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Tremor and Other Hyperkinetic Movements

Brief Reports

Does Pramipexole Treatment Improve Headache in Patients with Concomitant Migraine and Restless Legs Syndrome?

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Abstract

Background: Recent studies have suggested a strong link between migraines and restless legs syndrome (RLS). It is possible that these disorders share a dopaminergic dysfunction in the hypothalamic A11 nucleus that contributes to this association. However, there have been no clinical studies to evaluate the effect of dopaminergic treatment on migraine symptoms in patients with concomitant migraines and RLS.

Methods: We present an illustrative patient with concomitant RLS and migraine who showed improvement in her headache frequency and RLS symptoms following immediate-release pramipexole (P-IR) treatment and provide review results from the medical records of patients who experienced both migraines and RLS in our previous cross-sectional study.

Results: Ten patients (nine patients from the previously completed single-center study) received P-IR treatment were included in the study. RLS symptoms improved markedly in all of the subjects. Five out of the 10 patients (50%) reported improvement in migraine headaches. Of these five patients, four (80%) had reported morning headaches before P-IR treatment.

Discussion: Our results indicate that the identification of RLS in migraine patients is clinically significant and that dopaminergic treatment may improve both migraines, particularly morning headache (80% improvement in this study), and RLS symptoms. However, further clinical studies are warranted to verify our results.

Keywords: Pramipexole, migraine, restless legs syndrome, dopaminergic dysfunction, morning headache

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Introduction

A growing body of evidence suggests a strong link between migraines and restless legs syndrome (RLS),[1–4] which was recently confirmed by a large prospective population-based study consisting of 31,370 women. This study demonstrated that women with migraines with and without aura have an increased risk for developing RLS.[5] Thus, the frequent comorbidity of migraine and RLS and its shared clinical features, such as sleep disturbances and depression, indicate that the two disorders have an overlapping pathophysiology, such as dopaminergic dysfunction and dysfunctional brain iron metabolism.[6] In addition, a positive family history was common in the two disorders. In our previous study, approximately one-third of the subjects diagnosed with RLS and migraine had a positive family history for migraine and RLS.[4] Central dopaminergic dysfunction in the hypothalamic A11 area has been postulated in both migraines and RLS,[6,7] and it is likely to participate in the development or worsening of both symptoms because the A11 dopaminergic nucleus inhibits firing in the trigeminocervical complex,[7] a key region for the transmission of migraine information from the head and orofacial structures to the hypothalamus and brain. Moreover, the A11 nucleus also sends direct inhibitory projections to preganglionic sympathetic neurons and the dorsal and anterior horns in the spinal cord, innervating skeletal muscle. However, no clinical studies have been

Table 1. The Patient's Clinical Course Following Immediate-release Pramipexole Treatment

Follow-up (month)	Initial visit[1] 0	1	2	3	4	5
IRLS score	34	10	17	21	26	18
Migraine frequency (/month)	6	6	4	3	0	1

IRLS, International Restless Legs Syndrome Study Group Rating Scale.
[1]Immediate-release pramipexole treatment was initiated at 0.125 mg/day.

performed to evaluate the effect of chronic low-dose dopaminergic treatment on migraine symptoms in patients with concomitant migraines and RLS. We recently encountered a patient with concomitant RLS and migraine who exhibited improvement in her headache frequency and RLS symptoms following low-dose administration of immediate-release pramipexole (P-IR). This observation led us to investigate whether P-IR improves not only clinical RLS symptoms but also migraine headaches in patients with concomitant migraines and RLS. Here, we present the illustrative case and provide the review results of the medical records of patients who experienced both migraines and RLS from our previous cross-sectional study.[4]

Methods

We investigated whether P-IR improved RLS and migraine headache symptoms in patients who had both migraines and RLS and received long-term P-IR treatment by reviewing the patients' medical records and headache diaries. Most of the patients were identified from a previously performed cross-sectional single-center study on migraines and RLS.[4] This study was conducted in the outpatient headache clinic of the Department of Neurology at Dokkyo Medical University. A referral is recommended but not necessary; in fact, most of the patients who visited our headache outpatient clinic were not referral cases. The migraines were diagnosed according to the criteria from the International Classification of Headache Disorders II,[8] and RLS was diagnosed on the basis of four essential criteria, as described by the International Restless Legs Syndrome Study Group.[9] RLS was identified in 36 of 262 (13.7%) migraine patients and in three of 163 healthy control subjects (1.8%). Of the 36 patients, 11 received P-IR treatment. Of these 11 patients, two were lost to follow-up. In addition, one newly diagnosed patient (the present case) with both migraine and RLS was included. Thus, a total of 10 female patients (mean age 35.3 ± 14.0 years) were included in the study. The patients' background characteristics, including their Beck Depression Inventory-II (BDI-II),[10] International Restless Legs Syndrome Study Group Rating Scale (IRLS),[11] Pittsburgh Sleep Quality Index (PSQI),[12] and Epworth Sleepiness Scale (ESS),[13] were obtained from the patients' clinical records. Migraine characteristics (pulsating, tightening, or pressing), the onset age of RLS and migraine, changes in migraine headache frequency before and after P-IR treatment, P-IR daily dose, treatment duration, and concomitant medication in these patients were carefully assessed by reviewing the medical record and headache diary of each patient and by obtaining their comments from the repeated interview. The IRLS includes 10 questions related to RLS symptoms and their impacts on the patient's mood and daily functioning. The score ranges from 0 to 40 (1–10, mild; 11–20, moderate; 21–30, severe; 31–40, very severe symptoms of RLS).[11] All of the patients included in this study were given P-IR for their RLS symptoms and were not advised of the possible effect of P-IR on migraine as the effect of P-IR on migraine was initially not expected. None of the patients received any new treatment for migraine after the P-IR treatment was started.

All participants were informed about the study design to investigate the relationship between migraine and RLS and were informed that they could receive adequate treatment for underlying diseases including RLS during the study period, if identified. The study was approved by the institutional review board, and written informed consent was provided by all patients.

An illustrative case

A 35-year-old woman visited our outpatient clinic because of insomnia due to abnormal sensation in the legs. Since childhood, she had felt the urge to move her legs because of abnormal sensation, which occurred during daytime at school (during class) and was relieved by movement. She denied having either muscle cramp or intermittent claudication. Since the age of 18 years, her restlessness predominantly occurred in the late evening, causing difficulty falling asleep and nocturnal awakening. The patient did not smoke, drink alcohol, or take any regular medication apart from triptan for migraine attack. The past medical history included depression at the age of 23 years and dyslipidemia. She has suffered from migraine without aura since the age of 20 years. The characteristics of her migraine headache were bilateral, pulsatile, and moderate to severe in intensity with accompanying symptoms (photophobia, phonophobia, and osmophobia) but without nausea. The patient reported a favorable response to triptan; however, when left untreated, the migraine headaches lasted for more than 4 hours. The recent headache frequency was 6 days/month. On the initial examination, the patient weighed 53.0 kg and was 152.0 cm tall with a body mass index of 22.9 kg/m^2. There was no cutaneous lesion in the trunk or extremities. No edema or varicose vein in the legs was observed. Neurological examinations were unremarkable except for bilateral absence of Achilles tendon reflex. The ESS score was 15, and the PSQI global score was 13, indicating excessive daytime sleepiness and decreased quality of sleep. She scored 20 on the BDI-II. The patient fulfilled the four essential diagnostic

Table 2. Clinical Features of Patients with Migraines and RLS Who Received Immediate-release Pramipexole Treatment

No	Age (years)	IRLS	RLS onset age (years)	Migraine onset age (years)	Migraine Characteristics	Morning Headache before P-IR Treatment	Migraine Frequency Before/After P-IR Treatment (months)	P-IR Daily Dose (mg)/Treatment Duration (months)	BDI-II	PSQI	ESS	Concomitant Medication
1	22	26	6	6	Pulsating and pressing	+	>15/>15	0.375/10	20	7	4	Eletriptan 20 mg/as needed, naproxen 100 mg/as needed, domperidone 10 mg/as needed, brotizolam 0.25 mg/day, rabeprazole 10 mg/day
2[1]	27	31	25	15	Pulsating	–	12–14/12–14	0.5/16	42	13	16	Sumatriptan 6 mg sc/as needed, zolmitriptan 2.5 mg/as needed, naproxen 100 mg/as needed
3[1]	27	20	27	17	Pulsating	+	15/15	0.125/9	18	7	10	Eletriptan 20 mg/as needed, naproxen 100 mg/as needed, clonazepam 0.5 mg/day, amitriptyline 10 mg/day, topiramate 50 mg/day, omeprazole 10 mg/day, zolpidem 10 mg/day
4	53	21	27	16	Pulsating and pressing	–	>15/>15	0.375/30	5	5	4	Clonazepam 1 mg/day, etizolam 0.5 mg/day, betahistine mesilate 6 mg/as needed, ibudilast 30 mg/day
5	37	29	36	10	Pressing	–	10–14/10–14	0.125/29	5	10	8	Eletriptan 20 mg/as needed, valproic acid 100 mg/day, topiramate 100 mg/day, rabeprazole 10 mg/day
6	23	8	23	17	Pulsating	–	4/1	0.125/2	21	8	13	Rizatriptan 10 mg/as needed

Table 2. Continued

No	Age (years)	IRLS	RLS onset age (years)	Migraine onset age (years)	Migraine Characteristics	Morning Headache before P-IR Treatment	Migraine Frequency Before/After P-IR Treatment (months)	P-IR Daily Dose (mg)/Treatment Duration (months)	BDI-II	PSQI	ESS	Concomitant Medication
7[1]	57	22	56	30	Tightening	+	3–4/1	0.125/23	20	14	13	Loxoprofen 60 mg/as needed, atorvastatin 10 mg/day, mecobalamin 1500 μg/day, amlodipine 2.5 mg/day
8	52	19	57	30	Pulsating	+	15>/2–3	0.125/14	11	12	10	Rizatriptan 10 mg/as needed, naproxen 100 mg/as needed, amitriptyline 10 mg/day
9[1]	20	29	20	13	Pulsating and tightening	+	15>/3–4	0.125/2	40	14	20	Zolmitriptan 2.5 mg/as needed, loxoprofen 60 mg/as needed, betahistine mesilate 6 mg/as needed, amitriptyline 10 mg/day, clonazepam 0.5 mg/day, valproic acid 400 mg/day, omeprazole 10 mg/day, teprenone 150 mg/day
10	**35**	**34**	**7**	**20**	**Pulsating**	**+**	**6/1–2**	**0.125/5**	**20**	**13**	**15**	**Rizatriptan 10 mg/as needed, aspirin 330 mg/as needed, domperidone 10 mg/as needed, sennoside 12 mg/day**

ESS, Epworth Sleepiness Scale; BDI-II, Beck Depression Inventory-II; IRLS, International Restless Legs Syndrome Study Group Rating Scale; PSQI, Pittsburgh Sleep Quality Index; RLS, Restless legs syndrome; P-IR, immediate-release pramipexole.

[1]Pramipexole treatment began after the survey was performed between June and November 2010 from which the scores of BDI-II, PSQI and ESS of each patient was obtained.[4]

The present case (No. 10) is shown in bold.

criteria of RLS:[9] urge to move, worse at rest and evening, and improvement with movement. The patient's RLS symptoms were very severe according to the IRLS (34/40). The laboratory data were normal for liver, kidney, thyroid function, and blood count but showed decreased serum iron levels (30 μg/dl) with normal ferritin levels (62 ng/ml). RLS was diagnosed, and a low dose of P-IR treatment (0.125 mg, 2 hours before bedtime) was started. Her RLS symptoms markedly improved within a few days, and the IRLS score obtained on the fourth day after treatment was decreased to 19. Five months later, the patient was treated with an oral iron supplement for 2 months, based on the laboratory findings of decreased ferritin levels of 33 ng/ml (<50 ng/ml), and then instructed to eat iron-rich foods. Table 1 illustrates the patient's clinical course following the P-IR treatment, which reveals that P-IR treatment improved not only the IRLS score but also headache frequency as reported by the patient.

Results

All patients were female, with a mean age of 35.3 ± 14.0 years. Nine patients suffered from migraine without aura, while one (No. 5) had migraine with aura. Except for two patients (Nos. 1 and 9), the onset of migraine preceded the onset of RLS. P-IR treatment was markedly effective for the RLS symptoms in all of the subjects. The characteristics of the migraine patients with RLS who received chronic P-IR treatment are shown in Table 2. Five out of 10 patients (Nos. 6–10; 50%) reported significant improvements in migraine headache frequency and severity following P-IR treatment. Four of these patients (80%) had reported morning headaches before P-IR treatment in their headache diaries. One patient (No. 6) reported that pulsating headache spontaneously resolved without acute medication following P-IR treatment. No patient reported worsening of headache or any changes in their mood, appetite, or sleep habits after P-IR administration.

Discussion

In our study, our patient's RLS symptoms and migraine headaches exhibited favorable response to P-IR treatment, which is to our knowledge the first clinical observation to support estimated dopaminergic dysfunctions in both RLS and migraine. Combining the review results of our previous study with the present case, 50% of the patients who exhibited both migraines and RLS reported an improvement in their headaches following low-dose P-IR treatment. Our results indicated that the identification of RLS symptoms in migraine patients is clinically significant; we found that when migraines and RLS coexisted, dopaminergic treatment improved both migraine and RLS symptoms in some patients. In five patients whose RLS symptoms responded to P-IR, its effect on migraines was modest compared with the marked effect of P-IR on RLS. In addition, morning headache was frequently observed in these patients (Table 2, No. 7–10; four of five [80%]), suggesting that P-IR may have beneficial effects on migraine attack during sleep. In contrast to our study, which showed improvement in headache in P-IR-treated patients, previous randomized, double-blind, placebo-controlled studies of RLS patients showed that headache occurred in approximately 13–15% of the RLS patients who had received pramipexole treatment and in approximately 10–13% of those who had received placebo treatment.[14,15]

The involvement of dopamine in migraines is thought to be complicated. The administration of low-dose dopamine agonists has been shown to trigger attacks of premonitory symptoms such as nausea, yawning, and food cravings in patients with migraine, and dopamine antagonists have been reported to relieve these symptoms.[6] Administration of D2-like receptor antagonists has been shown to be effective for acute migraine attacks.[16] In contrast, animal studies suggest that dopamine agonists have a role in the headache phase of migraines because the administration of D2-like dopamine receptor agonists inhibits firing in the trigeminocervical complex.[7] A significant link between RLS and migraine has been suggested; however, the reported opposing effects of dopaminergic agonists and antagonists in the two diseases cannot be interpreted by a simplistic explanation at the level of neurotransmitter release or receptor sensitivity.[6] Thus, the mechanism by which pramipexole improves migraine headaches remains unclear. Specifically, it is unclear whether pramipexole directly alleviates migraine headaches by improving central dopaminergic dysfunction or whether it improves compromised sleep quality due to RLS and/or migraine. The latter possibility may be supported by findings that among patients whose migraine headaches responded to P-IR (Table 2, No. 6–10), the PSQI score was higher in patients with morning headaches (No. 7–10) than in patients without morning headaches (No. 6). Limitations of our study included the small number of subjects studied and the lack of detailed examinations before and after the administration of P-IR. In addition, improvement of migraine following P-IR treatment might have been related to other concomitant medications. Although our study did not include a placebo group, the patients were advised of the possible effect only for RLS and not for migraine. Nevertheless, placebo effects should still be considered when treating patients with migraine, as emphasized in the recent review paper.[17] Different percentages of placebo effect are shown in two conditions: 24–30% for acute treatment and 14–50% for prophylactic treatment of headache. In this regard, because our study evaluated both the acute and the prophylactic effect of pramipexole on migraine headache, placebo effects may have arisen from the acute or prophylactic nature of pramipexole, depending on the patients. However, improvement in migraine headache was observed following P-IR treatment in patients who had had morning headache before P-IR treatment, suggesting that P-IR acts as an acute treatment for migraine. In contrast, the observation that P-IR had no effects on migraine headache in patients who had not had morning headache before P-IR treatment may have resulted from insufficient duration of action of P-IR. An extended-release formulation of pramipexole (P-ER) may provide more stable dopaminergic stimulation than P-IR. Whether P-ER is more effective than P-IR in ameliorating daytime headaches in patients who do not have morning headaches requires further studies. We did not perform questionnaires regarding insomnia or sleepiness (PSQI or ESS) after P-IR treatment, and we could not evaluate whether sleep status improved following P-IR treatment. Further clinical studies are warranted to verify our results and to

elucidate the mechanistic role of the dopaminergic system in both migraines and RLS.

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