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Research article

Lower limb flexor reflex: Comparisons between drug-induced akathisia and restless legs syndrome

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HIGHLIGHTS

- Excitability of LLFR pathway is increased in both akathisia and RLS.
- Spatial spread of LLFR in akathisia is similar to healthy subjects and differs from RLS patients.
- Our results suggest a different origin for increased spinal excitability in akathisia and RLS.

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ABSTRACT

Background and objective: Akathisia is characterized by restlessness and crawling sensations similar to restless legs syndrome (RLS). Long latency flexor reflex (LLFR) which has helped to advance RLS pathophysiology has never been investigated in akathisia. Due to the clinical commonalities of akathisia and RLS, we investigated the behavior of LLFR in patients with akathisia aiming to understand pathophysiology of akathisia.
Patients and methods: Seven patients with neuroleptic-induced akathisia, 12 drug-naïve patients with primary RLS and 17 healthy subjects were prospectively enrolled in the study. LLFR was recorded from unilateral tibialis anterior (TA) and long head of biceps femoris (BF) muscles after stimulating the sole by trains of electrical stimuli. We measured amplitude, latency, duration, presence of response and compared between three groups.
Results: One-way ANOVA showed mean durations of early and late responses recorded over TA were the longest in akathisia group compared to both RLS group and healthy subjects ($p = 0.012$). The spatial spread of LLFR in akathisia patients was comparable to those of healthy subjects whereas presence of response on BF was significantly less in akathisia than RLS group.
Conclusions: Our findings indicate increased excitability of LLFR pathway in akathisia group. These findings are probably due to lack of inhibition originated in regions other than those known to downregulate in RLS.

1. Introduction

Akathisia is a movement disorder characterized by urge, inner restlessness and constant requirement to move the limbs. Akathisia symptoms may fluctuate throughout the day. The restlessness decreases by passive or active movements [1]. This neural disorder may be idiopathic or primary, as well as secondary to a number of factors including neuroleptic drugs. Interestingly, restlessness and crawling sensations are also clinical aspects of restless legs syndrome (RLS) [2]. Restlessness in RLS is also relieved by movement of the affected limb [3], and symptoms in RLS also fluctuate. In fact, RLS symptoms are less prominent during the morning and worsen during late afternoon [3].

The long latency flexor reflex (LLFR), also called flexor, flexion or withdrawal reflex, is a protective reflex characterized by synergistic flexion movement of lower extremities after receiving painful lower limb stimulus. RI component is currently not considered.

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RII is elicited by stimulation of A-beta fibers [4], and it appears at about 55 ms post- electrical stimulation. RIII is elicited by stimulation of A-delta fibers, and has a latency ranging from 85 to 180 ms [4,5]. LLFR is modulated by interneurons controlled by dopaminergic, cholinergic and GABAergic neural transmission [6–8]. LLFR has been used to investigate functional status of nociceptive spinal pathways as well as pathways contributing to the locomotion and sensorimotor integration at the spinal level [4].

Germane to this research, LLFR test has helped to advance RLS pathophysiology [9,10]. However, this reflex has never been investigated in akathisia. Due to the clinical commonalities of akathisia and RLS, we planned to investigate the behavior of LLFR in patients with akathisia aiming to disentangle akathisia pathophysiology. To accomplish such aim, we compared akathisia results with data obtained from RLS patients, and from a group of healthy individuals. We hypothesized that some, but not all, of the LLFR measures would differ among these three groups. The abnormal interneuronal activity in akathisia found in this study by measuring the LLFR will offer novel biological explanations for better understanding this neurological disorder.

2. Participants and methods

2.1. Participants

Seven patients with akathisia were studied who were diagnosed as neuroleptic-induced akathisia by psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders [11]. Five of these patients had schizophrenia, one had psychotic depression and one had bipolar disorder. All patients were receiving dopamine receptor antagonist medications (quetiapine, olanzapine, clozapine, zuclopenthixol or amisulpride). Three patients were also using selective serotonin reuptake inhibitors (SSRI), one patient also received valproic acid. The duration of medication use ranged from one month to 2 years. Akathisia was diagnosed one month before this study was made. The Barnes Akathisia Rating Scale (BARS) [12] was used to score akathisia. Two patients had mild, three patients had moderate and two patients had severe akathisia.

Table 1
Demographical findings of all participants.

	Akathisia n = 7	RLS n = 12	Healthy subjects n = 17	p
Age, year	38.0 ± 9.7	42.0 ± 11.4	47.1 ± 11.9	0.183
Gender, M/F, n	4/3	4/8	8/9	0.576

Twelve drug-naïve patients with primary RLS were also studied. RLS patients fulfilled the International RLS Study Group criteria [2,3]. Patients underwent detailed interviews that included the average number of days with RLS in the last four weeks. Neurological examination and routine biochemical investigations (serum ferritin, vitamin B12, folic acid, urea, and glucose) were also made. Polysomnography was performed when history indicated symptoms of concomitant sleep disorder such as periodic limb movement disorders (PLMD), insomnia or obstructive sleep apnea syndrome. The range of disease duration in RLS group was between 1 and 20 years. We asked patients about the average number of days with RLS symptoms in the last four weeks and calculated the mean frequency of symptoms per week for each patient. Afterwards, we calculated mean frequency of symptoms per week for the group which was 5.5 ± 2.3 days/week.

Seventeen healthy subjects were also studied. These participants were matched to patients as close as possible regarding age and gender. Table 1 shows demographical findings of groups.

2.2. Electrophysiological assessments

Studies were done in the afternoon, between 13:30–15:30 h, to minimize circadian influences [13]. Neuropack Sigma MEB-5504k machine (Nihon Kohden Medical, Tokyo, Japan) was used to perform the electrophysiological studies, which were made in a quiet room. Individuals were studied in supine position with both legs semi-flexed. Participants were asked to remain awake and relaxed as much as possible during the test.

The stimulating electrode for eliciting the LLFR was positioned on the sole of the right foot (Fig. 1). The recording electrodes were placed over the right-sided tibialis anterior (TA) and long head of biceps femoris (BF) muscles. A 20 ms electrical stimulation train of

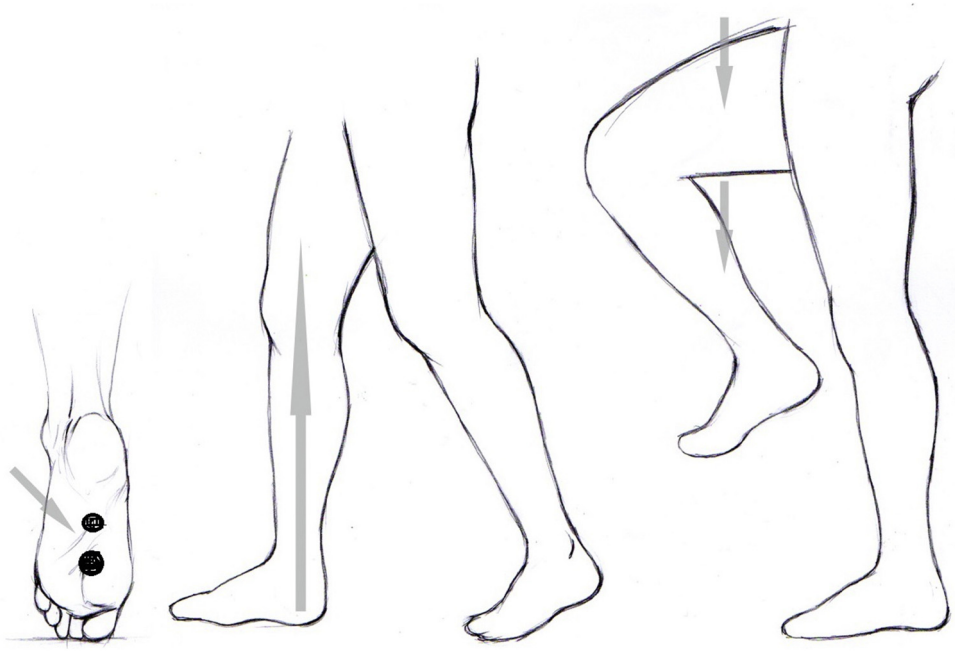

Fig. 1. Representative example of the positioning of stimulation electrode on the sole. Stimulation of sole leads to stimulation of nociceptive afferents which in turn activates motor neurons in spinal cord providing dorsiflexion of foot and flexion of knee.