The delayed sleep phase syndrome: clinical and investigative findings in 14 subjects

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Abstract
Fourteen subjects are described in whom a clinical diagnosis of the delayed sleep phase syndrome was made. The condition is multi-factorial, dependent on lifestyle, mood and personality, as well as on familial factors but no single factor in isolation is sufficient to explain the delay in sleep timing. Refusal to attend school may be important in some instances but will not explain cases with delayed age of onset. In half the subjects the delay in sleep phase started in childhood or adolescence. The syndrome causes severe disruption to education, work and family life. Polysomnography, motor activity monitoring of rest-activity cycles, plasma melatonin profiles and urinary melatonin metabolite excretion are normal. Different patterns of sleep phase delay seen in the syndrome include stable, progressive, irregular and non-24 hour sleep-wake cycles. These patterns may result from different social and other Zeitgebers ("time-markers", for example sunrise, sunset) in the normal environment. Treatment by forced sleep-wake phase advance or with melatonin resulted in a partial sleep-phase advance but this was not maintained on stopping treatment.

The existence of a specific delayed sleep phase syndrome has been questioned in the presence of the many normal environmental and social factors which disrupt the regular sleep-wake cycle. As an example of the extreme but normal range of sleep-wake pattern seen at adolescence, Wirz-Justice described the chaotic lifestyle of an undergraduate with near total loss of circadian sleep-wake rhythmics during most of the Oxford term, who could entrain normally at exam time. The conclusions of Weitzman et al have been supported by other similar accounts of a delayed sleep phase syndrome, often without specific environmental or psychiatric influences. Despite these reports the definition and recognition of the delayed sleep phase syndrome has remained difficult. We report here a series of 14 subjects with a delayed sleep phase syndrome seen over a five year period in a sleep disorders clinic, presenting with a primary complaint of insomnia.

Patients and methods
SUBJECTS
The criteria for the diagnosis of delayed sleep phase syndrome were adopted from those of Weitzman et al, Thorpy, and the American Sleep Disorders Association Classification. 1

1) Complaint of inability to fall asleep and wake spontaneously at the desired clock-time.
2) A phase delay of the major sleep episode in relation to the desired time for sleep.
3) Symptoms present for at least 12 months.
4) No evidence of any medical, psychological, environmental or psychiatric factor sufficient to explain the above symptoms.
5) Absence of any anatomic lesion on head CT scan; and normal polysomnographic findings apart from an atypical time of sleep onset and waking.

During the period 1985–90, 14 subjects, thirteen male and one female, all of white origin, were seen and took part in a prospective study.

CLINICAL EVALUATION
All subjects had a standard clinical evaluation including sleep-logs, pubertal assessment, tests of intelligence (Mill Hill vocabulary scale and Ravens Progressive Matrices—chosen for compatibility with previous studies of the delayed sleep phase syndrome); personality (Minnesota Multiphasic Personality Inventory, MMPI); mood (Beck Depression Inventory, BDI); and
sleep-wake history (King's College Hospital sleep-wake questionnaire\textsuperscript{18}). Twelve subjects consented to detailed investigation and had polysomnography, plasma melatonin and urinary sulphatoxy melatonin (aMT\textsubscript{6}s) profiles, head CT scan, tests of autonomic function, visual and brainstem evoked responses, and automatic recording of rest-activity cycles by actigraph.

**SLEEP-WAKE LOGS AND ALERTNESS SELF-RATING SCALES**

A sleep-wake subjective diary was kept over periods of four weeks to three years. Alertness was recorded on a self rating scale (drowsy-alert: 0–100 mm) completed at two hour intervals during wakefulness over a four week period.\textsuperscript{19}

**POLYSOMNOGRAPHY**

Polysomnography (first night recording) was carried out in a laboratory environment with a fixed light-dark: bed time-wake time schedule (dark, bed period 23.00–08.00). Sleep parameters and stages were determined by standard criteria using visual scoring.\textsuperscript{20}

**RESP-ACTIVITY CYCLE**

During a period of attempted phase-advance (see below), motor activity (rest-activity cycles) were recorded by an actigraph monitor on the dominant wrist (Gähwiler Electronics, Hombrektion, Switzerland). The actigraph was sensitive to acceleration of 0.1 g with pre-programmed time windows at 60 s intervals. Data storage of 32 kb was read through an IBM PC compatible interface, with a recording period of five days. Data are presented as summated text-file measures in clocktime at 15 min intervals.

**PLASMA MELATONIN AND URINARY SULPHATOXY MELATONIN (aMT\textsubscript{6}s) CONCENTRATION**

In view of the animal data indicating a central role of melatonin systems in circadian timekeeping,\textsuperscript{21,22} plasma melatonin and urinary melatonin metabolite profiles were determined. In a fixed light-dark ward environment (dark period 23.00–08.00) plasma samples for melatonin were obtained from an indwelling venous cannula at 1 hour intervals over a 24 hour period. Simultaneous urinary block collections were made between 08.00–12.00–16.00–20.00–24.00–08.00 for subsequent aMT\textsubscript{6}s analysis. Illumination levels for plasma sampling during the dark period were <0.1 lux. Plasma melatonin and urinary aMT\textsubscript{6}s were assayed by radioimmunoassay\textsuperscript{23–24} (plasma melatonin, n = 12; urinary aMT\textsubscript{6}s, n = 11).

**OTHER STUDIES**

In view of the association between the narcoleptic syndrome and HLA DR\textsubscript{w}15 (subtype of DR2), DQ\textsubscript{w}6 (subtype of DQ\textsubscript{w}1),\textsuperscript{25} and the finding of the narcoleptic syndrome in first degree relatives of index subjects with the delayed sleep phase syndrome (table 1), HLA serotyping was carried out (K Welsh, Tissue Typing Laboratory, Guy's Hospital).

**ATTEMPTED TREATMENT**

\textbf{a) Progressive sleep phase delay schedule}

Attempts were made in 5 subjects (cases 1, 3, 5, 10 and 14) to achieve conventional sleep-wake times by a programmed phase-delay schedule.\textsuperscript{14}

\textbf{b) Fixed sleep phase advance schedule}

In 9 subjects an attempt was made, using a phase-advance programme with fixed bed-wake, dark-light cycle timing (bed, dark period 23.00–08.00) over a 5-day period to reschedule sleep-wake cycles to a conventional time. The effects of attempted phase-advance were monitored by self-recorded sleep-wake logs, motor activity monitors, and alertness rating scales.

\textbf{c) Oral melatonin}

Eight subjects were given oral melatonin 5 mg

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**Table 1 Clinical features of 14 cases of delayed sleep phase syndrome**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Age at onset</th>
<th>Age onset puberty</th>
<th>Family history</th>
<th>Developmental/ environmental factors</th>
<th>HLA type</th>
<th>Sleep onset (Decimal time)</th>
<th>Wake (Decimal time)</th>
<th>Alternum acrophase</th>
<th>IQ</th>
<th>Performance</th>
<th>Verbal</th>
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<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>8</td>
<td>14</td>
<td>a</td>
<td>Prolonged labour</td>
<td>DR 1, 4</td>
<td>01:48</td>
<td>11:26</td>
<td>15:18</td>
<td>75</td>
<td>80</td>
<td>75</td>
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<tr>
<td>2</td>
<td>39</td>
<td>M</td>
<td>33</td>
<td>14</td>
<td>a</td>
<td>EBV</td>
<td>DQ 2, 6</td>
<td>07:45</td>
<td>11:18</td>
<td>13:45</td>
<td>70</td>
<td>125</td>
<td>103</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>M</td>
<td>16</td>
<td>13</td>
<td>b</td>
<td>Premature birth EBV\textsuperscript{1a}</td>
<td>E 4, 13</td>
<td>08:10</td>
<td>17:15</td>
<td>20:19</td>
<td>74</td>
<td>103</td>
<td>74</td>
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<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>45</td>
<td>13</td>
<td>b</td>
<td>Birth hypoxia</td>
<td>B 4, 13</td>
<td>04:05</td>
<td>15:17</td>
<td>20:15</td>
<td>92</td>
<td>126</td>
<td>92</td>
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<tr>
<td>5</td>
<td>22</td>
<td>M</td>
<td>12</td>
<td>15</td>
<td>c</td>
<td>Birth hypoxia</td>
<td>B 4, 13</td>
<td>01:17</td>
<td>09:12</td>
<td>02:45</td>
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<td>119</td>
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<tr>
<td>6</td>
<td>20</td>
<td>M</td>
<td>8</td>
<td>15</td>
<td>c</td>
<td>Birth hypoxia</td>
<td>B 4, 13</td>
<td>02:06</td>
<td>11:00</td>
<td>15:15</td>
<td>70</td>
<td>101</td>
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<td>7</td>
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<td>27</td>
<td>16</td>
<td>c</td>
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<td>B 4, 13</td>
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<td>20:02</td>
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<td>8</td>
<td>58</td>
<td>M</td>
<td>53</td>
<td>14</td>
<td>c</td>
<td>Birth hypoxia</td>
<td>B 4, 13</td>
<td>05:30</td>
<td>23:50</td>
<td>34:12</td>
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<td>9</td>
<td>22</td>
<td>M</td>
<td>16</td>
<td>12</td>
<td>d</td>
<td>Prolonged labour</td>
<td>DR 1, 4</td>
<td>00:02</td>
<td>12:00</td>
<td>02:08</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
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<tr>
<td>10</td>
<td>14</td>
<td>M</td>
<td>10</td>
<td>11</td>
<td>d</td>
<td>Prolonged labour</td>
<td>DQ 2, 6</td>
<td>03:00</td>
<td>12:28</td>
<td>20:11</td>
<td>126</td>
<td>126</td>
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<tr>
<td>11</td>
<td>17</td>
<td>M</td>
<td>25</td>
<td>15</td>
<td>d</td>
<td>Prolonged labour</td>
<td>DQ 2, 6</td>
<td>01:55</td>
<td>08:01</td>
<td>04:46</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>M</td>
<td>8</td>
<td>16</td>
<td>d</td>
<td>Prolonged labour</td>
<td>DQ 2, 6</td>
<td>02:00</td>
<td>09:00</td>
<td>03:50</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>M</td>
<td>18</td>
<td>12</td>
<td>d</td>
<td>Prolonged labour</td>
<td>DQ 2, 6</td>
<td>05:00</td>
<td>16:10</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>F</td>
<td>18</td>
<td>13</td>
<td>adopted</td>
<td>Tonic-clonic seizures, age 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Family history of daytime sleepiness.

\textsuperscript{b} Family history of narcolepsy and cataplexy.

\textsuperscript{c} Father and son.

\textsuperscript{d} Father and son. Of delayed sleep phase syndrome following Epstein-Barr viral infection.

\textsuperscript{e} Onset after influenza-like illness.

\textsuperscript{f} Failed HLA typing.

\textsuperscript{g} Sleep-wake parameters given in decimal time, ie 01:30 = 01:50. Sleep-wake data derived from mean 28-day sleep logs.

\textsuperscript{h} Acrophase: time of subjective highest alertness self rating (computed data by cosinor analysis: from mean 28-day self recording).

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\textsuperscript{1} Alvarez, Dahlitz, Vignau, Parkes
at 22.00 h for a four week period double blind with matched placebo for the same period in random order with a one week washout period between the alternative treatments in their normal home environment with monitoring of sleep-wake logs and alertness rating scales. Comparison of sleep-wake times and alertness ratings in the normal home environment and during the forced fixed-sleep phase advance schedule, was based on within-subject differences in changes of sleep log timings and alertness self-rating scales. Comparisons were made at the end of the study by Student's t test (two-tailed). Profiles of alertness rhythms, plasma melatonin and urinary aMT6s were examined for acrophase (estimated peak time) by cosinor analysis. The study was approved by the Institute of Psychiatry and King's College Hospital ethical committees. All subjects gave informed consent.

**Results**

The delayed sleep phase started between the ages of 8 and 53 (table 1). The onset was abrupt in 2, gradual in 12. In four subjects the condition started before puberty (age 8–11); in four at the onset of puberty (age 12–17) and in 6 following puberty (age 18–53). In the single female subject, the syndrome started at the age of 18 (menarche at 13).

**SYNDROME ANTECEDENTS**

A careful review of developmental and birth history was made in view of data linking the acquisition of some aspects of circadian rhythmicity with foetal as well as maternal factors. In seven of 14 subjects there was a history of prolonged or difficult birth, delayed milestones, dyslexia and congenital cataracts. Maternal health during pregnancy was described as poor by one subject, good by the remainder. Six subjects were breast-fed.

In three subjects the syndrome developed after an acute viral illness with malaise and sleepiness. All these subjects, and four others, were EBV IgG positive at the time of this study, indicating previous Epstein Barr viral infection.

**FAMILY HISTORY**

A family history of a sleep-wake disorder was given by six subjects (table 1). The father and son pair (subjects 7 and 10) lived apart from before the onset of the delayed sleep phase syndrome in the son. With the exception of these subjects, there was no report of abnormal sleep-wake timing in other first or second degree relatives of index subjects.

**SLEEP-WAKE TIMES**

Three different patterns of sleep-wake phase disturbance were described (fig 1).

A) Stable delay, constant over a 3–12 month period, with a sleep-wake cycle of 24 hours (10 subjects),

B) Progressive delay, with a non-24 hour sleep-wake cycle of approximately 25–26 hours however, with predominant phase delay rather than advance over a three month period (1 subject)

C) Irregular sleep-wake timing with a sleep-wake cycle of approximately 24 hours; however with predominant phase delay rather than advance (three subjects).

Sleep-wake times are shown in table 2. Mean sleep latency, recorded by sleep log (bed time to sleep onset time) in the home environment was a little less than 2 hours. Mean total sleep time: total wake time ratio over 24 hours was 8 hours 17 minutes: 15 hours 43 minutes (within normal values for adolescent and adult male subjects). The number of sleep periods (duration 2–18 hours) recorded by sleep log in individual subjects was between 18 and 56; and the number of naps (duration < 2 hours), was between two and 56 during a 28 day period.

Despite the unusual sleep timing, 10 subjects considered that sleep duration and quality, and also waking alertness, were normal. Four subjects described a habitual poor quality of sleep, irrespective of sleep timing, and also waking fatigue, sleepiness and sub-alertness. All subjects reported severe disability as a result of failure of morning arousal, with considerable educational, work and social problems. Education was severely disrupted in all nine subjects in whom the sleep-wake phase delay started in school years and prolonged periods of unemployment were reported in all but two adult subjects. Unhappy, unsatisfactory or unusual life styles, often with severe financial difficulties, were reported by 12 subjects, and marital problems in two of the
Table 2  Sleep and wake times in delayed sleep phase syndrome

<table>
<thead>
<tr>
<th></th>
<th>Attempted phase advance schedule with fixed bed-wake time 23:00-08:00</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Home environment</td>
</tr>
<tr>
<td>Bed time (clock time)</td>
<td>01:21 (2:00)</td>
</tr>
<tr>
<td>Sleep onset time (clock time; sleep log)</td>
<td>03:11 (5:50)</td>
</tr>
<tr>
<td>Wake time (clock time; sleep log)</td>
<td>11:28 (9:50)</td>
</tr>
<tr>
<td>Total sleep time (h min)</td>
<td>8:17 (0:46)</td>
</tr>
<tr>
<td>Alertness ratings (peak-score units)</td>
<td>75 (6)</td>
</tr>
<tr>
<td>Acrophase alertness (clock time)</td>
<td>18:50 (2:43)</td>
</tr>
<tr>
<td>Latency to NREM (stage II) (min)</td>
<td>89 ± 13</td>
</tr>
<tr>
<td>Latency to REM (min)</td>
<td>116 ± 26</td>
</tr>
<tr>
<td>Stage REM%</td>
<td>37</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>353 ± 43</td>
</tr>
</tbody>
</table>

24 hour clock times given as hours:minutes, not decimal time.

Time duration given as mins (polysomnographic data) or h:min (sleep log data).

Normal mean (SD) sleep latencies in late adolescence: first night recording.

Latency to Stage 2 NREM 31 (28) minutes.

Latency to REM 120 (52) minutes.

Total sleep time 426 (33) minutes.

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three married subjects were attributed, at least in part, to the syndrome. Only two adult subjects had remained in regular employment for periods over one year. One of these subjects worked regular night shifts, and the other took benzodiazepines to promote sleep onset and amphetamines with forced arousal to promote wakefulness over a 15-year period, remaining in 0900–1700 employment.

Before this study, no subject had been given a definite diagnosis, although school avoidance, "inadequate" personality and depressive illness had been considered in individual cases.

The syndrome duration was one to 53 years. All subjects had made several attempts to achieve a normal sleep onset time but this was only attained for a prolonged period by one subject (case 12). Seasonal variation in sleep timing and duration was reported by two subjects with shorter sleep latency and longer sleep duration in winter than summer. In the single female (case 14) menstruation was accompanied by earlier sleep onset and longer sleep duration than at other times in the oestrous cycle.

Physical examination, body habitus, growth and pubertal status were unremarkable. Five subjects had visual problems including cataracts, minor reduction in corrected visual acuity and corneal ulceration, but this did not cause significant visual handicap. No subject was blind or colour-blind.

**Psychological and psychiatric assessment**

**IQ assessment**

Performance IQ scores measured with Raven’s Progressive Matrices were within the normal range (mean 113, range 80–126 IQ points). Verbal IQ scores (Mill Hill Vocabulary Scale) were lower than performance scores (verbal score mean 88, range 70–112: difference performance-verbal IQ score p < 0.001, Student’s t test).

**Personality and mood**

Personality abnormality with high mean scores on the Minnesota Multiphasic Personality Inventory for paranoia, schizophrenia and depression occurred in two subjects with a trait deviance > 2 SD (cases two and five). One additional subject had a high depression rating on Beck Depression Inventory (score 23: case 8) and another was considered on clinical grounds to have a schizotypal personality (DSN III R) disorder although the MMPI and BDI scores were within the normal range.

**Symptoms accompanying forced arousal**

Six subjects reported frequent irritability, anger or dysphoria when forced arousal was attempted, and this was a conspicuous clinical feature in one adolescent male who terrorised his parents on attempted morning waking. Hypersexuality was not reported or observed.

**Investigational findings**

Polysomnography in a fixed light-dark, bed-wake time environment showed normal findings with normal sleep architecture apart from prolonged sleep latency to stage two NREM (mean 89, 1 SEM 13 minutes) and reduced total sleep time (with late sleep onset followed by forced arousal at 08.00) compared with normal values in adolescence-middle age.28 29

Once asleep, the latency to stage REM was within normal limits (table 2). Autonomic function tests and evoked potential studies, head CT scan, full blood count, serum biochemistry, cortisol at 09.00 and midnight and TSH were in the normal range in all subjects.

HLA serotyping (table 1) showed that 11 of 12 subjects typed were DQ1 positive. The two subjects with familial DR2 (DRw15) positive narcolepsy and cataplexy were DR3,x and DR1,x respectively. There were no syndrome-specific HLA A, B or C associations (not included in table). Variations in HLA antigens in linkage disequilibrium with DQ show that there are likely to be differences in DQ subtypes between subjects.

**Plasma melatonin and urinary αMT6s excretion**

Plasma melatonin profile, pulse duration, peak level, and urinary αMT6s excretion over the 24 hour cycle were within the normal range for adult males aged 20–60 years living under normal light-dark environmental conditions [acrophase data (time of computed highest peak by “best-fit” curve)] for melatonin in normal subjects, summer: 03.15 ± 01.00 hours (mean ± 1 SD): winter 03.22 ± 01.34).30 There was, however, considerable variation in plasma melatonin profile in individual subjects. No significant relationships were found between melatonin onset time (first detected in plasma), peak concentration or AUC; and sleep onset time, total sleep time or alertness acrophase (all p > 0.1).

**Attemped treatment**

A) Progressive sleep phase delay schedule

Despite high motivation and parental involvement, attempted establishment of conventional sleep-wake times with a progressive 2 hour phase delay schedule twice weekly was unsuccessful in two subjects, successful in three.

B) Fixed sleep phase advance schedule

Attempts at forced sleep phase advance, with
The delayed sleep phase syndrome: clinical and investigational findings in 14 subjects

The delayed sleep phase syndrome is characterized by a delay in sleep onset and wake times, with an increased tendency towards nocturnal activity and reduced daytime alertness. This disorder is often associated with difficulty in falling asleep, excessive daytime sleepiness, and decreased productivity. Treatment options for the delayed sleep phase syndrome include behavioral interventions, such as light therapy and sleep restriction, and pharmacological approaches, such as the use of melatonin or benzodiazepines. The natural history of the condition suggests a familial component and may be influenced by factors such as sleep habits, light exposure, and other zeitgebers.

Figure 2 Motor activity, alertness ratings, plasma melatonin and urinary sulphatoxy melatonin excretion in 8 patients with delayed sleep phase syndrome in fixed light-dark, bed-wake time (23.00-08.00 bed, dark; 08.00-23.00, wake, light) environment over five day period. During this period, the mean light:dark ratio was 15h:9h; and sleep-wake ratio 6h 28 min:17h 32 min.

C) Melatonin treatment

Oral melatonin 5 mg given at 22.00 caused a mean advance in sleep onset time of 82 minutes and in wake time of 117 minutes over a 28-day period compared with placebo treatment. Advance in sleep onset time with melatonin was comparable to that achieved by forced sleep-advance schedule. Neither treatment resulted in the establishment of normal sleep-wake timing. The phase shift with melatonin was independent of the time interval between the administration of exogenous melatonin and the time of the endogenous melatonin plasma peak. On stopping melatonin all subjects reverted to their previous sleep-wake times within 2–3 days.19

D) Other attempts at treatment

All subjects had made several attempts by pharmacological and non-pharmacological means to achieve conventional sleep onset and wake times. No treatment was successful in the long term with the exception of a combined benzodiazepine-amphetamine regime in case 13. Tricyclic drugs and MAO A inhibitors resulted in improvement in mood in cases 5, 8, 9 and 11 without definite alteration in sleep phase timing.

Discussion

About 75 subjects with the delayed sleep phase syndrome have been reported in the 10 years following the first description of the condition.14,15 The age of onset varies from infancy to the sixth decade and is often at adolescence. Most reports have stressed male preponderance with a male:female ratio of 10:1 or higher, although the sex incidence was equal in the 30 subjects initially reported by Weitzman et al.14 The syndrome presentation is similar in children and adults. The delayed sleep phase syndrome is more common than the condition of non-24 hour sleep-wake cycle, or the very unusual disorder of an advanced sleep phase syndrome, characterised by habitual sleep onset and wake times that are several hours earlier than desired.31 The syndrome causes considerable disability in children and adults. In a study of 22 adolescents, Thorpy et al reported that over half the subjects had a poor school record, and 10 showed a variety of problems including irritability at school and home, and truancy.10 In adults, the work record is usually poor with many short periods of employment followed by prolonged unemployment, and often with marital and financial problems and increasing social isolation. A case has been recorded where symptoms of the delayed sleep phase syndrome were considered to be a criminal offence in military service.14 The discrepancy between verbal and performance IQ in the present subjects may have been due, at least partially, to poor school attendance.

The exact contribution of psychopathology to the syndrome is uncertain, but it seems very unlikely that in all cases, the behaviour is due to refusal to attend school, depression, boredom, laziness or personality problems, or that it could be cured, for example, by a period of military discipline. Arousal at conventional times can be impossible to achieve on a regular
in an Levin duration, timing symptoms have been sleep-wake the progressive phase delay delayed sleep phase syndrome. This situation is similar to that found in animal experiments, after either enucleation of both eyes or transection of the optic nerves where entrainment to the light-dark cycle is lost.

Patients with the delayed sleep phase syndrome are sometimes successfully treated with progressive phase delay of their sleep schedule and then maintained in a socially convenient sleep-wake time period. However, results depend on motivation as well as environment. Most but not all reports stress the non-effectiveness of prolonged hypnotic treatment to promote sleep onset, or the use of morning central stimulant drugs to increase alertness. Other suggested treatments, including vitamin B12, evening alcohol, morning bright light and antidepressant drugs are not of proven efficacy. In contrast, oral melatonin results in a partial phase advance, associated with either a hypnotic or phase-setting action. Unfortunately, the advance in sleep and wake timing is not retained on stopping treatment.

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