Use of ropinirole for restless legs syndrome associated with agitated depression: a case report

Uso del ropinirolo nella sindrome da gambe senza riposo associata a depressione agitata: segnalazione di un caso

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Summary

We describe the unusual case of a young girl with agitated depression who was referred to our Sleep Centre, complaining severe insomnia. She underwent overnight polysomnography that disclosed periodic limb movements during sleep associated with increased sleep latency, supporting the clinical diagnosis of restless legs syndrome. Treatment with the dopamine agonist ropinirole, at the dose of 1.5 mg/day, improved significantly both sleep disturbance and psychiatric symptoms (Table I).

This case supports the importance of checking for the existence of restless legs syndrome in young people whose first episode of mood disorder is associated with severe insomnia and to eventually perform a complete polysomnographic study to confirm the clinical diagnosis and to evaluate the outcome.

Intoduction

One of the most frequent complaints in psychiatric disorders is insomnia [1], but also the reverse holds true, i.e., sleep disturbances, including a wide range of disorders like insomnia, hypersomnia, restless legs/periodic limb movements during sleep (PLMS), obstructive sleep apnea, and parasomnias, are frequently associated with psychiatric disorders.

Furthermore, insomnia may underlie other sleep disorders. Restless legs syndrome (RLS) can cause difficulty in sleep onset, while unsatisfactory sleep with repeated awakenings can be related to sleep respiratory disorders or, possibly, to periodic limb movements disorder (PLMD).

Insomnia is often reported by patients affected by depression, anxiety and mania [1]. Recently, lamotrigine has been reported to be effective in bipolar depression associated with a broad spectrum of physical and emotional symptoms, including restless legs syndrome and parkinsonian symptoms [2]. Lamotrigine has been proposed to treat restless legs syndrome [2]. An 11-year-old girl with RLS and depressive symptoms has been successfully treated with ropinirole [3].

We present here the unusual case of a young girl with symptoms of agitated depression who complained severe insomnia and was referred to our Sleep Centre because her sleep was too short. She underwent overnight polysomnography that disclosed the presence of PLMS, thus supporting the clinical diagnosis of restless legs syndrome. Treatment with the dopamine agonist ropinirole improved significantly both sleep disturbance and psychiatric symptoms.

Key words

Restless leg syndrome • Ropinirole • Dopamine agonists • Agitated depression • Sleep disorder

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Case report

A seventeen-year-old Caucasian girl was referred to our Sleep Research Centre, complaining of severe insomnia. She had a history of primary migraine and periodic abdominal and leg aches since the age of 11 years. Melatonin was prescribed at 14 years, due to the onset of early insomnia, without no apparent clinical effect. At the age of 15 years, her grandfather died and after a few days she manifested behavioral disorder. She was referred to a child psychiatrist who diagnosed disruptive behavioral disorder not otherwise specified [5]. Insomnia persisted. Many drugs were prescribed such as benzodiazepines, imidazopyridines, niaprazine, valproic acid, trazodone and promazine, with no symptom improvement.

When admitted to our Centre, she was drug-free and reported early insomnia with few hours of sleep per night. During the last three years she reported occasional daytime sleep. She also endorsed nocturnal and diurnal hyperkinesia with paraesthesia and leg restlessness when falling asleep. Her mood was depressive, with anxiety, increased motor activity, irritability, and disruptive-aggressive behaviour. Insight and judgement were poor. Snoring or apnoea during sleep were never noticed.

At admission, the Minnesota Multiphasic Personality Inventory-2 [6 7] showed depressive anxious traits, low self-esteem, social avoidance, impulsiveness, fears of being judged and abandoned. She scored 24 on both Young Mania [8] and Hamilton Depression Rating Scales [9]. Height and weight were within the normal range for her age (162 cm and 54 kg, respectively). The neurological examination was within the normal range. Routine blood laboratory, including thyroid function, electroncephalogram, brain CT scan, lung X rays, and electrocardiogram were normal. She had no history of smoking or substance abuse (alcohol, cannabis, or cocaine), and this was confirmed by laboratory tests.

She reported all four diagnostic features of RLS according to international criteria [10], i.e., urge to move the legs to relieve uncomfortable and unpleasant sensations, symptom worsening during rest periods, symptoms partially or totally relieved by movement, and worsening at evening and night. These symptoms had a chronic course, beginning with the onset of severe insomnia.

She underwent overnight video-polysomnography (PSG) in our sleep laboratory. The video-PSG included scalp electroencephalogram, electrocardiogram, electro-oculogram, chin, right and left tibialis anterior electromyogram. The video-PSG showed severe insomnia associated with leg restlessness during the wake period preceding sleep onset and PLMS (Table I).

After three days, the patient was discharged with a diagnosis of RLS. She was started on ropinirole 0.50 mg. Paroxetine 20 mg, was also prescribed to reduce the prominent anxious and depressive symptoms. Sleep disturbances responded immediately. After one week she reported mood improvement, but insomnia reappeared after 3 months, and ropinirole was gradually increased to 1.5 mg per day.

A follow-up visit after 6 months showed general improvement in psychiatric symptoms. The patient did not report any RLS symptoms, according to the international criteria [10]. A new video-PSG showed the persistence of periodic limb movements, but a decrease of PLM index and an increase of sleep continuity. Scores on the Young Mania and Hamilton Depression Rating Scales dropped to 10 and 6, respectively.

Sleep analysis

Beside the classic staging scored visually according to international criteria [11] (Table I), we also analyzed the cyclic alternating pattern (CAP) according to the criteria previously reported by Terzano et al. [12]. CAP is a periodic EEG activity of NREM sleep characterized by repeated sequences of transient events (phase A), subdivided into a 3-stage hierarchy of arousal strength (from A1 to A3). The EEG arousal was also analyzed following the international criteria (13 Iber).

Leg movements (LMs) were scored following the criteria set by the WASM-IRLSSG [13] set and slightly modified by the AASM [14].

Sleep variables were acquired digitally and stored in European Data Format and analyzed by means of the Hypnolab 1.2 sleep software analysis (SWS Soft, Italy). Sleep analysis was performed visually by one of the investigators (SM) blinded to the order of the recordings.

Sleep analysis (Table I)

Sleep analysis showed many differences between the PSG with treatment with ropirinole and PSG at baseline: longer total sleep time, higher sleep efficiency, reduction in wakefulness after sleep onset, lower CAP rate, lower A1 and A2 index, conversely arousal index did not change significantly.

TABLE I.
Sleep-related variables. *Variabili legate al sonno.*

Sleep Staging			CAP Analysis		
	Baseline	After ropinirole		Baseline	After ropinirole
TIB, min	529.5	573.5	CAP Rate, %	50.4	34.2
SPT, min	461.5	527	During S1	35.3	9
TST, min	357	495.5	During S2	39.8	36.8
SOL, min	20	47	During SWS	73.2	46.4
FRL, min	126	277.5	A1 index	37.2	19
SS, n/h	8.8	8.8	During S1	0	0
AWN, n/h	5.5	3.3	During S2	9.3	16
MT, n/h	0	0.8	During SWS	102.2	67.4
SE, %	67.4	86.4	A2 index	17.8	9.4
REM periods, n	4	3	During S1	10	0.9
WASO, %	22.6	6	During S2	32.5	19.2
S1, %	1.3	12.3	During SWS	2.6	3.1
S2, %	40.4	49.2	A3 index	17.8	17.6
SWS, %	19.7	14.7	During S1	60	23.1
REM, %	15.9	17.7	During S2	30.6	26.6
			During SWS	0	1.5
Limb Movement Analysis			A1%	47.1	40.4
LMI tot	15.27	14.4	A2%	27.1	22.8
LMI tot NREM	9.95	11.64	A3%	25.8	36.8
LMI tot REM	35.92	26.31	A mean duration, s	8.7	8.5
LMI is	7.72	9.19	B mean duration, s	19.9	22.5
LMI is NREM	6.14	5.97	Cycle mean duration, s	28.5	31
LMI is REM	13.88	23.1	Seq mean duration, s	210.8	201.8
PLMI	7.55	5.2	Total arousal index	36.6	30.1
PLMI NREM	3.81	5.67	REM arousal index	7.3	12.2
PLMI REM	22.04	3.21	NREM arousal index	43.8	40.3

TIB: time in bed; TST: total sleep time; SOL: sleep onset latency; SE: sleep efficiency; WASO: wake after sleep onset; S1, S2, S3, S4, SWS, REM%: percentage of stage 1, stage 2, stage 3, and stage 4 NREM sleep, slow-wave sleep, and REM sleep; AWN/h: the number of awakenings per hour; MT n/h: the amount of movement time per hour; CAP rate: percentage of total NREM sleep S1, S2 and SWS time occupied by CAP sequences; A index n/h: number of A phases (A1, A2, A3) per hour of total NREM sleep, S1, S2 and SWS, PLMI: periodic leg movement index, LMI : total.

Total PLM index decreased after treatment, mostly during REM sleep, total LM index did not change significantly and LM isolated index increased.

Discussion

To our knowledge there are no reports of RLS associated with agitated depression, which was disclosed by our clinical and polysomongraphic investigation and resolved with dopamine-agonist therapy. We attributed the resolution of psychiatric symptoms to the association of paroxetine with ropinirole, because it proved to be effective in improving them after few days of drug therapy, in coincidence with the improvement of severe insomnia.

Sleep disorders and psychiatric disorders are reported to reciprocally influence each other [1]. RLS

and PLMD have been previously associated to attention deficit hyperactivity disorder, oppositional defiant disorder, anxiety disorders, and depression in childhood and adolescence [4 15].

In this case, we believe that the severe insomnia due to RLS might have directly influenced the patient's psychiatric condition, because the onset of insomnia preceded by one year the onset of psychiatric symptoms, and dopamine-agonist treatment improved simultaneously both sleep pattern and mood symptoms. Therefore, the psychiatric condition was secondary to RLS. Moreover, paroxetine improved agitated depression since symptoms were not related to the presence of an underlying bipolar disorder. Paroxetine is widely known to be effective on anxious and depressive symptoms and it is known that might worsen bipolar mixed symptoms with agitated depression [16].

Our case suggests the importance of checking for RLS in young subjects presenting with their first mood disorder episode in association with severe insomnia and the need to perform a complete polysomnographic study to confirm the clinical diagnosis and to evaluate outcomes.

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