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Growth hormone response to low-dose apomorphine in restless legs syndrome

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Abstract

Introduction: Low-dose apomorphine challenge has been shown to cause a rise in growth hormone (GH) in patients with Parkinson's disease (PD). This was interpreted as an increased postsynaptic sensitivity of hypothalamic dopamine receptors in the course of a generalized degeneration of dopaminergic neurons. The dopaminergic system in the restless legs syndrome (RLS) has been assumed to play a role in its pathophysiology. It is therefore the aim of this study to determine whether the GH response to subcutaneously applied low-dose apomorphine is generally altered in patients with RLS as compared to healthy controls.
Patients and methods: We examined 40 patients with idiopathic RLS as well as 20 age- and sex-matched healthy control subjects by means of the low-dose apomorphine test. GH was analyzed at baseline, as well as 45 and 60 min after subcutaneous low-dose apomorphine injection in the morning.
Results: Forty RLS patients (58.3 ± 11.9 years, 32 females) with a mean RLS severity scale score of 23.9 ± 6.6 (range 10–37) were examined. GH was not significantly increased 45 and 60 min after injection ($p = 0.397$) (2.44 ± 2.35 ng/ml at baseline versus 2.71 ± 2.29 ng/ml after 45 min and 2.18 ± 1.83 ng/ml after 60 min). The results were independent of pre-treatment with levodopa. Age, sex, duration, and severity of the disease did not show a covariate effect with GH levels. There was no difference compared with healthy controls.
Conclusions: RLS patients did not show an increase in GH after stimulation with low-dose apomorphine. Lack of sensitivity alteration of extrastriatal hypothalamic dopamine receptors suggests that RLS is not a general dopaminergic degenerative disease or might only show circadian alterations.

Keywords: Restless legs syndrome (RLS); Apomorphine; Growth hormone (GH); Cortisol; Hypothalamus

1. Introduction

The restless legs syndrome (RLS) is characterized by leg paresthesias/dysesthesias occurring at rest with an irresistible urge to move the legs. Sensory symptoms are worst or exclusively present at rest and during the evening or night and are at least partially or temporarily relieved by activity [1]. Accordingly, patients are less bothered by symptoms during the daytime. More than 90% of RLS patients have sleep disturbances involving either initiating or maintaining sleep, often resulting in daytime tiredness [2]. Adult prevalence of RLS in the white Caucasian population ranges between 5% and

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10%, increasing with age [2–8]. Abnormal involuntary movements such as periodic leg movements during sleep (PLMS) are reported to be associated with RLS in up to 90% of patients with RLS [9–11]. The aetiology of RLS and PLMS remains unknown. An involvement of the dopaminergic system as well as of the opioidergic system and of iron metabolism as underlying pathomechanism is suggested.

Recently, it was hypothesized that an apomorphine-induced rise in growth hormone (GH) reflects an increased sensitivity of hypothalamic receptors due to the generalized dopaminergic deficit in Parkinson's disease (PD) [12]. A challenge with a subthreshold dosage of subcutaneously injected apomorphine causes a rise in GH in patients with PD, independent of a pretreatment with levodopa [12,13]. The low-dose apomorphine test can thus be used as an endocrinological stimulation test for the examination of extrastriatal dopaminergic receptor function even in patients already under treatment with levodopa. To determine whether there is a similar general deficit in the dopaminergic system of RLS patients, we used the same challenge test as in PD patients in either de novo or levodopa pretreated RLS patients.

2. Patients and methods

2.1. Patients

All patients in this study had idiopathic RLS, were pretreated only with levodopa or not treated at all, and were recruited consecutively between February 2003 and June 2004 from the specialized outpatient clinics for RLS at the Department of Clinical Neurophysiology, University of Göttingen, Germany. The clinical diagnosis was made by experienced neurologists according to the Essential Criteria of the International Restless Legs Syndrome Study Group (IRLSSG) [1]. Blood analyses and clinical examinations were performed to exclude symptomatic forms of RLS. Disease severity was evaluated using the restless legs syndrome severity scale (IRLS) [14]. Twenty patients under treatment with levodopa and 20 RLS patients without any RLS-specific therapy at the time of the investigations were included. We also investigated 20 age- and sex-matched healthy controls, recruited from relatives accompanying the RLS patients and from an advertisement in the hospital; none of the controls showed any signs or symptoms of RLS. For clinical and demographic data, see Table 1. Before participating in the study, all patients and healthy controls gave informed consent. The experimental protocol was approved by the local ethics committee of the Medical Faculty of the University of Göttingen, Germany.

2.2. Low-dose apomorphine test

According to the protocol described by Corn et al. [15], all patients and controls received 0.005 mg/kg of body weight subcutaneous apomorphine hydrochloride (Teclapharm GmbH, Lüneburg, Germany) after an overnight fast. All participants were studied around 8:30 AM after they had been lying supine for 30 min, and all RLS patients were free of symptoms during the testing period. Since GH increases with moving [16], controlled GH values can only be measured directly after getting up in the morning. Blood samples were taken from a cannulated antecubital vein. GH and cortisol were analyzed at baseline as well as 45 and 60 min after subcutaneous apomorphine injection (see [12,15]).

The blood specimens were analyzed with commercially available radioimmunoassay kits (GH: DPC Biermann GmbH, Germany sensitivity, 0.9 ng/ml; cortisol: DPC Biermann GmbH, Germany [sensitivity, 1.00 nmol/l)]. The interassay and intraassay variation coefficients of the radioimmunoassays were all less than 8%. The low-dose apomorphine tests were performed at the Department of Clinical Neurophysiology, the tests for GH and cortisol were analyzed at the Department of Clinical and Experimental Endocrinology, University of Göttingen, Germany.

2.3. Statistics

The statistical design of the GH and cortisol data is a repeated measures design, i.e., the same patient was repeatedly observed at several time points [17]. If any hypothesis was rejected in this procedure (significance level was set to 5%) subsequent post-hoc analyses were performed. Kruskal–Wallis and Mann–Whitney-U tests were carried out to see whether the covariates age, duration, and severity of disease had the same distribution in the groups. Correlations were calculated to analyze the influences of these covariates on GH using Spearman's rank correlation coefficient.

3. Results

3.1. Clinical characteristics and demographics

Matching was done by age and gender, therefore, these parameters were not different between the groups. Patients in the levodopa group showed a shorter disease duration ($p = 0.011$) and a higher RLS severity score ($p = 0.038$) than patients not treated with levodopa, probably because five patients under levodopa showed mild symptoms of augmentation (see Table 1). The frequency of cardiovascular and metabolic comorbidities and disease-specific treatment was not different between the groups (data not shown).