

Ten years of chronic cluster – attacks still cluster

Cephalalgia
30(9) 1123–1126
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DOI: 10.1177/0333102409351754
cep.sagepub.com



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Abstract

The chronic variant can be found in 10–20% of all cluster headache patients. While circadian and circannual rhythmicity are characteristic of the episodic variant, little is known on chronobiology in chronic cluster headache. We report a patient with chronic cluster evolved from episodic who recorded a total of 5447 attacks over 10 years. After spectral analysis, cosinor models were calculated within the frequency ranges of 23–25 h (circadian) and 11–13 months (circannual), respectively. Significant results ($P < 0.01$) were found for 24-h periods, but not for circannual intervals (12 months). However, with regard to circannual periodicity, a semi-circannual rhythm (5–7 months) was suitable for curve fit and yielded significant results in the cosinor analysis at 6 months ($P < 0.05$). This remarkable long observation period of 10 years shows that, at least for secondary chronic cluster headache which evolved from the episodic form, a typical circadian and circannual rhythmicity comparable to that of episodic cluster headache exists.

Keywords

chronic cluster headache, circadian rhythm, long-term, chronobiology

Date received: 1 September 2009; accepted: 17 September 2009

Introduction

Chronic cluster headache with remission periods of less than 4 weeks occurs in 10–20% of patients with cluster headache (cluster headache) (1). Secondary chronic forms (or ‘chronic cluster headache evolved from episodic’) can be observed after years of an episodic course with acute attacks over weeks or months (2). In addition, primary chronic forms have been described with cluster headache unremitting from onset. While circadian and circannual rhythmicity is considered typical in episodic cluster headache, little is known on rhythmicity in chronic cluster headache.

Case report

We report the case of a 65-year-old man with chronic cluster headache, who experienced his first attack in August 1995 at the age of 51 years. Three years later, episodic cluster headache was diagnosed and an appropriate treatment was started. From July 2000 the ICHD-II criteria for chronic cluster headach (2). were fulfilled. As acute medication, oxygen and intranasal zolmitriptan were given; as short-term prophylactic treatment, naratriptan 5 mg/day or intranasal zolmitriptan were taken (the latter two for up to 6 weeks

to ameliorate periods of exacerbation). Prophylactic treatment with the following substances was discontinued due to insufficient efficacy or side-effects: pizotifen, lithium, lamotrigine, and topiramate. Although clinical effects are minute, verapamil 480–600 mg/day is currently taken.

From January 1999 until December 2008, all relevant details were recorded electronically. In this period, the patient documented a total of 5447 attacks. Mean duration of treated attacks was 23.2 min; mean monthly attack frequency was 45.4. All data were subjected to spectral analysis in order to detect relevant, underlying, basic, biological rhythms. The basic rhythms were used for subsequent cosinor models. In an exploratory spectral analysis of circannual rhythms, we found a trend for ultra- (peak from 13–15 months) and infra-annual rhythms of attacks (peaks around 2,

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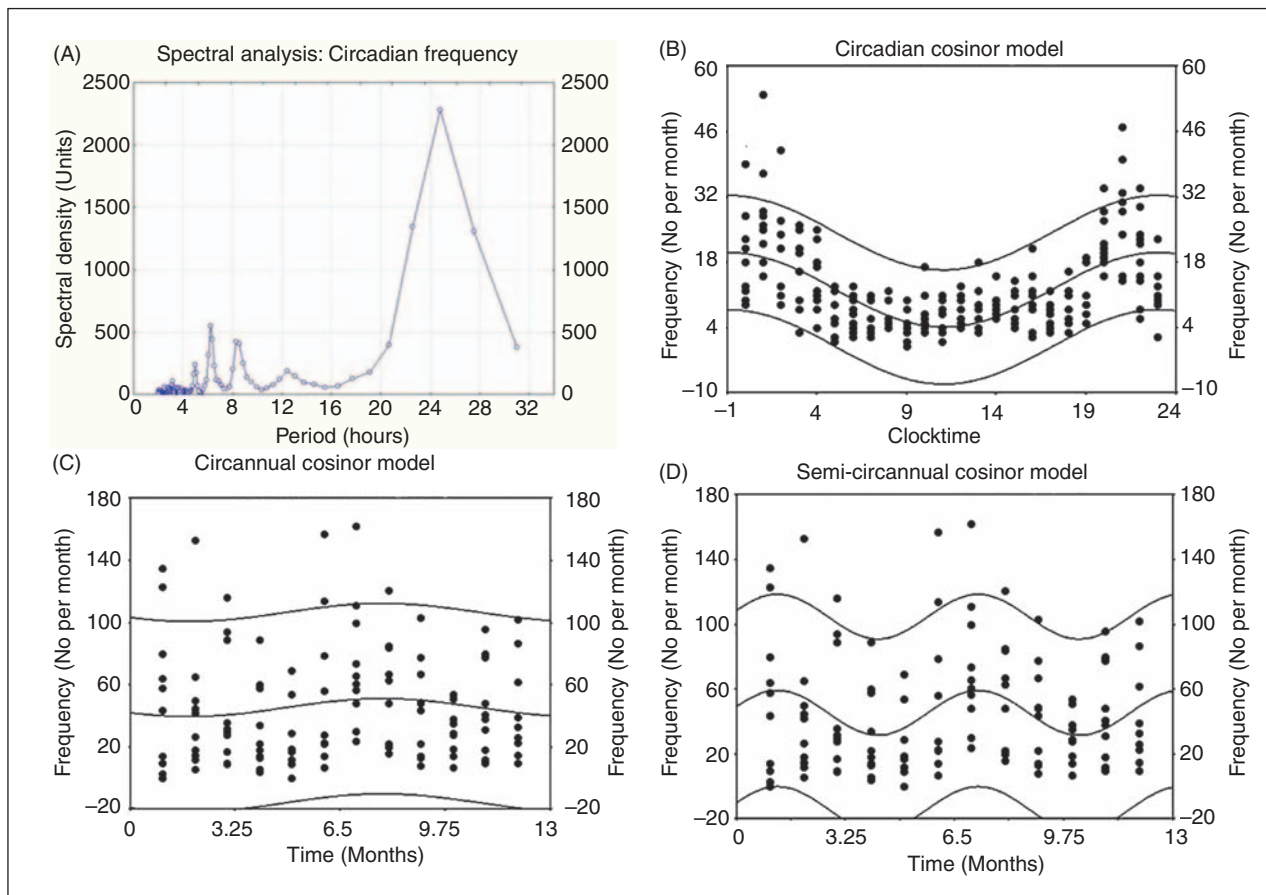


Figure 1. Chronobiological observations over 10 years of chronic cluster headache. (A) Spectral analysis of the circadian frequency of attacks. (B) Circadian distribution of attacks in the cosinor model with a period of 24 h (90% prediction limits): MESOR = 12.1 attacks/h, amplitude = 7.9 attacks/h ($P < 0.01$). (C) Circannual distribution of attacks in the cosinor model with a period of 12 months (90% prediction limits) without statistically significant results ($P > 0.05$). (D) Semi-circannual distribution of attacks in the cosinor model with a period of 6 months (90% prediction limits): MESOR = 45.4 attacks/month, amplitude = 13.8 ($P < 0.05$). Reference period 1999–2008.

4, 6, 7, and 9 months). The spectrum of circadian time series data (Figure 1A) shows an evident peak at 24.5 h. In addition, some minor peaks for infradian periods of 12, 8 and 6 h were found which correspond to harmonics of a 24-h rhythm. However, the statistical power in only one patient does not allow any further conclusions.

In the subsequent cosinor analysis, a significant fit for a circadian period of 24 h was found ($P < 0.01$; Figure 1B): MESOR (midline estimated statistics of rhythm) adjusted mean, 12.1 attacks/h, standard error of mean (SEM) 0.48; amplitude, 7.9 (SEM 0.67), acrophase (maximum with regard to reference time 00:00): 11 23:00. (SEM 0.08). Despite the slightly longer interval identified in spectral analysis, we used a 24-h interval since most circadian rhythms are synchronized to that period. Besides, a cosinor analysis for an interval of 24.5 h resulted in significant results as well ($P < 0.01$, data not shown).

The cosinor analysis for a circannual period of (Figure 1C) did not yield any significant results ($P > 0.05$). However, for semi-circannual rhythms (period of 6 months; Figure 1D), a significant fit was found ($P < 0.005$): MESOR, adjusted mean, 45.4 attacks/month (SEM 3.3); amplitude, 13.8 (SEM 4.6), acrophase (maximum) 7.2 months (SEM 0.3). The disease reached its climax between 2002 and 2004 with more than 600 attacks/year (Figure 2).

Discussion

While there is ample evidence for circadian and circannual rhythmicity in episodic cluster headache, little is known about chronobiological characteristics in chronic cluster headache (1). One prospective study with 180 cluster headache patients (19 with chronic cluster headache) described three peaks of attacks in

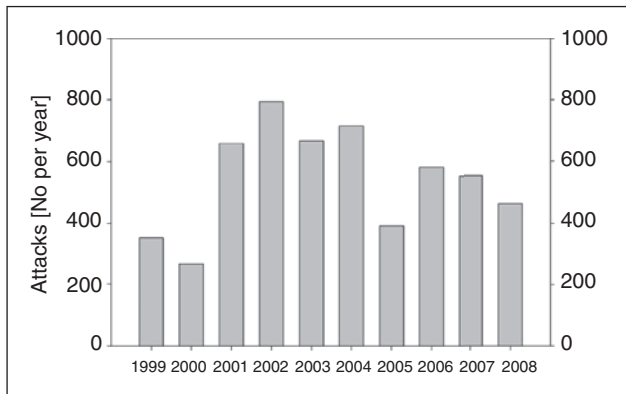


Figure 2. Distribution of attacks per year from 1999 to 2008.

a 24-h cycle (around 1 a.m., 2 p.m. and 9 p.m.). Of these patients, 47% described attacks exclusively during the daytime (3). However, in another prospective study, a nocturnal predominance of attacks was observed in 59% of 77 patients with cluster headache (one with chronic cluster headache) with peaks around 10 p.m. and 6 a.m. (4). In a retrospective series of 105 cluster headache patients, 47% reported a 'clock-wise regularity' with a nocturnal preponderance in 63% (5). As in the studies of Manzoni et al., (3) and Russell (4), our patient described a peak in attack frequency in the late evening and early morning, while the other peak around 2 p.m. was only observed in the Italian patients, who relaxed during these hours. As in Russell's study (4), our patient noticed no attacks during the afternoon. A general limitation of the cited studies is the fact that they mainly examined episodic cluster headache patients. Only two studies have focused on chronobiology in chronic cluster headache patients, of which one ($n = 230$, 21% with chronic cluster headache) found nocturnal attacks in both episodic cluster headache and chronic cluster headache at a predictable time in 71% and 74%, respectively (6). However, in a second study ($n = 113$ with chronic cluster headache), the majority indicated a daytime preponderance, likewise at fixed times (7). Thus, there is contradicting evidence for a general nocturnal preponderance of attacks despite the clear pattern in our patient, while 'clock-wise' circadian rhythmicity seems to be common in both episodic cluster headache and chronic cluster headache.

The issue of seasonal propensity of active periods is controversial as well. Ekbo (5) observed the occurrence of 'bouts', predominantly in spring and autumn, Kudro (8) in February and June – as in our patient. Others could not substantiate a preponderance of active periods at specific seasons or months (3,9). It is however noteworthy, that, on an individual basis, stereotypical circannual patterns have been reported and seem to be common in cluster headache (3,6).

Sjaasta (1) suggested that episodic cluster headache and secondary chronic cluster headache have only minute differences and display smooth transitions, while primary chronic cluster headache is a separate entity lacking the criterion of clustered attacks. The temporal profile meticulously compiled by our patient supports this theory, at least for secondary chronic cluster headache. At present, no prospective chronobiological data for larger groups of patients with chronic cluster headache are available which would be necessary to explore further the differences between the primary and secondary form of this rare disorder. As we did not correct our statistical analysis for the use of preventative treatment, our analysis may be confounded. This is unlikely, however, as the patient described only a mild-to-moderate effect of any given preventative medication.

One potential explanation for this striking circadian rhythmicity itself could be a connection between the posterior hypothalamus and the suprachiasmatic nucleus which is located in the anterior hypothalamus and serves as a 'master clock'. Orexins have been found to modulate not only neuronal activity in the suprachiasmatic nucleus (10) but also that of the trigeminal nucleus via afferents from the posterior hypothalamus (11). The orexins could serve as mediators between these two systems and explain the connection between pain and rhythmicity.

Conclusions

This is a remarkable, long-term course of chronic cluster headache prospectively documented over 10 years with a distinct circadian and semi-circannual rhythmicity over time. Infra- and supra-annual exacerbations over several weeks occur, independent of a 12-month cycle. This is important for clinicians, as, depending on the level of activity of the disease, a preventative treatment may be effective at some times but not at others. This implies that missing the effects of preventative treatment should not be misinterpreted as a failure – the prophylactic drugs may well be efficient again when the activity of the disease levels out again. In addition, a 'clock-wise' circadian rhythmicity of attacks and an individual circannual preponderance should be considered as a hallmark for cluster headache. Finally, after the initial episodic course and its climax between 2002 and 2004 (Figure 2), the headache shows a tendency to ameliorate progressively, which supports the notion that cluster headache tends to remit with age (6).

Acknowledgement

The authors thank the patient for providing his thorough collection of data for analysis and publication.

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