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REVIEW

Current Understanding of the Chronobiology of Cluster Headache and the Role of Sleep in Its Management

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Abstract: Cluster headache is uniquely rhythmic in its occurrence both diurnally and annually. This has implications for the clinical approach to the patient but also for our understanding of the role of central structures in its pathological basis. Many intrinsic and extrinsic factors seem to influence CH rhythmicity, including genetics. The proclivity for attacks to occur at night and the possible association with particular sleep phenomena, including sleep apnea, have motivated a number of studies which has improved our understanding but many questions remain unanswered. The sleep-headache interaction seems to be bidirectional and possibly both direct and indirect. The latter could involve more disperse networks of homeostatic regulation, which may better encompass recent observations. Treatment of the headache patient with concurrent sleep problems can be particularly challenging, especially considering side-effects and interactions of commonly used medications. While current treatment guidelines do not incorporate chronotherapeutic thinking, some evidence may suggest that application of such principles on an individual level may be beneficial.

Keywords: cluster headache, chronobiology, sleep, chronotherapy

Introduction

Cluster headache (CH) is a primary headache disorder which constitutes a unique clinical challenge. Two attack features stand out: The extreme pain and predictability. The former has been described as worse than childbirth, extensive limb fracture and kidney stones[1] and is included in the diagnostic criteria in The International Classification of Headache Disorders, 3rd Edition,[2] (ICHD-3). The unilateral, 15–180 min attacks may occur from once every other day up to eight times daily and are accompanied by ipsilateral cranial autonomic symptoms such as lacrimation, rhinorrhea and conjunctival injection. CH is a trigeminal autonomic cephalalgia – an umbrella term for disorders with such commonalities of which CH has the highest prevalence, longest attack duration and lowest frequency.[3] CH patients can sometimes routinely predict attacks to the hour[4] and attacks occur in week- or month-long clusters (hence the name), the presence and duration of which dichotomizes the disorder into episodic (eCH, longer attack free periods) and chronic (cCH, no meaningful attack free periods) CH. This differentiation serves mainly to describe the burden with no known pathophysiological differences. There is a male predominance of around 2 to 1, and debut in the third or fourth decade.[5]

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Patients are heavily burdened by the disorder[6] and the social and economic consequences are considerable.[7,8]

CH is sometimes characterized as a rare disorder with a prevalence of 0.1%[9] which is reflected in our understanding of the pathophysiology that in many areas remains speculative. Putative mechanisms revolve around pathological activation or disinhibition of the trigeminal autonomic reflex with involvement of the hypothalamus and other diencephalic and brainstem nuclei. This hinges on the relapsing-remitting nature and on the concept of CH as a sleep-related headache.[10,11] Generally, headache and sleep amalgamate clinically, physiologically and anatomically[12–17] but CH is likely the primary headache disorder with the closest relationship with sleep exempting the exceedingly rare hypnic headache.

It is easy to portray CH as a somewhat enigmatic condition with limited therapeutic options and many un- and misdiagnosed cases. However, the last three decades have seen some progress in therapeutics and in our understanding of the disorder. Still, studying sleep, headache and chronobiology is difficult, time-consuming and requires expertise. Few groups have undertaken the combined endeavor but recent results justify a combined look at the rhythmicity of the disorder which is the aim of this narrative review. These topics will be covered below and put into context of the clinical approach to the CH patient.

Chronobiology

Other neurological disorders also have chronobiological elements[18] but arguably not as pronounced as CH where the prevalence of retrospectively, self-reported diurnal rhythmicity is around 60–80%.[19–22] Despite some variation, it is a highly reliable finding also described in historical accounts and across varying populations.[23] Studies in the eighties showed clear hours of increased attack occurrence, possibly associated with sleep, and recurring clusters around the solstices in June and December.[24,25] These findings corroborated earlier reports showing a connection with relative states of activity and a proclivity for attacks to arise during times of relaxation.[26–29]

Modern studies of diurnal rhythmicity are mostly consistent. This author published findings from 351 patients showing that the most common time of attacks is around 1–2 a.m.[30] The concept of chronorisk was also suggested to describe the attack patterns as this term may better encompass the multiple identified extrinsic and intrinsic factors

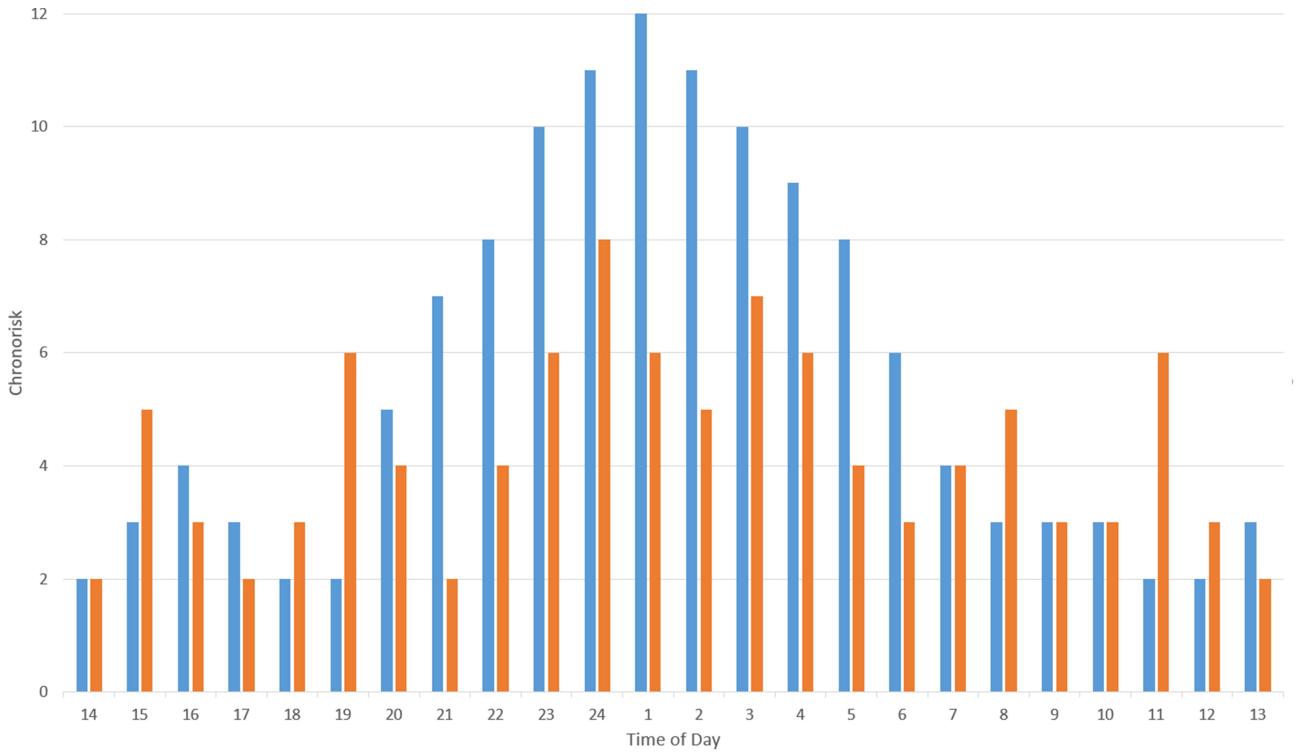

Figure 1 Representative chronorisk analysis of episodic (eCH, blue bars) and chronic (cCH, orange bars) cluster headache patients showing peaks of chronorisk during the 24 hours of the day. Chronic patients have more peaks throughout the day indicating more ultradian oscillation in chronorisk compared to eCH. A detailed description of the methodology behind this analysis is available in references.[30,36]

affecting rhythmicity. For example, in men compared to women, chronorisk peaks appear to be phase-shifted forward, with the nocturnal peak occurring 1 hour earlier, at 1–2 a.m. vs 3 a.m., despite similar bed-times and chronotypes.[5] Using signal-analysis methods, eCH patients have been shown to have much stronger circadian oscillations of chronorisk than cCH patients who have more prominent ultradian oscillations (Figure 1).[30] Since the suprachiasmatic nucleus is responsible for generating near 24-hour rhythms, speculatively, this phenotype may result from diminished influence of this structure on other diencephalic and brainstem circuits in cCH. This notion is partly supported by the differential treatment response to melatonin and lithium (enhances circadian PER2 protein rhythms[31]) in these patients.[32–34]

Annually, CH cluster occurrence has also been described to be predictable but studies have shown quite dissimilar results.[19–21,24] However, with closer scrutiny, there does seem to be one commonality between these which is clinical improvement in the summer months. Otherwise, different patterns have been observed with clusters around the summer and winter solstice.[24] It was speculated that at these times of the year, with the maximum difference in the duration of night and day, lacking entrainment somehow results in a destabilization of the suprachiasmatic nucleus (SCN) leading to cluster penetrance. Two other studies have shown worsening in the spring and fall[19,20] and a fourth have shown worsening in fall, winter and spring (Figure 2).[21] The latter suggested a relationship with hours of daylight since cluster activity was lowest during the brighter months of the year.

Another feature of CH rhythmicity is that it seems non-static with some inter- and intra-individual variation.[22] However, with disease progression, there seems to be a trend from randomness towards consolidation into nocturnal and midday attacks. This highlights a weakness in cross-sectional studies where individual variability cannot emerge. Another outstanding issue is that of rhythmicity with a phase longer than 24 hours (infradian) which can only be addressed through prospective recording which hitherto has not been undertaken on a large scale.

A genetic component in CH is supported epidemiologically and ties in with the strong chronobiological features.[35,36] Remarkably, it has been shown that in familial CH, relative nocturnal chronorisk is more than double that of sporadic CH.[36] Three possible culprit genes, which pertain to the topic of this review, have been identified.[35,37,38] First, a genetic polymorphism of the *CLOCK* (Circadian Locomotor Output Cycles Kaput) was recently found to be associated with CH. This signal strengthened after stratifying according to diurnal rhythmicity.[39] Second, a possible, albeit contended, association with the hypocretin (also known as orexin) 2 receptor gene has been suggested which together with the finding of lower CSF-hypocretin levels[40] implicate this system in CH pathology (discussed further below).[41–44] Lastly, the parasympathetic and hypothalamic signaling molecule pituitary adenylate cyclase-activating peptide (PACAP) represents another point of confluence between sleep, trigeminal-vascular coupling and chronoregulation and has garnered considerable

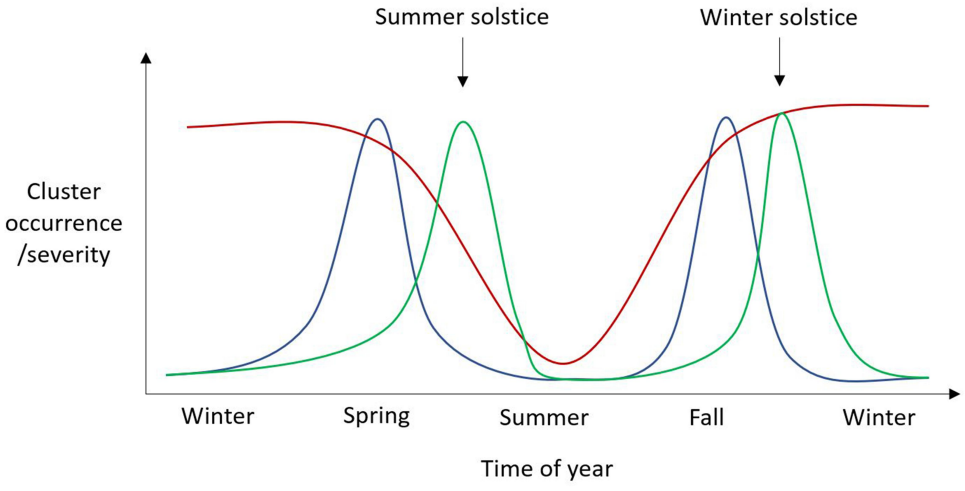

Figure 2 Schematic representation of three possible annual patterns of cluster occurrence/severity. Red line – cluster occurrence/severity improves during the summer months, possibly due to number of daylight hours. Blue line – Clusters occur during the spring and autumn months. Green line – clusters occur around the time of the solstices, possibly due to an inability to synchronize the internal circannual pacemaker.

interest.[45] A genetic study has shown an association between the PACAP receptor gene and CH[46] but decisive findings are still lacking.[47,48]

Sleep in Cluster Headache

Sleep and headache are entwined which is especially true for CH.[15] Nocturnal attacks result in a direct perturbation of sleep, but there is also evidence of an indirect, bidirectional interaction. Sleep as a trigger of attacks is reported by 80% of patients and napping by 30%.[21] Subjective sleep quality is reduced in CH, both in the cluster period and outside[21] and insomnia is also frequently reported.[20,49] Anecdotally, nighttime attacks may be averted by skipping the night's sleep.[50] Such findings and observations have justified a number of polysomnographic studies in CH. Generally, these are quite heterogenous, mostly uncontrolled, of limited size with only few observed attacks during full polysomnography. The hypotheses in these studies have been an association between CH and REM-sleep and sleep apnea.[51]

That CH is somehow associated with REM-sleep is suggested by the reported proclivity of the attacks for arising 90 min after sleep onset and the basic assumption that this coincides with the first REM-phase.[21,25,52] Early sleep studies confirmed this with the differentiation that it is only eCH-, and not cCH-attacks that show this tendency.[53,54] However, a 1991 case report with multiple sleep investigations in an eCH patient with narcolepsy with cataplexy sowed doubt with regards to any REM-association as there was no attack preponderance during the sleep-onset and excessive REM sleep characteristic of this sleep disorder.[55] Later studies added to this doubt,[56–58] although a simple tally of all reported attacks does in fact show a numerical overrepresentation of eCH attacks arising from REM-sleep, assuming that this stage makes up around 17% of total sleep time[57] in these patients (Table 1). However, REM-sleep cannot be a prerequisite as in these studies attacks have also been observed arising out of other stages in the same patients. This has led to the hypothesis that it is rather the end or beginning of sleep cycles that is vulnerable.[57] cCH patients trend towards more fragmented sleep, shorter total sleep time, longer REM-latency and more limb movement[56,57] and this less consolidated sleep pattern could explain why nocturnal attacks here are more randomly distributed. CH attacks have also been reported to arise at times of parasympathetic dominance or during times of shifting towards parasympathetic dominance from relative sympathetic dominance which may be the common factor between day- and nighttime attacks.[21,26] This could explain why spontaneous attacks are sparse during investigations as patients may be apprehensive due to the setting of an in-hospital investigation.

Table 1 Observed Nocturnal Cluster Headache Attacks

	Diagnosis (n)	Attacks Arising from	
		REM	Non-REM
Dexter et Weitzman[53]	eCH (3)	5	4
Pfaffenrath et al[56]	cCH (9)	5	17
Nobre et al[59]	eCH (37)	2	0
Della Marca et al[60]	eCH (1)	2	0
Terzaghi et al[58]	eCH (7)	1	4
Zaremba et al[61]	eCH (2)	0	8
Zaremba et al[61]	cCH (3)	0	8
Barloese et al[57]	eCH (20)	9	15
Barloese et al[57]	cCH (17)	2	6
	Total	26 (30%)	62 (70%)
	cCH	7 (18%)	31 (82%)
	eCH	19 (38%)	31 (62%)

Sleep apnea is one of the most studied aspects of CH and a long-debated topic. The disorder encompasses the partial or complete cessation of breathing during sleep due to anatomical and neuromuscular factors.[62] Obstructive sleep apnea has a prevalence of 2–14% but in patients being investigated for sleep disturbances it may increase to 20–90%.[63] Whether there is coincidental coexistence in populations with overlapping predisposing factors or a causal relationship with CH remains unresolved. A possible pathological correlate does exist in the form of disturbed autonomic homeostasis,[64] perhaps stemming from dysregulated or suppressed hypothalamic function.[65]

In mainly uncontrolled studies, using different methodologies and definitions, the prevalence of sleep apnea in CH has been reported to approach 80%.[54,59,66–69] One controlled study found increased occurrence in CH patients (29%) compared to age-, sex- and BMI-matched controls (7%) and a possible association with the cluster periods.[70] Reports of attacks being abolished by adequate treatment of sleep apnea and bruxism[71–73] would certainly suggest a causal nature as would a possible temporal proximity between sleep apnea events and attacks.[68]

However, two controlled Danish studies, with overlapping populations, found no difference in presence of sleep apnea between patients and controls, no association between attacks and apnea events[57] and no difference between the cluster and remission periods.[74] The latter partly corroborating older findings.[69] Further, in 6 patients treated with CPAP, there was no certain effect on the occurrence of CH.[57] The matching to controls in these three studies may not be entirely adequate, unfortunately, as up to 80% of CH patients are current or past smokers.[21,75] Smoking has been shown to worsen pre-existing apneic tendencies through several pathways[76] and strongly predicts sleep apnea after age and sleepiness.[77]

Here it is prudent to interject a distinction between CH and its possible association with sleep apnea and headache secondary to sleep apnea. The ICHD-3 deals with sleep apnea headache as a secondary headache (attributed to disorder of homeostasis) described as a morning headache with no accompanying features, bilateral in location, lasting under 4 hours and resolving with treatment of the sleep apnea.[2] This obviously is not reminiscent of CH but whether CH still can be secondary to sleep apnea, or vice versa, remains undecided and possibly nosological. Whether one can exacerbate the other is also undecided since the severity of the described morning headaches may not be related to the severity of the sleep apnea.[78–80] This may also pertain to other headaches and exacerbating and alleviating factors in general.

Lastly, the sleep disturbances in CH seemingly do not strictly follow a bout-remission pattern as does the headache attacks. This has been shown using subjective data where sleep quality, as measured using the Pittsburgh Sleep Quality Index, remained pathological up to 1 year after the last CH attack, a result which was reproduced across multiple subgroups without correlation to presence or absence of nocturnal attacks.[21] This pattern was reproduced objectively. Compared to controls, CH patients have shorter total sleep time, reduced efficiency, longer sleep and REM-latency but there are no differences in these measures in- and outside of the cluster.[74] Two models were proposed in which either a persisting, underlying pathology prevents sleep from normalizing outside of the cluster, or sleep normalization is a protracted process with a duration of a year or more. Overall, these findings support an indirect, complex relationship between CH and sleep.

The Hypothalamus and Hypocretin

Housing the organism's pacemaker, the attack rhythmicity of CH alone may implicate the hypothalamus and SCN. However, evidence for this particular structure's involvement in CH pathology is substantially stronger. Firstly, neuroimaging studies have shown mostly consistent structural changes as well as peri-ictal activation in the hypothalamus of CH patients.[81,82] Secondly, several hormones controlled by the hypothalamus are affected[83] including melatonin where the nocturnal melatonin peak is blunted and phase-shifted.[84–86] This could result from desynchronization between internal and environmental cues,[83] altered autonomic functioning but changes could also be secondary to the direct effects on sleep of nocturnal attacks. Thirdly, findings of sleep-[51] and autonomic alterations[64] implicate the hypothalamus/diencephalon as a nexus of homeostatic control. Lastly, as discussed briefly above, DBS of the posterior hypothalamus is effective in some CH patients[87] and its stimulation may influence both sleep[88,89] and rectify diminished sympathoexcitatory output in these patients.[90] Based on these observations the role of the hypothalamus in CH pathology has been suggested to be 1) a primum movens, 2) as that which ends the attack or 3) as responsible for diminished descending antinociceptive control putting the implicated circuits in a permissive or attack-susceptible state.

Although the hypothalamus has not classically been considered part of the central pain processing network in the headaches it may play a significant role. It does have bidirectional connections with limbic structures, the raphe nuclei, periaqueductal gray, rostroventromedial medulla, and the solitary tract. A bidirectional trigeminohypothalamic tract has been identified[91,92] and as an integrator of sensory information the hypothalamus in turn exerts descending control over the trigeminal cervical complex as well as the superior salivatory nucleus, the primary parasympathetic nucleus supplying the facial and cranial anatomy.[93] Some of these projections have been identified as hypocretinergic.[94,95] Thus, besides REM-sleep and apnea, this system could be a third possible point of convergence between CH and sleep.[96] Hypocretin-1 and -2 has differential pro- and antinociceptive effects and has through CSF-measurements, animal studies and the genetic studies mentioned above been implicated in CH pathophysiology.[40,97] Remarkably, hypocretin seems to exhibit seasonal variation inverse to the cluster pattern.[21,98] Still, the causality of the observed alterations

pointing towards hypothalamic dysregulation is undetermined and changes could well be secondary.

Clinical Approach and Management

CH is a uniquely chronobiological disorder which can be a substantial clinical challenge. While it remains hypothetical, the predictable nocturnal attacks, subclinical homeostatic disturbance and response to known chronotherapeutics implicate hypothalamic and diencephalic networks which engage in pathological interaction with trigeminal nociceptive processing. On this basis, attacks may worsen sleep and poor sleep may lead to more frequent attacks in a vicious circle.

CH is treated with a combination of acute, transitional and preventive measures.[99] Acutely, patients use injectable triptans or 100% oxygen inhalation. To provide immediate, fast-acting, preventive relief glucocorticoids per os or greater occipital nerve blocks can prevent or weaken attacks before prophylactic medication is titrated to effective levels. Typically, patients are offered 200–1000 mg verapamil daily although lithium is also effective, primarily in cCH. Recently, calcitonin gene-related peptide (CGRP) antibodies have become available and are effective in migraine[100] and eCH[101] but not cCH.[102] Invasive and non-invasive neuromodulation options are also available.

There are no treatment guidelines for CH which encompass sleep-related or chronobiological thinking[99,103] which is remarkable considering that out of the eleven preventive medications which are considered at least possibly effective in CH, four are known to manipulate molecular circadian feedback loops (melatonin, corticosteroids, lithium, valproic acid).[4] However, preliminary reports suggest that there may be therapeutic gains in tailoring treatment to the individual chrono-profile of the patient.[104] In one open-label study, 52 ECH and 18 CCH patients were administered 200–960 mg daily of immediate-release verapamil to time maximum plasma concentration with peak individual chronorisk. Results were impressive with complete termination of attacks in 94% of eCH patients and 56% of cCH patients. These results have yet to be confirmed in controlled setups but none the less act as proof-of-concept.

Melatonin has been shown to have some efficacy in eCH but not cCH (level C recommendation).[32] As stated above, sleep deprivation has anecdotal support[50] and explorations of the therapeutic effect of bright light therapy may also be warranted considering the inverse relationship between cluster occurrence and daylight found in one study.[21] It is clear that the medications commonly used in CH, and indeed in headache, may influence sleep in numerous ways and this area is quite complex (Table 2).[13]

Table 2 Frequently Used Headache Drugs and Their Possible Effect on Sleep

Headache Drug	Possible Sleep-Related Adverse Side-Effects
NSAIDs	Dampens amplitude of nocturnal melatonin Lowers sleep efficiency Worsens sleep disordered breathing
Triptans and ergots	Somnolence Decreases REM sleep
Serotonin antagonists	Increase wakefulness, reduces sleep Insomnia Boosts NREM sleep
Beta-blockers	Tiredness Insomnia Parasomnias and vivid dreams Lower melatonin – reduced circadian signal
Antidepressants	Delayed REM-onset Reduced REM-density Increased sleep fragmentation Worsens/induces RLS Worsens/induces PLMD Reduces dream recall
Anticonvulsants	Increased REM, reduced latency Somnolence/Insomnia Reduces RLS and PLMD
Melatonin	Increases sleep efficiency Possible effect on REM density Reduces symptoms of RBD Phase shift
Corticosteroids	Insomnia Reduces REM Increases nocturnal awakenings
Lithium	Reduces REM Enhances SWS Phase lengthening Enhances amplitude of circadian signal Worsens RLS
Ca-channel antagonists	Drowsiness Fatigue Insomnia Vivid dreaming
Caffeine	Boosts SWS in second sleep cycle

Whether the novel CGRP monoclonal antibodies affect sleep is theoretically possible. CGRP antibodies only cross the blood-brain barrier in minuscule amounts (<1%) and therefore a direct effect on sleep regulation is unlikely. However, areas not within the blood-brain barrier, including the anterior pituitary gland, choroid plexus, median eminence, area postrema and circumventricular organs, are exposed to the effects of the antibodies.[105] Consequently, there is a host of indirect pathways through which CGRP potentially could affect sleep but this remains hypothetical.

In the clinic, full polysomnography should be considered for headache patients when there are symptoms potentially associated with sleep disorders. Neither headache nor sleep disorder diagnosis should be delayed as causality cannot be expected and improvement of one is not guaranteed as the other is treated. Treatment and diagnosis should therefore be parallel and not sequential. When that is said, there is evidence from other headache disorders that treating sleep disorders and improving sleep hygiene may improve the headache[106–108] which may also be the case in CH where situational insomnia can be seen.[49] CH patients should not routinely be referred for cardio-pulmonary monitoring on the suspicion of sleep apnea, as CH is not an established, independent risk factor. However, patients with other risk factors and symptoms, which is frequent in this patient group,[75] should of course be referred for a proper workup.

With regards to sleep hygiene, CH patients have been reported to present a high proportion of shift workers[20] which may be the cause of circadian misalignment. A remedy for this is not straightforward, but maintaining an otherwise normal schedule of diet, exercise and caffeine may be helpful. Hypnotics should be avoided as these may worsen a preexisting headache.[109] Instead, melatonin with its very high tolerability and possible positive effect on CH should be used.

Conclusion

Many aspects of CH pathology remain unclear and this, together with the severity of the attacks and sparse treatment options, is the reason behind it being a clinical challenge. It is likely that a number of factors may worsen co-existing sleep disorders and with a keen eye on the possible detrimental effects of life-style factors and medication, the role of the clinician should be to ensure optimal treatment of CH and any possible sleep disorder. Keeping in mind that CH attack frequency, intensity and rhythmicity are non-static, continuous treatment adjustment and patient education are critically important. Further, high-rigor studies of the possible benefits of applying chronotherapeutic principles in CH and headache in general are highly warranted.

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