JCSM
Journal of Clinical Sleep Medicine

LETTERS TO THE EDITOR

Non-24-Hour Sleep-Wake Disorder in Sighted Patients: Dealing With an Orphan Disease

Comment on Malkani et al. Diagnostic and treatment challenges of sighted non-24-hour sleep-wake disorder. *J Clin Sleep Med*. 2018;14(4):603–613.

Corrado Garbazza, MD

Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Basel, Switzerland; Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland.

We read with interest the work by Malkani et al., who emphasize the difficulties that can be met in everyday clinical practice by diagnosing and treating non-24-hour sleep-wake disorder (N24SWD), especially in sighted subjects.[1] In fact, while this condition has been early investigated in totally blind people, given its high prevalence and its intuitive pathophysiology (lack of light perception to entrain circadian rhythms), leading some authors to define it "the quintessential circadian rhythm disorder,"[2] less attention has been dedicated to the study of sighted patients.

Apart from the pioneering temporal isolation studies conducted in natural bunkers, where healthy volunteers showed a "free-running rhythm" after deprivation of fundamental time cues, such as daylight, clinical cases of sighted individuals, who spontaneously develop N24SWD have been considered extremely rare. However, reports of similar, sporadic cases are growing in the literature, including some recently published in the *Journal of Clinical Sleep Medicine*[3–5] prior to the case series by Malkani et al.[1] Thus, while the epidemiology of sighted N24SWD remains overall unknown, its prevalence may have been underestimated so far, especially since the correct diagnosis is often overlooked.

Secondarily, while specific clock genes have been associated with some circadian rhythm sleep-wake disorders, the molecular mechanisms underlying N24SWD, by lacking familial clusters, are unexplored. Therefore, genome-wide association studies may contribute to better understand the role of genetics,[6] eg, regarding a possible predisposition to disease or response to treatment.

Finally, although the combination of light and melatonin represents the best available therapeutic strategy for sighted N24SWD, circadian rhythm resynchronization is not always achieved. No randomized controlled trials have been conducted so far, and the sole pharmacologic agent on the market (Tasimelteon) is only approved for use in blind patients.

In conclusion, when considering N24SWD in sighted subjects, we are confronted with an "orphan disease," listed on the European online portal Orphanet (https://www.orpha.net), and which is not only rare and underinvestigated, but also commercially rather unattractive. This condition has nevertheless dramatic consequences for the affected people, due to the severe circadian misalignment, going from the inability to work at regular times, to social isolation, as well as physical and mental disorders.

At our institution, we are collecting clinical cases of N24SWD diagnosed in Switzerland in a database, with the aim to create an international registry of patients assessed worldwide through standardized and comparable methods. This may represent a pivotal step forward to reach further scientific evidence and knowledge about the disorder, moving from the description of individual cases using different tools, to a shared data repository that will help us to better understand the pathophysiology, epidemiology and treatment of sighted N24SWD.

CITATION

Garbazza C. Non-24-hour sleep-wake disorder in sighted patients: dealing with an orphan disease. *J Clin Sleep Med*. 2018;14(8):1445–1446.

REFERENCES

1. Malkani RG, Abbott SM, Reid KJ, Zee PC. Diagnostic and treatment challenges of sighted non-24-hour sleep-wake disorder. *J Clin Sleep Med*. 2018;14(4):603–613.
2. Emens JS, Laurie AL, Songer JB, Lewy AJ. Non-24-hour disorder in blind individuals revisited: variability and the influence of environmental time cues. *Sleep*. 2013;36(7):1091–1100.
3. Ferri L, Filardi M, Moresco M, et al. Non-24-hour sleep-wake rhythm disorder and melatonin secretion impairment in a patient with pineal cyst. *J Clin Sleep Med*. 2017;13(11):1355–1357.
4. Solaiman SS, Agrawal R. Non-24-hour sleep-wake circadian rhythm disorder in a sighted male with normal functioning. *J Clin Sleep Med*. 2018;14(3):483–484.
5. Watanabe A, Hirose M, Arakawa C, Iwata N, Kitajima T. A case of non-24-hour sleep-wake rhythm disorder treated with a low dose of ramelteon and behavioral education. *J Clin Sleep Med*. 2018;14(7):1265–1267.

6. Mishima K. Pathophysiology and strategic treatment of sighted non-24-h sleep–wake rhythm disorders. *Sleep Biol Rhythms*. 2017;15(1):11–20.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June 11, 2018
Submitted in final revised form June 11, 2018
Accepted for publication June 14, 2018

Address correspondence to: Corrado Garbazza, Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Wilhelm Klein-Strasse 27, CH-4002 Basel, Switzerland; Email: corrado.garbazza@upkbs.ch

DISCLOSURE STATEMENT

This work was performed at the Centre for Chronobiology, University of Basel. The author reports no conflicts of interest.