REVIEW ARTICLE

Circadian rhythm sleep disorders

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Introduction and Basic physiology of circadian sleep rhythms

The human sleep wake cycle is the prototypic example of all the circadian physiological processes in the body. The mammalian circadian clock is located at the "Suprachiasmatic nucleus of the hypothalamus' through lesional studies in rodents and through neural transplantation experiments. Recipients whose SCN was lesioned experienced restoration in their circadian rhythms, after they were transplanted with fetal SCN tissue. Some reciprocal grafting studies also brought out similar observations; circadian cycles of grafted tissue could be restored while those of host remained disturbed[1].

Consistent with their clock function, the SCN neurons exhibit an internal rhythmic activity, which is generated by cyclic expression, transcription, and feedback regulation of recently identified genes (CLOCK, PER, and others), arrested by the inhibition of protein synthesis, and preserved in isolation from the surrounding brain tissue in cell cultures[2].

The endogenous circadian clock in humans is slightly longer than the regular clock day (24 hours), measuring about 24.2 hours[3]. If the endogenous circadian clock would be required to function independent of the external environment clock, there would be continuous phase delay and no synchrony would be established between the two circadian cycles. Certain external stimuli, among which light is probably the one most important, can bring about synchronicity of the biological clock with the environmental clock. These external stimuli are called 'zeitgebers'. The process of establishing phase synchronization between biological and planetary periodicities, i.e., setting the biologic clock, is referred to as *entrainment*.

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Disorders of circadian sleep rhythm

Conditions in which this delicately balanced circadian cycle of sleep wake periods is disturbed for sustained periods of time, with or without environmental influences, are referred to as circadian rhythm sleep disorders (CRSD) (Table-1).

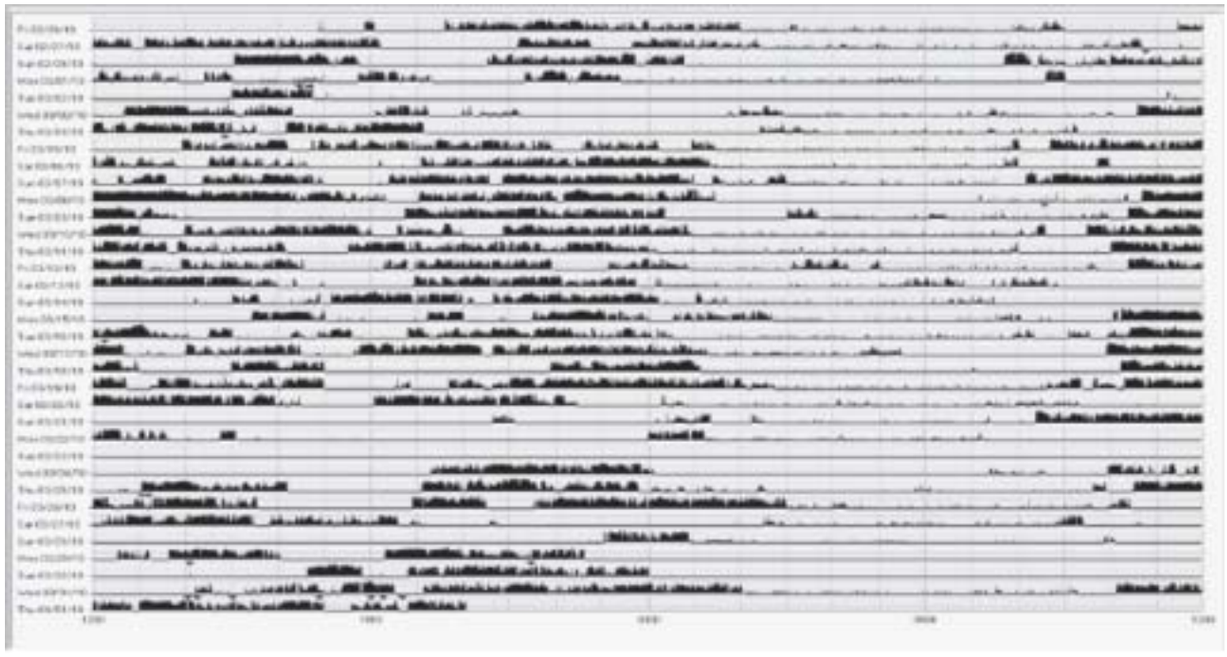
Table 1: The table displayed below shows the various classes of the CRSDs[4,5]

Primary		Secondary	Not otherwise specified
Intrinsic	Extrinsic		
Delayed sleep phase syndrome	Jet lag disorder	Head injury	
Advanced sleep phase syndrome	Shift work disorder	Alzheimer's disease	
Free running Disorder		HIV and other neuroinfections	
Irregular sleep wake rhythm		Parkinson's disease	
		Epilepsy	
		Depressive disorders	

CRSD-Delayed Sleep phase type:

Case#1

A 21-year-old student presents to us with a history of not being able to fall asleep for hours after going to bed.



15 day Actigraphy record showing delayed sleep phase with grossly irregular cycles

His usual bedtime is 3-4 am and usual wake up time is 7 am. He tries to nap in the daytime, but cannot and feels unrefreshed. On exploring, he admits that this is a long-standing problem, at least since the age of 14-15 years. No psychological stressors were reported and no history to suggest depressive or anxiety features were found.

Presentations

- Usually presents during adolescence or early adulthood[6].
- Long-standing initiation insomnia
- Sleep timings delayed 3-6 hrs relative to socially acceptable timings
- Missing classes, office in the morning often
- Enforced unconventional wake times lead to chronic sleep deprivation, morning fatigue and difficult to wake up in morning.
- Usual sleep onset: 2-6 am, wake time: 10 am -1 pm.
- On weekends/vacations, patients usually extend their sleep times significantly.

Prevalence

The delayed sleep phase syndrome is the commonest among intrinsic primary CRSDs, with the prevalence among the general population being 0.13 to 0.17% and 7-16% among adolescents [6,7,8].

Pathophysiology

This CRSD type results from an interaction of various genetric, physiological, behavioral and environmental factors. The genetic hypothesis gathers strength from the autosomal dominant pattern seen in one large family reported[9], and with evidence of polymorphisms in circadian rhythm genes like *hPer3*, arylalkylamine N-acetyltransferase, HLA and *Clock*[10-13].

Abnormal entrainment of the circadian clock to synchronizing agents like light might also be contributory to development of this condition into a disorder[14].

Diagnosis

Diagnosis mainly based on history and Sleep log or actigraphy at least for 7 days[15]. To assess the timing of physiologic markers, such as continuous recording of body temperature and dim light melatonin onset (DLMO) may also add in diagnostic information[16,17]. Nocturnal Polysomnography is some time needed to exclude other sleep disorders.

Treatment

Chronotherapy – This technique involves strict adherence to changed routines, good sleep hygiene and directions

to delay sleep and wake times by about three hours every two days until the desired sleep times are achieved[18-19].

Bright light therapy – Daily morning exposure to bright light (2000 to 10,000 lux, around 6-9 am), with restricted evening light helps in restoring the sleep rhythms significantly[18-20]. Dewan et al observe that longer periods of moderate intensity light may be more effective than a shorter exposure period of high intensity light[21].

Melatonin: In a recently published meta-analysis, Melatonin was found to be effective in patients with DSPS irrespective of dosage used[22]. Benefit has been observed with 0.3 or 3 mg or even higher doses of melatonin[23].

Sleep hygiene

- Keep a regular sleep-wake schedule, including weekends.
- Avoid caffeinated beverages after lunch.
- Avoid smoking, especially in the evening.
- Avoid alcohol near bedtime.
- Restrict sleep to amount needed to feel rested.
- Do not go to bed hungry.
- Adjust bedroom environment
- Do not engage in planning the next day's activities at bedtimes.
- Exercise regularly for about 20 to 30 minutes, preferably 4 to 5 hours before bedtime and not immediately before bedtime.

CRSD – Advanced sleep phase type

This CRSD type is much uncommon as compared to the delayed sleep phase type. It typically has the following presentations, which aid recognition of the condition, more dramatic and more recognizable. With advancing age, its prevalence may rise to approximately 1%[24].

Presentation

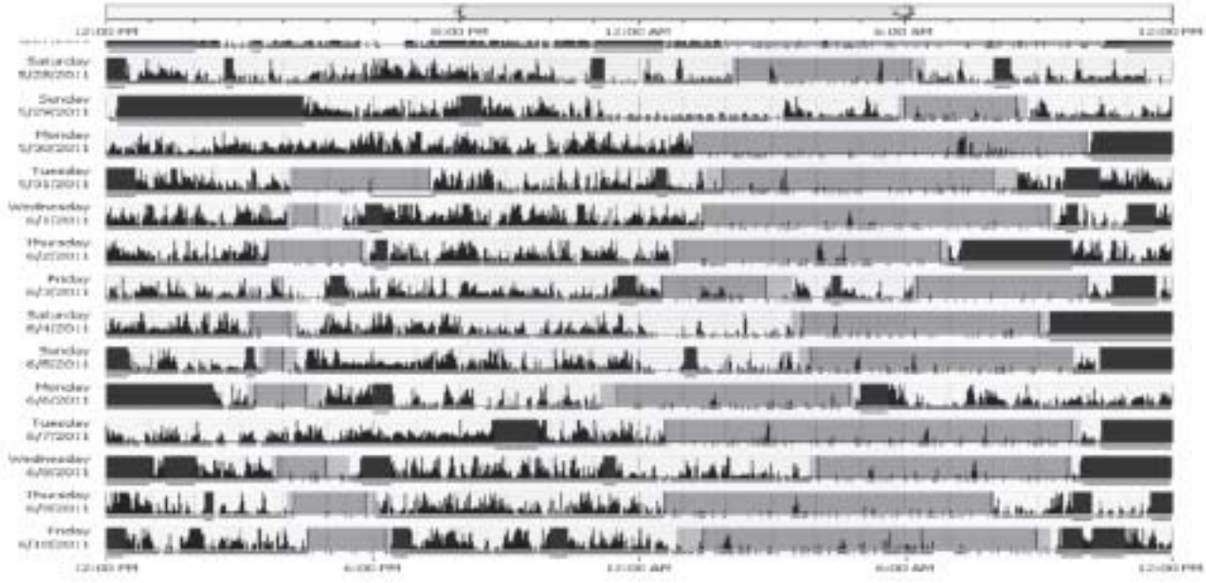
- Maintenance insomnia/ early morning awakenings.
- Habitual and involuntary sleep timings 3-4 hours in advance of usual social timings.
- Tendency to nap in late afternoons or early evenings.
- Socially less problematic.

CRSD – Free running type

This disorder is typically seen among almost 50% of visually challenged individuals[25], is characterized by a steady drift of timing of major sleep and wake periods.

CRSD – Irregular sleep wake rhythm type

This circadian sleep wake pattern is commonly seen among patients suffering from neurological disorders like dementia, brain injury, mental retardation and others.



Actigraphy record of shift-worker presenting with complaint of unrefreshing sleep despite opportunity to sleep. Record of time when patient took leave, did not go to work

There is no discernible pattern of sleep wake timings and their logs reflect patterns seen among patients with poor sleep hygiene.

CRSD - Shift work type

This disorder seen among approximately 10% of people working in night (or early morning) shifts and among rotating shift workers[26]. They often present with either history of insomnia, unrefreshing sleep or excessive daytime somnolence.

Case#2

A 34 year old loco-pilot of Indian Railways, presented with history of right hemicranial headache off and on for last 6 years. He reported feeling of being unfresh in the mornings, without any history to suggest initiation or maintenance insomnia. He is barely able to sleep when he gets the opportunity to sleep according to the shift he is working in.

CRSD - Jet lag type

This commonly encountered disorder occurs when people travel across time zones. Change in time zones leads to misalignment of the endogenous circadian sleep wake cycle with external environment. Jet lag suffered is worse when one undertakes eastward travel as compared to westward travel.

The presentation is with sleepiness according to the time zone of origin: associated with malaise, GI upset and mood changes[27].

Secondary CRSDs

There is not much literature on the highly prevalent CRSDs among patients with various neurological and psychiatric conditions.

Reports from patients with head trauma, some infections like HIV and tubercular meningitis, dementia, depression, and others, have suggested the occurrence of CRSD in a significant proportion of patients.

Recognition of co-existing CRSD and initiation of treatment for the same, would go a long way to improve the quality of life of these patients.

Evaluation of the CRSDs

A detailed history and a high index of suspicion are very useful in identifying the CRSDs, especially the most common CRSD-delayed sleep phase type[18-19].

Some investigation tools are essential in establishing the diagnosis of these conditions:

1. Sleep logs and diaries: A simple tool, this should be mandatory in the evaluation of patients with CRSDs. It has been found to be fairly reliable. The log should be simple but comprehensive, with details about sleep versus wake timings clearly visible by shading. Additionally, details about meals, caffeinated beverages, alcohol and drug intake should be marked clearly with symbols.
2. Actigraphy: The actigraphy device is a small portable wrist watch, which records movements over extended periods of time. Actigraphy is a requirement for the diagnosis of most CRSDs according to the ICSD-2 diagnostic criteria. It has been found to be the most usable, accurate tool for diagnosis of the CRSDs.
3. Circadian phase markers

- *Core body temperature:* This tool is not very useful and utilized only in research settings, mainly since the temperature rhythm is easily masked by activity, food intake and by sleep.
- *Melatonin estimation in plasma, saliva:* periodic assay of melatonin in these body fluids helps determine the transition from low daytime levels to high levels at night, referred to as the 'dim light melatonin onset (DLMO)'.

Treatment of CRSDs

Treatment strategies mainly include

- Chronotherapy
- Bright light therapy
- Melatonin and
- Behavioral modifications

The use of each is specific for specific conditions as well as on a case to case basis (figure 1)

Acknowledgement

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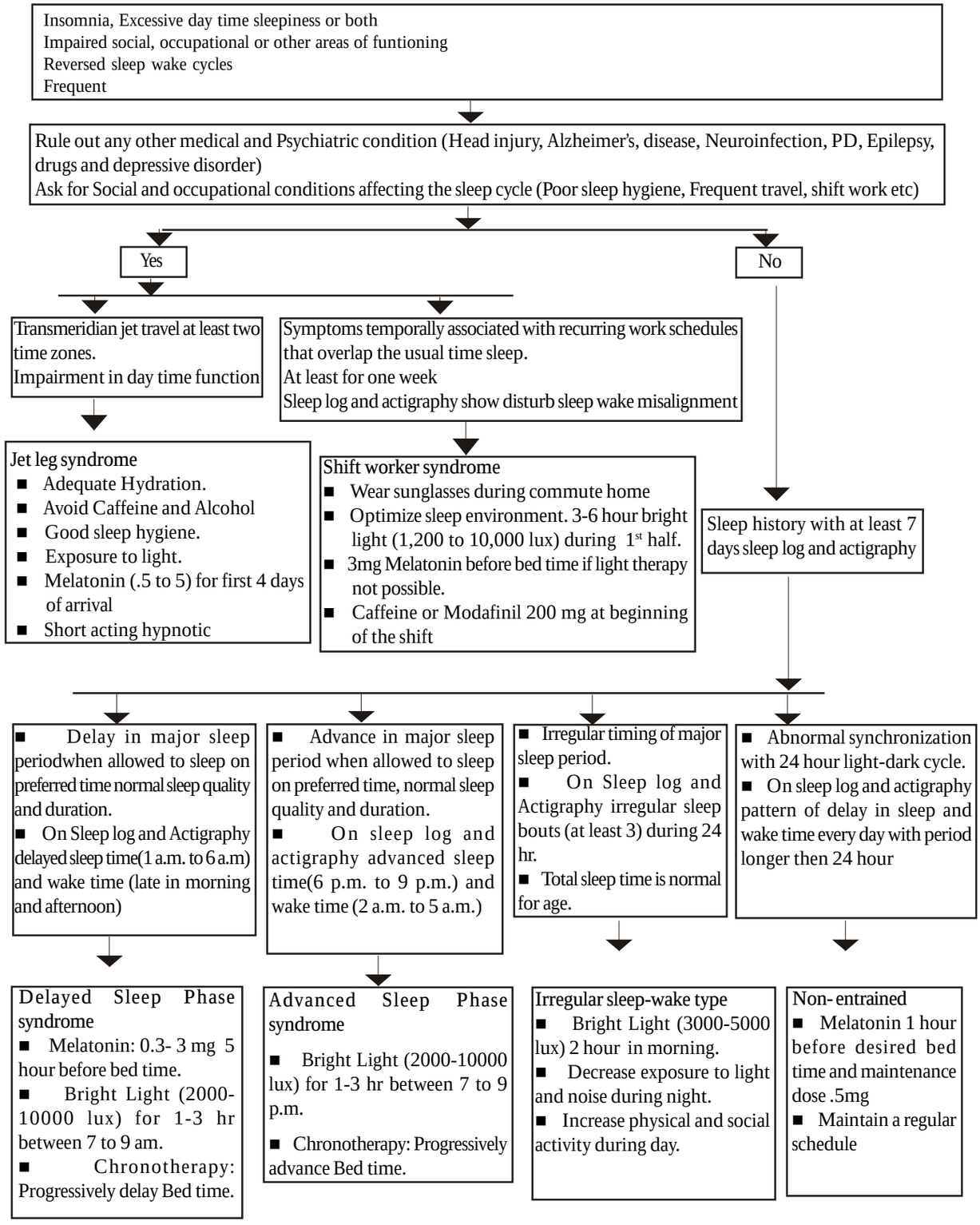

Figure 1: Dignostic and treatment algorithm for Circadian rhythm sleep disorders

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