of Horton's patient series, there was a veritable explosion of interest regarding this type of headache in the world headache community. In 1964 Greppi and Sicuteri presented at the National Congress of Internal Medicine Society in Rome a lecture entitled "Migraine: aspects of physiopathogenesis and therapy" with an appendix by Franchi and Fanciullacci in which they reported 71 cases of histaminic cephalalgia [7]. But how were the patients managed at that time? I remember many of these patients were examined every day during their hospitalisation. Every day courage was required to say "I do not know" and to show greater commitment to try to help these patients. Every day it was necessary to explain to our colleagues not involved in headache how to manage the uncontrolled manifestations sometimes shown by these patients, and explain the intensity of their sufferings to avoid a psychiatric interpretation of their behaviour during the attack.

The most important factor in therapy was the assurance that a dedicated and understanding physician would stick with each patient over the year through the trials and tribulations of this miserable malady. More than 20 years ago a chronic cluster patient described his terrible painful experience in a book named "Horton", dedicated to all of Horton's patients, which is composed of a series of dramatic poems on his suffering. He gave me the book as a gift, with this dedication "With great estimation and gratitude. The care of a dedicated doctor, with experience of this terrible disease, like myself, became of great value for the patient, despite the poor therapeutic possibility represented by the empiric histamine desensitisation, ergotamine compound and methysergide. In fact, the patient's suffering put special demands on the treating physician concerning his empathy and understanding of the patient's whole situation. Histamine desensitisation has been used for many years for the treatment of patients affected by Horton's headache. This therapy usually entails a prolonged hospital stay during which the interrelation between doctor and patient is very strong. I remember our technique of "protected" histamine desensitisation for slow infusion of histamine bichloride or the histamine releaser compound 48/80, gradually increasing the dose up to 5–6 mg/day. The protection was carried out with preventive or simultaneous administration of antihistaminic drugs and sometimes with dihydroergotamine in the same phleboclysis to prevent the induction of a crisis. The scenario was that of a patient engaged in following the speed of infusion in order to avoid the trigger of an attack and the doctor's intervention to block the possible attack with parenteral dihydroergotamine. The hospitalised patient illustrates how the histamine administration in desensitising amount effected by a physician in whom he had complete confidence and reassurance, when compared with the past chaotic management, may have had same effect in alleviating his headache for some time.

Cluster headache. The first direct approach to pupillary neural innervation

The term proposed in the 1950s by Kunkle et al., i.e., cluster headache [8], has been widely accepted, in Italy as well, and our Horton's patients had their name changed to CH patients. With youthful enthusiasm, my colleagues and I achieved a craftsmanlike photographic technique with the aim of directly exploring the neural structures of the pupil, which are unilaterally affected during the attack. With a battery of sympathetically acting eye drops, the pupillary impairment of sympathetic neuronal activity was demonstrated. Tyramine eye drops in CH patients induced an anisocoric pattern characterised by the pupil on the symptomatic side being smaller than the other pupil [9, 10]. Asymmetric mydriatic response to the noradrenaline releaser tyra-

mine was proposed as an objective diagnostic test for cluster patients. Also, it was pointed out that chronic lithium treatment corrects the asymmetric response to tyramine in CH patients [11]. We considered that this peripheral adrenergic disorder could reflect an analogue disturbance in the central nervous system and therefore it may be applicable to Sicuteri's central theory, which considers primary headaches to be due to a brain deficiency of a monoamine, particularly serotonin [12]. Some years later our group also showed a dysfunction in the trigeminal iris innervation on the symptomatic side [13].

In one of the first Italian books about primary headaches, Nappi and Savoldi presented hypothalamic-limbic injury involving both dysfunction of central oscillators and dysfunction of central lateral organisation with lateral asymmetry increase in neurotransmitter systems [14]. These were Italian researchers' intuitions of a central origin of the pupillary dysfunction that was considered peripheral in origin by the majority of world headache researchers. In fact it was supposed that the inflammatory process, present during CH periods in the walls of the cavernous sinus, caused a lesion of the adjacent sympathetic fibres and possibly also pain fibres [15].

My first time with sumatriptan

In the past, CH attacks were the most difficult to treat. Parenteral administration of ergotamine compounds represented the most effective symptomatic therapy. Horton first demonstrated the termination of an attack with parenteral ergotamine tartrate (0.30 mg).

Dihydroergotamine has a more favourable tolerability profile than ergotamine and it was used extensively in its parenteral form (1 mg). Because of their long duration of action, they were used also to prevent the attack if the headache was recurring at a predictable time. However their action was very slow and a pain-free effect has rarely been obtained. In the late 1980s in a pilot study the first results concerning subcutaneous sumatriptan in CH acute treatment were obtained. These results prompted further placebo-controlled studies to determine the efficacy, safety and tolerability of sumatriptan in CH. I had the opportunity to participate in the first randomised, double-blind, placebo-controlled crossover study [16]. Two minutes after active drug injection the patient said "my crisis is disappearing…". After the first moment of incredulity, I felt great emotion and satisfaction: it was evident that sumatriptan would improve the quality of life in patients with CH attacks, as the optimal treatment for rapid resolution of attacks, which are commonly very severe, was emerging. Moreover, the effect of sumatriptan, a 5HT receptor agonist, seemed to agree with our results obtained a long time before, which indicated the therapeutic drugs ergotamine and methysergide as serotonin agents [17].

The past, the present and the future

My "amarcord" is not sad but full of enthusiastic perspectives. My colleagues and I, interested not only in the diagnosis and treatment of headaches but also in research, had a great opportunity to participate in pioneering frontline research and clinical practice into CH. In the mid 1960s only three or four papers on CH appeared every year. During the 1970s some investigators became interested in this topic and, in order to promote research ideas, a group was set up by Ottar Sjaastad. It was called the "International Cluster Headache Research Group", but for practical reasons this name was abbreviated to the "Cluster Club" [18]. I had the opportunity to be a member of the club, representing the Florence Headache Center, accepting the challenge to consider the vascular component of CH as a secondary factor. At that time, the majority of headache experts considered that the speculation concerning the possibility of the central nervous system being an essential factor in CH did not fit the facts. Past research has contributed to stimulate the current research, which has confirmed the central basic neural cause of CH. Recent decades in fact have brought a considerable increase in clinical and experimental research suggesting a role for hypothalamus in the disorder. Consequently, the vascular theory has been superseded by recognition that neurovascular factors are more important. Neuroimaging has broadened this pathophysiological view and has led to successful treatment by deep brain stimulation of the hypothalamus [19]. Bearing in mind the excruciating pain in CH, we must now accept the challenge of avoiding diagnostic delay and the mismanagement of CH, which still occurs [20]. My regret is the fact that many patients are not optimally managed in their early disease course. Possibly, this could avoid more invasive procedures. Every effort must be made to minimise the patient's disability and suffering. The challenge is to establish a clinical background capable of giving the optimal modern management to CH patients, similar to patients with other seriously disabling diseases. It is reasonable to believe that in the near future better education and new treatments will reach this target and I hope to say again "I was there…".

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