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CASE REPORT

Unusual presentations of free-running circadian rhythm disorder in the sighted – Case report and Discussion

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Abstract

Free-running disorder (FRD) is characterized by inability to maintain stable entrainment to a 24h sleep-wake pattern. Patients with FRD show a sleep/wake pattern similar to those observed in time-free environments bereft of *zeitgebers*.

FRD is common in blind patients, and rarely occurs in sighted individuals. In individuals with no visual impairment, males are more commonly affected. Here, two unusual cases of FRD in young, sighted females are presented. Both patients responded to treatment with melatonin, but derived no perceived benefit from phototherapy.

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Background

Free-running disorder (FRD) or non-24h sleep/wake syndrome is characterized by an inability to maintain stable entrainment to a 24h sleep/wake pattern, resulting in progressive delay of the sleep/wake period over time. This may impact on the individual's ability to function within 24h societal constraints.

In a research environment with all environmental time cues (*zeitgebers*) removed, the human circadian period is normally longer than 24h.[1] Patients with FRD show a sleep/wake pattern similar to that observed in these time-free environments. Totally blind people with inability to perceive light, the most powerful *zeitgeber*, are commonly affected.[2] The condition is rare in sighted individuals; therefore, much of the available evidence in patients with no visual impairment is based on case reports or small cohort studies.[3] One large cohort study suggests that, in sighted individuals, FRD is much more common in males, with onset during the teenage years.[2]

Here, we discuss two unusual presentations of FRD in young, sighted females.

Case Report

Case 1

A 19-year-old female student was referred to the sleep clinic having failed the first year of her university studies due to sleeping in and missing lectures.

She presented with a history of excessive daytime sleepiness (EDS) since secondary school, regularly sleeping through her 7 a.m. alarm. Though perceived to be due to poor motivation, she was, in fact, often awake until 4 a.m. She denied symptoms of sleep-disordered breathing (SDB), such as snoring, witnessed apnoeas or choking episodes. There was no history of parasomnias, movements during sleep or symptoms of narcolepsy. She did not use tobacco, alcohol, caffeine or drugs. There was no family history of note, although she alluded to a "difficult childhood" and family expectation that she should be a high achiever. She had recently been diagnosed with depression, but was not on any medication. She had tried cognitive behavioural therapy, with limited success.

On examination, she was overweight (BMI 31.3 kg/m^2). Her Epworth Sleepiness Score (ESS) was 12/24 – a score of >10 on this validated measure of subjective daytime sleepiness is indicative of excessive sleepiness.[4] She had a Mallampati grade 2 oropharynx; the Mallampati score grades the level of crowding of the oropharynx and has been shown to be of clinical value in assessment of SDB.[5] Her sleep diary was consistent with a free-running circadian rhythm, her sleep phase delaying progressively over the 2-week period (Figure 1). She had no regular bedtime or waking time, and was sleeping for 7–9h/night. Actigraphy (a non-invasive technique using a wrist-worn accelerometer to measure activity and non-activity as a proxy for sleep and wake) was not performed since the diary was completed in a satisfactory manner.

Melatonin (2 mg) was prescribed for administration approximately 2h before her preferred bedtime, along with phototherapy at 7 a.m. On review in clinic after 7 weeks, she reported great benefit from melatonin,

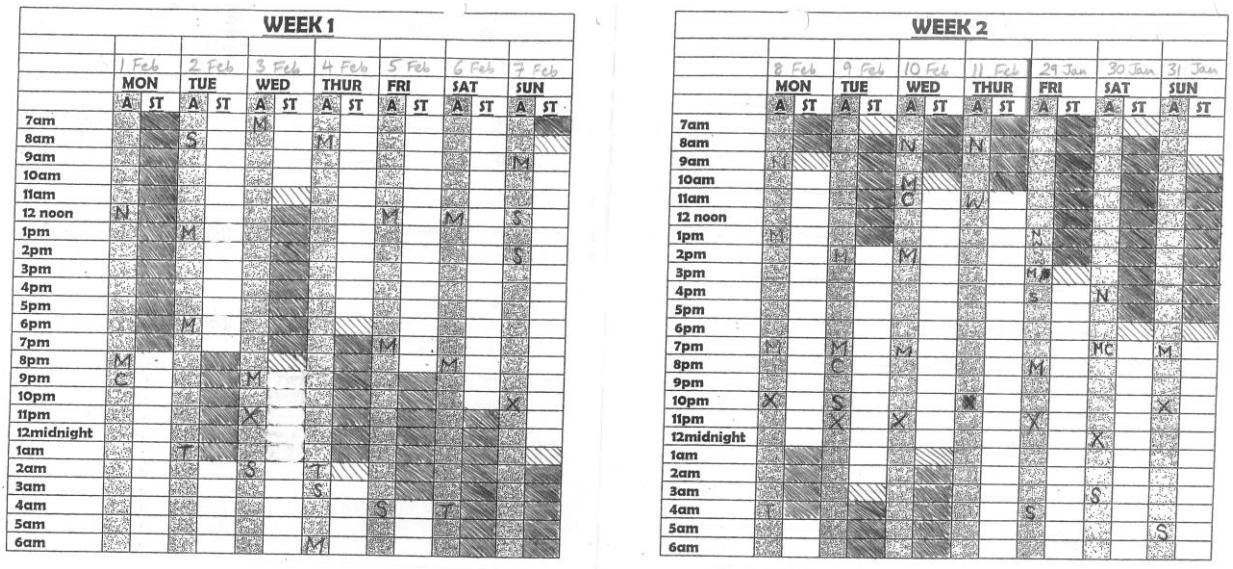

Figure 1. Sleep diary from Case 1 showing progressive delay of sleep period (black bars) over a 2-week period.

retiring at midnight, rising at 8 a.m. and sleeping for 7–8h/night. Her sleep/wake pattern was resetting well, and she perceived an overall improvement in her symptoms. She reported no benefit from phototherapy and discontinued from treatment. She was still depressed and was referred to psychology, continuing on melatonin. After 12 months, her depression and FRD had corrected completely, with no further treatment required.

CASE 2

A 19-year-old woman presented with a history of "poor sleep" since birth. This was first investigated at age 14, at which time she was tired during the day with poor concentration and had missed much of her schooling. Her weight was normal (BMI 22.6 kg/m^2) and she did not exhibit symptoms of SDB or narcolepsy. Assessment by a clinical psychologist found no evidence of depression. She retired late, had difficulty initiating sleep, lay awake until 4–5 a.m. and consequently slept late into the following day. Her sleep diary showed variable sleep duration of 1–16h sleep per day and a diagnosis of delayed sleep phase syndrome (DSPS) was made.

The patient was investigated further at age 15. By then, she was retiring at 5 a.m., falling asleep at 6 a.m. and waking refreshed at 4 p.m. the following day. A 2-week actigraphy study showed a non-24h sleep/wake cycle. She was prescribed melatonin to take at 10 p.m., with phototherapy in the morning. After 2 weeks, there was no improvement in her symptoms, perhaps due to incorrect use of the lightbox when awakening at 4 p.m.

When seen in our clinic, the patient had passed all her school exams, albeit by sitting them at flexible times during the day and night. She was unemployed. She was slightly overweight (BMI 26.9 kg/m^2) and did not report EDS (ESS 0/24). She had a Mallampati grade 1 oropharynx, with no symptoms of SDB, narcolepsy or parasomnias. She was an ex-smoker of 2 months, having smoked 20 cigarettes/day since age 13 years. She drank only occasional

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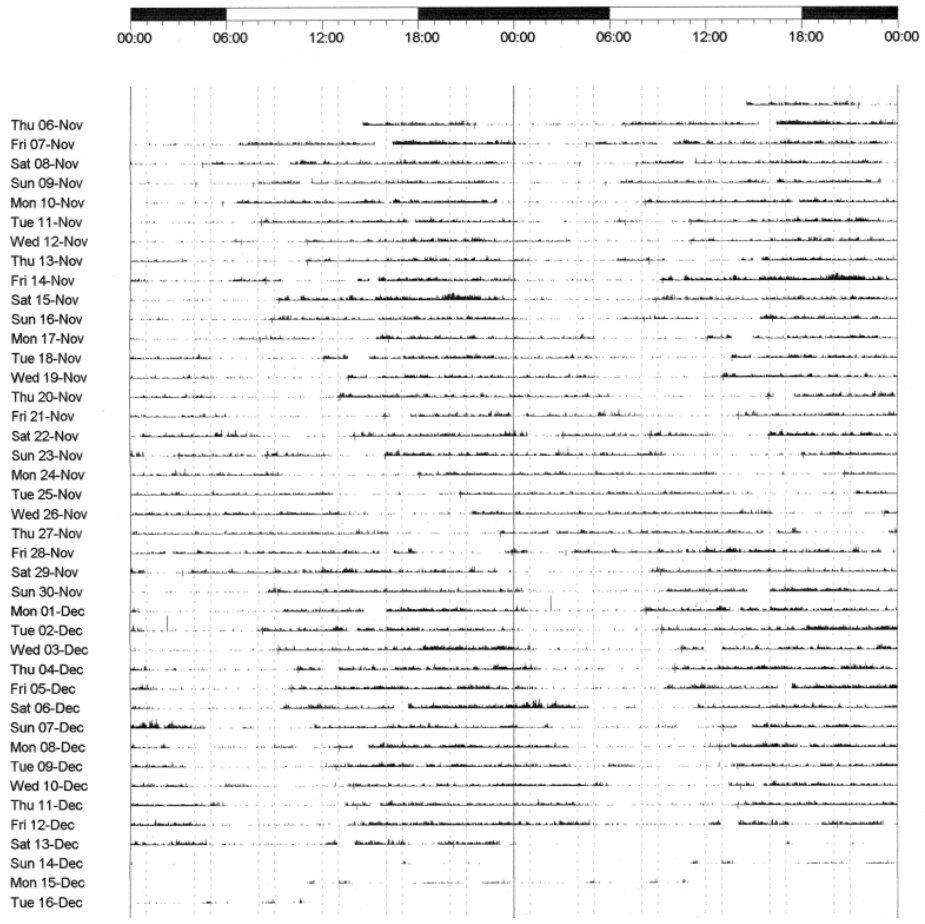

Figure 2. Actigraphy report (actogram) from Case 2. Note the aslant pattern, which is indicative of a classical free-running disorder.

alcohol and caffeine. She denied any hyperphagia, anorexia or hypersexuality. There was no mood disturbance. Her only medication was a progestogen-only oral contraceptive (OCP). Her mother had a history of discoid lupus and pernicious anaemia. There was no family history of sleep problems. Blood tests showed a vitamin B_{12} level at the lower end of normal, and low late-afternoon cortisol level. However, intrinsic factor antibody was normal, as was a short synacthen test.

A 1-month actigraphy study confirmed a classical free-running circadian rhythm (Figure 2).

The patient commenced 1 mg melatonin, to be taken 5h before bedtime while she was in a suitable day/night phase, along with oral B_{12} supplementation. Phototherapy was discontinued, with the intention of reinstating this once settled into a more regular rhythm. At a 5-month review, the patient was falling asleep around midnight and, although she was still sleeping until midday, there was now a consistent wake-period during the daytime. Although still unemployed and lacking in daytime structure, she appeared more positive and committed to improving her sleep patterns.

Discussion

Diagnostic criteria for FRD are outlined in the *International Classification of Sleep Disorders 2nd Edition (ICSD-2)* as a primary complaint of either insomnia or excessive sleepiness related to abnormal synchronization between the external 24h light/dark cycle and internal circadian sleep/wake rhythm, which cannot be better explained by another sleep, medical, neurological or psychiatric disorder, or drug use.[6] Although the absence of light perception is the cause in most blind subjects, the aetiology and pathogenesis of FRD in sighted individuals remains problematic; risk factors include cranial trauma,[7] dementia[8] and intellectual disability.[8] Neither of our cases presented such a history.

A previously published cohort of patients with FRD[2] (n=57) suggests that, in sighted individuals, FRD is more common in males (male:female ratio 2.6:1) with age of onset typically during teenage years. Both of our cases experienced onset or worsening of symptoms in adolescence. DSPS (characterized by a consistent sleep schedule that is delayed beyond the conventionally desired time)[7] and psychiatric problems preceded the symptoms of FRD in 26% and 28% of the cohort respectively.[2] Of the group exhibiting premorbid psychiatric problems 94% experienced secondary social withdrawal suggesting this to be an important aetiological factor in the pathogenesis of FRD. Nearly all patients (98%) experienced severely disrupted social functioning. This is reflected in our cases with both patients struggling to remain in education or employment. Patient 1 was depressed but it is possible that this was a result of, rather than a precursor to, the sleep disturbance with both her depression and FRD resolved by the use of melatonin. Patient 2 did not exhibit psychiatric problems but had been initially diagnosed with DSPS.

Both *ICSD-2*[6] and practice parameters published by the American Academy of Sleep Medicine (AASM)[10] recommend use of sleep diaries and/or actigraphy over multiple weeks for evaluation of FRD. AASM practice parameters support the measurement of circadian phase markers, e.g. melatonin rhythm, as an alternative diagnostic tool in cases where diary or actigraphy data are considered unreliable. However, we found this unnecessary since an adequate diagnosis was obtained using conventional methods.

Recommended treatments for FRD include timed bright light exposure in the morning to increase the body's production of endogenous melatonin, timed exogenous melatonin administration a few hours before bedtime, and prescribed sleep-wake scheduling.[10] Both patients perceived benefit when using melatonin. Though neither found phototherapy useful, issues with correct use of the treatment were evident. Anecdotally, there is some evidence for the administration of vitamin B_{12} (oral or intramuscular) as a potential stimulus for entrainment, although the physiological basis for this is unclear. A multicentre trial of vitamin B_{12} for treatment of DSPS did not show any benefit.[11] Patient 2 had a borderline low serum B_{12} level, possibly secondary to the OCP.

It is important that interventions such as melatonin and phototherapy are reinforced by behavioural modifications and good sleep hygiene, such as maintaining a bedtime routine, creating a favourable sleeping environment and controlling light exposure. Patient 2 was particularly withdrawn and

isolated with no social cues to reinforce a 24h rhythm.

In conclusion, further research is required to better understand the aetiology and mechanisms of FRD in sighted patients. The link between psychiatric, behavioural and social factors as contributors and consequences of FRD is complex and merits investigation. However, the paucity of reported cases in this patient group presents a significant challenge.

Key Learning Points

- Free-running disorder (FRD) is common in people with visual impairments who lack light perception, but can occur, rarely, in the sighted.
- Diagnostic criteria for FRD include a primary complaint of either insomnia or excessive sleepiness related to abnormal synchronisation between the external light/dark cycle and internal sleep/wake rhythm, which cannot be better explained by another disorder or drug use.
- Recommended screening tools include actigraphy and/or sleep diaries over a number of weeks.
- International guidelines recommend the use of melatonin and/or bright light therapy for treatment of FRD. However, correct administration and use is key to the success of these treatments, which should be reinforced by behavioural modifications and good sleep hygiene.
- Psychiatric, behavioural and social factors may be contributors to or consequences of FRD in the sighted, but further research is required to better understand the aetiology.

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