Familial periodicity in a multigenerational family of cluster headache: A case report

Cyprian Popescu

Abstract
I describe an unusual phenotypic phenomenon in two members of a multigenerational family of cluster headache (CH) with anticipation features. The index case, a 44-year-old woman, and her sister, a 40-year-old woman, have a CH phenotype with atypical features as the burning of the nose. Besides identically circadian and circannual features, they present distinct chronobiological features with the onset of the episodic pain attack every third day between them. I propose to entitle this clinical feature “familial periodicity” because of the remarkable phenotypic correlation and probably a similar genotype in the two sisters. Pathophysiologically, this phenomenon may be the result of the dysfunction of the suprachiasmatic nucleus of the hypothalamus on a genetic basis. This is the first case of familial periodicity, which allows extending the clinical spectrum of CH.

Keywords
cluster headache, familial periodicity, genetic anticipation

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Introduction
Epidemiological studies have shown that first-degree relatives of cluster headache (CH) patients are more likely to have CH than the general population.1,2 The occurrence of CHs in three-generation families was already noted.3 I report a new CH multigenerational Caucasian French family (Figure 1). Three of the six female subjects have the typical, periodical, CH phenotype, in which the headaches occur in cluster periods lasting about 1 month, more than once a year. Moreover, two patients showed a distinctive pattern of symptoms with infradian rhythmicity. The study participants gave their written informed consent prior to the study, which was approved by the local ethical committee.

Case report

Patient 1

The index-case, IV:5, a 44-year-old woman suffers from episodic CH since the age of 15. The attacks of excruciating intensity as stretching or squeezing of the right eye radiates toward the ipsilateral teeth, ear, and occipital region are accompanied by miosis, conjunctival injection, nasal stuffiness, and the sensation that her nose is burning. After the attack, she feels exhausted, shivers, and presents running nose. Attacks occur thrice every day and systematically one by night, last 15–30 min with a cyclic seasonal pattern, invariably in March and November. Attacks are aborted by injection of sumatriptan subcutaneously, twice a day, and oxygen inhalation, respectively, 480 mg of verapamil by day. The indomethacin test was performed to completely exclude paroxysmal hemicrania.

Patient 2

The sister of the index case, IV:6, a 40-year-old woman, follow-up for schizophrenia, presents episodic CH since the age of 15 like her sister. The attacks, lasting about 30 min, arrive systematically 2 days after those of her sister and...
have the same vasomotor, vasosecretory, and topography pattern. She reports similar circadian and circannual features occurring three times a day time of which one at nighttime, with the same clockwise regularity in March and November. She has the same clinical features with Horner syndrome, conjunctival redness, running nose, restlessness, and the sensation that her nose is burning. Attacks are aborted by an oral triptan (frovatriptan). The indotest was negative. She is also treated with olanzapine and benzodiazepines for schizophrenia.

Patient 3
The mother of the index-case, III:3, a 76-year-old woman, also had typical episodes of pain of the periorbital region radiating to the nuchal region. Hemifacial flushing, ptosis, miosis, and running nose are also systematically presented. There is no cyclic pattern of attacks, which occur rarely twice by day time and last about 30 min. Prophylactic management is not available.

Patient 4
The daughter of the index case, V:5, a 17-year-old girl, has severe pain behind the left eye radiating to the vertex, shoulder, and mandible with Horner syndrome, ipsilateral cheek flushing, conjunctival injection, and running nose. The attacks emerged at the age of 13 and occur periodically every 3 months, twice daily, last 30 min to 2 h and responded to oral triptans. She reports also migraine-like headaches with pulsatile hemicrania and nausea, thrice a month.

Patient 5
The daughter of the index case’s sister, V:4, an 18-year-old girl, described right periorbital pain like a stretching of the eye, lacrimation, and rhinorrhea. There are no circadian and circannual features and she seldom uses triptan treatment.

In addition, the maternal great-uncle of the index case, II:3, today deceased, had severe headaches associated with agitation and violent self-harm after the memento of his sister, II:2, currently under care for Alzheimer disease. Her daughter, subject III:3, remembers that her mother suffered years ago from sporadic severe headaches with vomiting for one-third of the headaches (Table 1).

Discussion
The onset, course, and severity of this multigenerational family of CH are compatible with the anticipation phenomenon. The mother of the index-case has had only episodic CH with late onset, but her daughters have debilitating conditions with earlier onset. The existence of the anticipation phenomenon was already suggested in some families with CH confirmed in a three-generation family of CH, but there are doubts about the reliability of the phenomenon. Specifically, compared to other reports, the two sisters of our family present causalgic pain of the nose and

Figure 1. Clinical presentation of an autosomal dominant cluster headache family.
distinct chronobiological features with the onset of the episodic pain attack 2 days apart. I have chosen to entitle this phenomenon “familial periodicity” because of the remarkable phenotypic correlation with reference to a probable similar genotypic pattern in the two sisters. The relationship between circadian regulation and CH stress the pivotal role of the hypothalamus in the homeostatic regulation. Abnormalities in the secretion of hormones in patients with CH with possible genetic mutations disturbing specific biological ways could underlie these peculiar and never noticed clinical condition. Hypothalamus dysfunction contributes to the cephalalgic and autonomic features as well as circadian and circannual periodicity of headaches. This observation of a particular infradian rhythm like the diurnal and seasonal periodicity in CH’s patients may involve the suprachiasmatic nucleus of the hypothalamus. In some families, the first-degree relatives of CH patients are more likely to have CHs than the general population with an autosomal dominant mode of transmission. Hypocretin receptor-2 (HCRTR2) gene 1246G-A polymorphism was considered as a putative factor in CH but more plausibly modulate the genetic risk for CH. A protective effect of the rs3122156 minor allele G on the HCRTR2 gene in Sweden was suggested. Hypocretin was involved in the circadian and infradian rhythm genesis, which regulate the CH attacks. However, HCRTR2 gene variant was never identified in the multigenerational families of CH. In contrast with a male-to-female ratio of 5:1 in sporadic cases, in familial cases, the ratio is only 3:1 probably due to sex-regulated factors. An Italian cohort study found a gender disparity with earlier age of onset and an upper representation of women in the familial cases. In our case, the predominance of females raises the matter of a particular genetically background with probably hormonal participation. Until today, association studies between CH and hormonal events were inconclusive. Because of the female gender of our patients, migraine and paroxysmal hemicrania diagnosis were also considered. However, an alternative diagnosis was excluded through extensive examination. A relationship of CH and migraine was already reported in monozygotic twin sisters. The CH phenotype and duration were typical for most of them, however, comorbidity with migraine was noted in two of our patients and might be explained at least in part by shared genetic factors. Further evaluation includes testing of CLOCK gene that could play a role in the pathogenesis of CH. It is worth to note that both sisters have a tremendous phenotypic similarity with, besides CH classical features, neuropathic pain, which could be also underlined by circadian rhythms. The neuropathic mechanisms by central modulation of nociception of the posterior hypothalamus were already involved in the CH physiopathology.

Clinical implications

- Extension of the clinical spectrum of CH in a multigenerational family of CH with anticipation features.
- Description of a periodic phenomenon, not related to circadian periodicity but rather to the infradian rhythmicity.
- Comprehension of the CH physiopathology in the context of particular chronobiological features and neuropathic mechanisms closely intertwined with CHs involving the posterior hypothalamus.

Author contributions

The author conceived and designed the study, examined the patients, analyzed the data, and wrote the manuscript.

Declaration of conflicting interests

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ORCID iD

Cyprian Popescu https://orcid.org/0000-0001-6108-8681

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