Chronobiological correlates of headache: three decades on

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Michele Viana, MD
Giuseppe Nappi, MD

Headache Science Center, C. Mondino National Neurological Institute, Pavia, Italy.

Correspondence to: Michele Viana
E-mail: michele.viana@mondino.it

Summary

In 1983 an international symposium entitled "Chronobiological Correlates of Headache" was held in Capri. This meeting provided an opportunity to debate new and stimulating aspects of headache, in particular the temporal pattern of headache and the periodicity of the underlying biological and environmental phenomena. Giuseppe Nappi presented his dyschronic hypothesis of primary headaches, which was based on the observation that these conditions involve not only a dysfunction in pain control systems, but also a vulnerability of the rhythmic physiological organization of the central nervous system. He suggested that the hypothalamus played a key role in this vulnerability. Several decades on, thanks to the advent of new technologies (functional neuroimaging and neurophysiological studies), this hypothesis has been supported by scientific data.

KEY WORDS: chronobiological, cluster headache, dyschronic, hypothalamus, migraine.

"Primary headache belongs to a big group of neurological diseases in which there is not a discrete, structural lesion of the central nervous system but an impairment in the function of neuronal networks. [...] Along with dysfunction in the pain control systems, there is an impaired ability of biological function to adjust, or better to display an adaptive response, to internal or external environmental change. [...] Migraine and other primary headaches can be considered psychoendocrine disturbances of the adaptive responses to internal or external environmental change" (Nappi et al., 1983). Thus opened a communication delivered by Prof. Nappi at a symposium in Capri in 1983. The symposium focused on the chronobiological correlates of headache and was organized by the Headache Center, Department of Neurology, University of Pavia. These lines show that, three decades ago, there was already an awareness of the complexity of the problem of primary headaches (in terms of functional alterations of adaptive networks) and above all of the relations between some of these forms and environmental changes. In particular, the concepts of periodicity and cyclicity, adapted to established timeframes (24 hours, seven days, the months, the seasons), had become fundamental. Hence, the attention of a few groups of headache researchers, such as the one headed by Giuseppe Nappi, was systematically being paid to "internal" factors of synchronization (or desynchronization), such as hormonal biorhythms and the sleep/wake cycle (the *milieu interieur*), and to "external" or environmental ones, such as the alternation of light and dark, geographical latitudes, lifestyles and habits (work shifts, mealtimes, etc.). On the basis of these observations, Giuseppe Nappi formulated the *dyschronic hypothesis* of primary headache, according to which these headache forms were underpinned not only by dysfunctions in the pain control systems, but also by a vulnerability of the rhythmic physiological organization of the central nervous system (Nappi et al., 1983). The malfunction of "biological clocks", and in particular of the hypothalamus, as already mentioned before by a few authors (Selby and Lance, 1960; Pearce, 1969) was reported to be a key factor in the pathogenesis of primary headaches (Nappi and Sjaastad, 1983).

At that time, numerous studies were being undertaken with the aim of establishing relations between these factors, primary headache patterns and changes in biohumoral, neurovegetative and neurophysiological parameters in man. However, many of these were abandoned after a few years due to various methodological limitations, linked mainly to the limited technology then available.

In more recent times, functional neuroimaging techniques have instead made it possible to give scientific support these early insights. In 1998, a PET study showed that cluster headache attacks are underlain by ipsilateral activation in the posterior hypothalamus (May et al., 1998). Much more recently, it has been shown that the hypothalamus is activated primarily in the early stages of migraine attacks (Maniyar et al.,

2014). The study that led to this finding was deemed so significant that it received the Harold G. Wolff Lecture Award conferred by the American Headache Society at the latest International Headache Congress, held in June 2013 in Boston (Maniyar et al., 2013).

Giuseppe Nappi et al., still in 1983, argued not only that environmental changes can lead to the triggering of headaches in susceptible patients, but also that this susceptibility (the *terrain* - the *trait*) can vary rhythmically over time. This further insight was another theory that was not confirmed until many years later, when it was demonstrated mainly through the neurophysiological studies conducted by the Liège group. Indeed, Prof. Schoenen and colleagues showed that migraine patients have exclusive neurophysiological characteristics (Schoenen et al., 1995), and that these can vary depending on when the patient is investigated: in the intercritical period, during an attack, or just before an attack (Judit et al., 2000, Coppola et al., 2013).

We believe that this historical overview demonstrates once again that clinical observation, if performed carefully, rigorously and critically, can be fundamental in clarifying not just the pathophysiology of some primary headache forms, such as migraine and cluster headache, but also the functioning of the central nervous system, which is probably the most complex structure in the known universe (Silvestri et al., 2013).

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