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Case report

Severe, childhood-onset, idiopathic, life-long insomnia responding selectively to opiate therapy: case report with 19 year follow-up

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Abstract

Background: Idiopathic (primary) insomnia can be difficult to treat; only two prior cases responsive to opiate therapy have been reported. A case is now presented of severe, idiopathic, childhood-onset, familial insomnia, with increased libido, absence of psychopathology, tardive emergence of restless legs syndrome (RLS), and selective response to opiate therapy.

Case report: A 39-year-old woman was referred in 1981 by her physician who had discovered 3 years earlier that propoxyphene treatment of migraines also controlled her chronic insomnia. She had experienced severe insomnia since childhood, and during early adulthood the insomnia intensified, as she would sleep 0–3 h nightly and never napped. Daily generalized motor restlessness resulted in her frequently walking around the house while feeling exhausted. The quality of her life was considerably compromised by her insomnia, motor restlessness, and by an increased libido that was present since puberty and that was only partially relieved by having sex repeatedly with her husband.

Results: Nightly opiate therapy for 19 years has controlled the insomnia, motor restlessness, and excessive libido without affecting her normal libido. The insomnia had not responded to treatment with >25 agents covering >10 pharmacologic categories. During her first (unmedicated) polysomnographic (PSG) study in 1981, she slept 0 min while spending 436 min in bed. In 1984, four consecutive PSG studies were conducted in a design that confirmed the efficacy of propoxyphene therapy of her insomnia. In 1990, an ambulatory PSG revealed two runs of EEG rhythmic paroxysmal activity arising from sleep and wakefulness, without clinical correlate. Neurologic history was negative for seizures, but positive for complete right carotid artery occlusion and three transient ischemic attacks. At age 55 years, typical RLS emerged that was controlled with levodopa therapy, and a concurrent relapse of insomnia was controlled with oxycodone replacing propoxyphene.

Conclusions: Nightly opiate therapy of severe idiopathic (primary) insomnia can remain effective during very long-term clinical follow-up. Guidelines are provided for when to consider such an unusual treatment in other cases of severe, chronic insomnia.

Keywords: Insomnia; Idiopathic/primary insomnia; Familial insomnia; Childhood-onset insomnia; Polysomnography; EEG; Libido/sexuality; Restless legs syndrome; Opiate therapy; Dopaminergic therapy

1. Introduction

Idiopathic (primary) insomnia [1,2] can be difficult to treat [3–5]. Although benzodiazepines can be effective in chronic insomnia [6–8], the relentless and severe — and at times incapacitating — nature of

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idiopathic insomnia requires an open-minded therapeutic approach, with nightly treatment and novel pharmacotherapy at times being necessary [3–6,9]. As Hauri has stated [9], "No consistent treatment approach to childhood-onset insomnia has evolved. Because each case is typically different from any of the others, a highly empirical approach is necessary."

To our knowledge, only two cases have been reported of idiopathic insomnia that was responsive to opiate (hydromorphone) therapy [3,4]. In an accompanying editorial, Hauri endorsed the idiosyncratic therapy of severe insomnia when standard treatments fail, provided that diligent clinical evaluation and careful follow-up take place [5]. We now report a case of severe, idiopathic, childhood-onset, familial insomnia, with increased libido, absence of psychopathology, tardive emergence of restless legs syndrome (RLS), and selective response to opiate therapy in a woman who underwent multiple polysomnographic (PSG) studies, and subsequent 19 year follow-up.

2. Case report

A 39-year-old woman was referred by her primary physician in 1981 for evaluation of severe, chronic insomnia, and for our opinion about her remarkable response to darvocet (propoxyphene/acetaminophen) treatment and the advisability of continuing nightly opiate therapy on a long-term basis. As far back as early childhood, she could recall having prominent insomnia symptoms with motor restlessness, as she would wander around the house most nights until 01:00–03:00 h. During early adulthood, the insomnia became progressively worse, with exacerbations occurring during her three pregnancies. She has never been able to nap.

When she was 34, she had a hysterectomy (on account of fibroid tumors), and 2 years later developed common migraines that were relieved by pentazocine, but which made her feel 'spacey'. Fiorinal (butalbital/caffeine/aspirin, with or without codeine) and midrin (isometheptene mucate/dichloralphenazone/acetaminophen) were ineffective. However, when darvocet-N 100 (propoxyphene/acetaminophen) was prescribed for her migraines, she experienced immediate relief from both the headaches and the insomnia. She began to sleep for 6–8 h uninterrupted most nights (instead of 0–3 h), and felt rested in the morning. For the 3 years before referral, she had taken two to three tablets every night, and continued to sleep well, without medication side effects. Throughout her life, she has abstained from alcohol and caffeine. There is no history of chemical dependency.

She described motor restlessness (without pain), which was present throughout each day of her life, as "a motor running inside me all the time, revved up, with surges of electricity and high energy going all over me". The sensation of being highly energized and the strong urge to move were not linked with any distinct sensation of restlessness in the limbs or trunk. She continually moved around the house while vacuuming and cleaning, and took long walks outdoors in an attempt to discharge the excessive energy she felt inside. During the daytime, she experienced the unpleasant paradox of "having my mind and body feel speeded up, but at the same time feeling exhausted". As a result, she had a diminished capacity to enjoy herself with family and friends, function optimally at work, and enjoy her usual recreational activities. Furthermore, anyone who wanted to converse with her would have to constantly pace around with her.

Increased libido has bothered her nearly every day since puberty, manifesting as strong sexual sensations in the vulva, and general sexual heightening without erotic thoughts or peculiar consciousness, which would be only partially and briefly relieved by having sex with her husband (multiple times daily on many days). She could readily distinguish between this type of 'hyper sex' (physical discharge, devoid of emotion) from 'emotional sex' which was pleasurable and intimate. The induction of satisfactory nocturnal sleep with opiate therapy has suppressed the increased libido without affecting her normal libido and sexuality.

There was no childhood or subsequent history of sleepwalking, sleep terrors, confusional arousals, head banging/rhythmic movements, enuresis, or nightmares, nor was there any history of automatic behavior or states of altered consciousness suggestive of seizures or dissociative states.

3. Results

The list of medications that were of no benefit or of limited benefit for the insomnia, or that caused intoler-

able side effects or paradoxical reactions (viz. hyperaroused states) include: (i) benzodiazepines (flurazepam, lorazepam, clonazepam, alprazolam, diazepam, clorazepate); (ii) tricyclic antidepressants (amitriptyline, doxepin); (iii) antihistamines; (iv) anti-convulsants (phenobarbital, carbamazepine, valproic acid, diphenylhydantoin, gabapentin; (v) anti-psychotics (thioridazine, mesoridazine); (vi) beta-blockers (propranolol, pindolol); (vii) other agents (zolpidem, lithium, clonidine, amantadine, L-tryptophan, over-the-counter drugs). These agents were mostly tried before the initiation of chronic opiate therapy, except for anti-convulsant trials during 1988–1990 and 1997, lithium and thioridazine in 1990, and zolpidem in 1998. The patient was also taught a self-hypnosis exercise, which she found to be 'pleasant', but it did not help induce sleep.

Her first PSG study (1981) at our hospital sleep lab documented 0 min of sleep during 436 min in bed. She did not take any medication for this PSG study. Four additional PSG studies were conducted 3 years later (1984) to search for any objective sleep pathology, to document the effect of treatment, and to determine whether acetaminophen was necessary. Table 1 contains data from the four consecutive PSG studies. The 3.5 min of total sleep during the first PSG study indicates an overwhelming 'first night effect' that began to attenuate over the next two nights. Although acetaminophen did not appear to have therapeutic value, propoxyphene efficacy was supported by the placebo design. Urine toxicology studies were negative for any illicit substances. For ethical reasons — given the severity of her insomnia — a PSG was not conducted after a drug-free period of $\geq$2 weeks. A multiple sleep latency test was not performed, given her inability to nap.

This patient has been followed for 19 years (the past 17 years by C.H.S.), usually every 3–6 months, with her husband attending each clinic visit. They have been asked about manic/hypomanic mood states, panic and obsessive-compulsive anxiety states, attention-deficit/hyperactivity states, and paraphilias, without any of these conditions being detected. Administration of the SCID (validated Structured Clinical Interview for DSM-III-R; American Psychiatric Press, Inc., 1990) did not detect any current or lifetime Axis 1 psychiatric disorder. Her mood was reported by her family to be consistently 'upbeat'. She was divorced in 1986, and remarried in 1992. She is a high-school graduate who has worked as a silk screener.

Psychometric testing, completed during maintenance opiate treatment, did not reveal any psychopathology: Symptom Checklist-90 (non-elevated index score and nine sub-scale scores); Beck Depression Inventory (score of 13, borderline mild depression); Zung Self-Rating Anxiety Scale (index score of

Table 1
PSG data from four consecutive nights of hospital-based monitoring[a]

	Night #1	Night #2	Night #3	Night #4
Bedtime medication	Darvocet-N 100 (three tablets)	Darvocet-N 100 (three tablets)	Darvon-N 100 (three tablets)	Placebo (three tablets)
Total sleep time (min)	3.5	151.0	185.5	0
Sleep latency (min)	45.5	24.0	19.0	N/A
REM latency (min)	N/A	57.0	55.0	N/A
Stage 1 (%)	71.4	10.3	3.0	N/A
Stage 2 (%)	28.6	27.8	22.9	N/A
Stage 3/4 (%)	0	54.3	52.0	N/A
REM (%)	0	7.6	21.3	N/A
Awakenings (*n*)	N/A	1	1	N/A
Mean cardiac rate (wake/sleep)	74/68	70/66	70/64	78
Mean respiratory rate (wake/sleep)	18/20	16/18	18/23	20
Periodic limb movements	N/A	–	–	N/A
Sleep-disordered breathing	N/A	–	–	N/A

[a] The patient's written informed consent was obtained. The study was a blinded design, with the patient, sleep laboratory technologists, and clinical polysomnographer who reviewed and interpreted the polysomnogram all being blind to the medication or placebo status for each night of monitoring. Standard recording and scoring methods were used [11].

40, no anxiety); and Minnesota Multiphasic Personality Inventory (no T-score elevation, valid profile, interpreted to be within normal limits. Welsh Code: 43 7819-62/50: K-F/?:L#).

Clinical evaluations by various psychiatrists over the years have not identified a psychiatric disorder, apart from possible chemical dependency, since periodically she took opiates during the day when she felt extreme motor restlessness, and on several occasions became toxic and was hospitalized. Consequently, her opiate prescriptions have been written for 1–2 week intervals, to discourage overuse and inadvertent toxicity.

The patient described the ongoing benefit of opiate therapy as "slowing down the motor inside me, gradually taking the foot off the accelerator to the point where I suddenly drop off to sleep". She usually sleeps 5–7 h nightly. The quality of her life has greatly improved in tandem with the restoration of satisfactory sleep. She feels physically and mentally rested, she can remain seated and engage in relaxed conversations with people (instead of 'talking on the run'), and she can calmly read or watch TV.

The patient experienced the tardive emergence of typical RLS [2] at the age of 55 years (unrelated to any change of medication or dosage), with rapid symptom escalation and daytime intrusion. RLS symptoms were diminished by walking around, especially if she moved quickly. She described the RLS symptoms as "something vibrating under my skin that was creeping up and down my legs. If I couldn't move my legs, then I felt that I would go insane." For the past 2–3 years, she has been effectively maintained on carbidopa/L-dopa, currently at a dose of two tablets of 10/100 mg taken six times per 24 h. The emergence of frank RLS coincided with a compromise in the long-standing efficacy of darvocet-N 100 hs therapy of her insomnia. Furthermore, the insomnia did not improve despite control of RLS with dopaminergic therapy. The patient was then successfully switched in 1998 from darvocet-N 100 (three tablets qHS) to oxycodone 5 mg/acetaminophen 325 mg (two tablets qHS; easier to tolerate than oxycodone combined with aspirin in Percodan®). For the past 3 years, ongoing control of insomnia has been maintained with the same opiate dosage, and ongoing control of RLS has been maintained with the same dopaminergic regimen. The patient had never undergone a dopaminergic treatment trial of insomnia before the onset of RLS.

Neurologic exams have been normal, with symmetrical reflexes and absence of hyperreflexia, clonus, or tremor. Several magnetic resonance and CT brain scans and EEGs over the years have not detected any specific pathology — with the exception of two runs of EEG rhythmic paroxysmal activity (one from sleep at 05:30 h, one from wakefulness at 10:30 h) that appeared to be electrical seizure activity (without clinical correlates) during the first night of a two-night ambulatory PSG monitoring (Oxford Medilog) in 1990 (which were the only other PSG studies conducted on this patient). Extensive blood chemical screening, complete blood counts, and thyroid functions (including T3 levels) have not detected any basis for her insomnia, such as hyperthyroidism, autoimmune disease, etc.

Her medical history has been further complicated by a complete right carotid artery occlusion (diagnosed by arteriography at age 54 years), three transient ischemic attacks (an episode of complete left-sided paralysis, with dizziness, 'feeling hot all over', and malaise lasting 1 h, at age 54 years; an episode of slurred speech lasting several hours, at age 55 years; and an episode of bilateral visual clouding, during which she could distinguish colors but not shapes, lasting several hours, at age 56 years), hypertension (diagnosed at age 56 years, treated with atenolol), coronary artery disease, angioplasty (two procedures, at age 52 years), cholelithiasis/cholecystitis (with cholecystectomy at age 45 years), pancreatitis (diagnosed at age 45 years, considered to be secondary to cholecystitis), hypercholesterolemia, and prominent menopausal symptoms (hot flashes emerged at age 53 years).

The family history is remarkable for migraines in various members, and for similar (but less severe) histories of chronic, childhood-onset insomnia affecting all three children (two sons, one daughter, aged 24–32 years), a maternal aunt, maternal grandmother, and three maternal cousins (two male, one female).

The timeline for the most pertinent clinical history can be summarized as follows: 1978 (36 years old), develops migraines and discovers the efficacy of opiates for both insomnia and migraines; 1981 (39 years old), presents to our sleep center, has 0 min of sleep during PSG, and chronic, nightly opiate (propoxyphene) therapy is continued; 1984 (42 years old), four PSGs further confirm the diagnosis of severe insomnia and the efficacy of opiate therapy;

1990 (48 years old), an ambulatory PSG identifies two runs of paroxysmal EEG activity without clinical correlate; 1998 (56 years old), develops frank RLS, along with exacerbation of insomnia, which have been subsequently controlled with dopaminergic therapy, and a different opiate agent (oxycodone), respectively.

4. Discussion

In idiopathic (primary) insomnia, the chronic inability to obtain sufficient sleep "is presumably due to an abnormality of the neurological control of the sleep–wake system… with excessive arousal" [2]. Bonnet has published autonomic, metabolic and other compelling data that support the hypothesis that 'hyperarousal' is a core component of idiopathic insomnia, as discussed [9]. This hyperarousal, with hyposomnia, "cannot be explained either by psychological trauma starting in early childhood or by medical problems… that originate outside of the sleep–wake system" [2]. Furthermore, "Psychologically, most patients with idiopathic insomnia are remarkably healthy, given their chronic lack of sleep." [2]. These comments aptly refer to our patient.

Although the prevalence of idiopathic/primary insomnia in the general population is estimated to be 1.3% [10], the prevalence of childhood-onset insomnia is unknown. However, in a group of 73 chronic insomniacs evaluated at a sleep center, 20 (27.4%) had idiopathic, childhood-onset insomnia [1].

To our knowledge, daily motor restlessness and increased libido have not previously been reported with idiopathic insomnia [1–4], and may represent other facets of presumed central nervous system hyperarousal, along with the inability to nap, and perhaps also RLS (for which opiates and dopaminergics are recognized treatments). An unusual epileptic component of her insomnia remains a remote possibility, given the two runs of paroxysmal epileptiform EEG activity found during one of her (ambulatory) PSG studies.

We suggest that a trial of opiate therapy of idiopathic insomnia be considered in one of the two following sets of circumstances. First, a case similar to our case, involving the serendipitous and selective control of chronic insomnia with opiate therapy of a non-sleep disorder (e.g. migraines). Second, a constellation of the following conditions: a history of severe insomnia — with prominent sleep-deprivation symptoms and quality-of-life impairment — is present; careful medical, neurologic and psychiatric evaluations do not detect any disorder that could cause or promote insomnia, or else do identify such a disorder, but treatment does not improve the insomnia; actigraphic monitoring and consecutive-night PSG studies (with urine toxicology screens) confirm the diagnosis of insomnia and exclude other pertinent sleep–wake disorders; appropriate cognitive-behavioral treatments of insomnia [9] are ineffective; hypnotic medication trials are ineffective; careful, ongoing clinical follow-up — with close monitoring of prescriptions — is obtained; the potential hazard of opiate abuse and addiction with long-term therapy is discussed viz-a-viz the severity of the insomnia, and any pertinent medical history, or propensity for chemical dependency.

As to the mechanism of opiate action in our patient, the most parsimonious explanation is that opiate administration reversed an insomnia-promoting deficiency in an intrinsic opioid system. The tardive emergence of RLS was controlled with dopaminergic therapy, but not with opiate therapy (at least not at the dose needed for control of insomnia). Therefore, it seems unlikely that the chronic insomnia in our case is an atypical form of RLS, although the association of these two sleep disorders in our patient is intriguing.

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