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Factors associated with augmentation in patients with restless legs syndrome

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Abstract

Background and purpose: Augmentation is a paradoxical reaction mainly to dopaminergic medication in patients with restless legs syndrome (RLS), but the exact pathomechanism remains unclear. The aim of this study was to identify factors associated with augmentation in RLS patients.

Methods: RLS patients with and without current or previous augmentation were recruited. Demographic characteristics, history of smoking, questionnaires for depression, alexithymia, and impulsivity, and RLS severity were obtained.

Results: We included 122 patients, of whom half had a history of augmentation. Patients with augmentation had a longer disease duration ($p = 0.001$), had higher RLS severity scores ($p = 0.013$), had higher levodopa equivalent doses ($p < 0.001$), had higher scores for alexithymia ($p = 0.028$), had higher prevalence of impulse control disorders ($p < 0.001$), more often had a history of smoking ($p = 0.039$), were more often currently smoking ($p = 0.015$), and had more average pack-years ($p = 0.016$).

Conclusions: Here, we describe several factors commonly associated with augmentation in RLS. These may help clinicians to screen and treat patients carefully to avoid the challenging side effect of augmentation.

KEYWORDS
augmentation, impulsivity, neurobehavioral changes, RLS

INTRODUCTION

Augmentation (AUG) is a well-known paradoxical reaction mainly to dopaminergic medication in patients with restless legs syndrome (RLS) [1]. Clinically, these patients complain of increased symptom severity, an emergence of RLS symptoms earlier in the day, symptoms in previously unaffected body parts, a shorter effect of medication, and a shorter latency to symptom onset during periods of inactivity [2]. The pathophysiology of augmentation is unclear and complex, but it is thought that dopaminergic overstimulation resulting in neuroplastic changes is the main trigger [3]. In line with this, impulse control disorders (ICDs), another major side effect of

dopaminergic medication, often coexist in RLS patients with augmentation [4].

Apart from the dopaminergic medication itself, the duration of treatment is also an established risk factor. Whereas the risk of augmentation is <10% after short-term use, the prevalence of augmentation increases sharply after long-term use [5]. Furthermore, especially low ferritin levels have been established as a known risk factor for augmentation in RLS [5].

However, little is known about the neuropsychological traits and demographic characteristics of RLS patients with augmentation compared to those without [6]. Previous studies have reported that decision-making with a high degree of uncertainty and particularly

irrational decision-making, as well as an impairment in emotional recognition, higher scores for alexithymia, and poorer performance on the frontal assessment battery are more common in RLS patients with augmentation compared to those without and healthy controls [4,6–9]. Here we compared a large group of RLS patients with and without augmentation to screen for potential factors that may help clinicians to detect augmentation early on.

Given the high prevalence of additional addictive behaviours in RLS patients with augmentation [4,8], we explicitly screened for behavioural factors including excessive alcohol consumption or smoking, for alexithymia, and for demographic features that may be linked to a higher prevalence of augmentation in RLS.

METHODS

The study was approved by the local ethics committee of the Medical University of Innsbruck, Austria, and all participants provided written informed consent according to the declaration of Helsinki (Medical University of Innsbruck, ethics committe number: AN2014-0251). We aimed to prospectively recruit the same number of RLS patients with and without current or previous augmentation from the sleep disorders outpatient clinic and sleep laboratory of the Department of Neurology, Medical University of Innsbruck. RLS severity was assessed using the International Restless Legs Syndrome Study Group Rating Scale(IRLS). RLS diagnosis was made according to the International Restless Legs Syndrome Study Group criteria [10] by board-specified sleep specialists.

RLS patients were categorized into patients without a history of augmentation (RLS-AUG) and patients with a history of augmentation (RLS+AUG) as previously described [4,9]. Patients who did not completely fulfil criteria for augmentation were classified as subthreshold augmentation and were also included in the AUG group [2]. All patients in the AUG group were currently or previously treated with dopaminergic therapy.

Detailed medical assessments as well as relevant demographic characteristics were obtained (Table 1). Paper-based questionnaires for depression and impulsivity (Barratt Impulsiveness Scale [BIS-11], Hospital Anxiety and Depression Scale [HADS]) and alexithymia (Toronto Alexithymia Scale [TAS-20] were obtained. Furthermore, semistructured interviews including individual risk factors (e.g. history of smoking [past history of smoking/never smoker/currently smoking], cumulative smoking exposure [pack-years], excessive alcohol consumption [11], illicit substance abuse, prevalent psychiatric disorder) and symptoms of impulsive behaviour based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease, were performed. Excessive alcohol consumption was defined as three or more drinks on any day or more than seven drinks per week in women, and four or more drinks on any day or more than 14 drinks per week in men [11].

Furthermore, only patients who scored more than 26/30 points on the Mini-Mental State Examination (MMSE), who had no major psychiatric disorder, and who had no other medical condition possibly associated with RLS symptoms (e.g., anaemia or kidney failure)

were included. Levodopa equivalent dose (LED) for dopaminergic replacement therapy was calculated as described elsewhere [12].

Statistics

Statistical analyses were performed using SPSS Statistics 22.0 (IBM). To test for normality, the Kolmogorov–Smirnov test was used. Parametric and nonparametric tests as well as the Fisher exact test were used for statistical analysis depending on the distribution and the scale type of the variables. An analysis of covariance was employed to correct for age and gender. In addition, we performed logistic regression analyses as sensitivity analysis to document the associations of the potential risk factors with augmentation, given as odds ratios (ORs) and 95% confidence intervals. All potential risk factors were treated as continuous and categorical variables. ORs of continuous variables were calculated for 1 SD unit change of the respective variable to render odds comparable. The significance level was set at two-sided p-value of <0.05 using a Bonferroni adjustment for multiple comparisons.

RESULTS

Demographic data are reported in Table 1. We included a total of 122 RLS patients with (RLS+AUG, $n = 61$) and without augmentation (RLS-AUG, $n = 61$). We found significant group differences between RLS+AUG and RLS-AUG; RLS+AUG had a longer disease duration ($p = 0.001$), had higher IRLS scores ($p = 0.013$), had higher LED ($p < 0.001$), scored higher on the TAS-20 ($p = 0.028$), had a higher rate of ever-smokers ($p = 0.039$), and had significantly more often ICD symptoms ($p < 0.001$). Moreover, RLS patients with augmentation were more often currently smoking ($p = 0.015$) and showed higher cumulative smoking exposure, as measured by pack-years ($p = 0.016$), than RLS patients without augmentation.

The logistic regression analyses confirmed the reliability of the empirical findings, and the associations remained significant after correction for age and gender (see Table 2): history of smoking ($p = 0.003$), currently smoking ($p = 0.002$), pack-years ($p = 0.019$), LED ($p < 0.001$), IRLS ($p = 0.002$), TAS-20 ($p = 0.013$), and ICD symptoms ($p < 0.001$).

We found no group differences in gender, BIS-11, HADS, MMSE, education, or age at symptom onset (all p-values > 0.05; see Tables 1 and 2).

Only two patients reported excessive alcohol intake (both RLS+AUG), and no patient reported illicit substance abuse.

DISCUSSION

In this study, we have identified several important factors that are significantly more common in RLS patients with augmentation than those without. As expected, RLS patients with augmentation had a longer disease duration, higher LED, and higher scores on the IRLS, which is consistent with a community sampled study in

TABLE 1 Demographic characteristics (N = 122)

Characteristic	RLS+AUG	RLS-AUG	p
n	61	61	
Male/female[a]	27/34	25/36	0.855
MMSE[b]	28.3 ± 1.3	28.7 ± 1.4	0.186
Age, years[c]	64.1 ± 11.8	59.2 ± 13.0	0.019[d]
Education[b]	10.7 ± 2.4	11.6 ± 2.6	0.057
IRLS[c]	22.9 ± 8.1	19.5 ± 8.4	0.013[d]
LED[b]	101.9 ± 123.8	35.8 ± 31.2	<0.001[d]
Disease duration[c]	17.2 ± 12.1	11.0 ± 9.2	0.001[d]
Age at symptom onset[c]	46.5 ± 15.1	48.0 ± 14.0	0.900
TAS-20[c]	53.9 ± 13.5	47.5 ± 14.9	0.028[d]
BIS-11[c]	66.4 ± 8.5	65.1 ± 7.3	0.720
HADS[c]	13.3 ± 6.4	13.5 ± 7.2	0.858
History of smoking, yes/no[a]	30/31	16/45	0.039[d]
Currently smoking, yes/no[c]	15/46	5/56	0.015[d]
Pack-years[c]	14.1 ± 21.4	6.5 ± 13.6	0.016[d]
Excessive alcohol consumption, yes/no[c,d]	2/59	0/61	0.156
Illicit substance abuse, yes/no[c,e]	0/61	0/61	1.000
ICD symptoms, yes/no[a]	31/30	12/49	<0.001[d]

Note: The significance level is set at $p < 0.05$; *p*-values of post hoc comparisons are adjusted by Bonferroni correction for multiple comparisons.

Abbreviations: ANOVA, analysis of variance; BIS-11, Barratt Impulsiveness Scale; HADS, Hospital Anxiety and Depression Scale; ICD, impulse control disorder; IRLS, International Restless Leg Scale; LED, levodopa equivalent dose; MMSE, Mini-Mental State Examination; RLS, restless legs syndrome; RLS+AUG, RLS patients with augmentation; RLS-AUG, RLS patients without augmentation; TAS-20, Toronto Alexithymia Scale.

[a]Fisher exact test.

[b]Parametric tests (unpaired *t*-test, univariate one-way ANOVA).

[c]Nonparametric tests (Mann–Whitney *U*-test, Kruskal–Wallis one-way ANOVA).

[d]Statistically significant.

[e]For women, three or more drinks on any day or more than seven drinks per week; for men, four or more drinks on any day or more than 14 drinks per week [11].

266 RLS patients by Allen et al. in 2011 [1]. However, in this study, all patients were seen by a sleep expert, which is in contrast to the previous online study. Furthermore, we found that augmented RLS patients had more ICD symptoms. This is in line with our previous study, which demonstrated that RLS patients with augmentation had a sixfold higher risk of having in addition symptoms of at least one addictive behaviour, although there was a partial overlap of patients included in the current and the previous study [4]. Moreover, RLS patients with augmentation had significantly more often a history of smoking, were more often currently smoking, and showed higher cumulative smoking exposure (pack-years) than RLS patients without augmentation. This is particularly interesting as cigarette smoking has also been identified as a risk factor for substance abuse [13] and impulse control disorders [14]. Furthermore, smoking has been associated with impairment in decision-making, temporal discounting task, and risk-taking [15]. In line with this, it has been shown that RLS patients with augmentation gather less information and make more decisions against

the evidence than RLS patients without augmentation and healthy controls [7,8].

Although age was significantly different between the two RLS groups, age at disease onset was not, indicating that disease duration is responsible for developing augmentation.

Furthermore, we found higher scores on the alexithymia questionnaire (TAS-20) in augmented than in nonaugmented RLS patients. The mean scores in the augmentation group (>53) were above the cutoff score of borderline alexithymia (i.e., ≤50). Augmentation and impulsivity may share a similar pathomechanism, in line with this higher scores on the TAS-20 have been linked with impulsivity, substance abuse, and aggression [16]. It is likely that a higher LED causes neuroplastic changes within the striatum and its connections to the limbic areas that may explain the higher alexithymia scores [6].

Nevertheless, there are also limitations of our study. First, we did not assess the exact onset and duration of augmentation. Furthermore, several additional risk factors (e.g., family history of RLS, family history of ICD symptoms, caffeine intake) have not been

Variable	Unadjusted		Adjusted[a]	
	OR (95% CI)	p	OR (95% CI)	P
Age	1.570 (1.073–2.299)	0.020[b]		
Gender	0.874 (0.426–1.793)	0.714		
IRLS	1.1645 (1.123–2.409)	0.011[b]	1.825 (1.222–2.725)	0.003[b]
LED	4.795 (2.019–11.389)	<0.001[b]	4.258 (1.800–10.070)	<0.001[b]
Disease duration	1.960 (1.261–3.047)	0.003[b]	1.815 (1.161–2.838)	0.009[b]
TAS-20	1.702 (1.091–2.656)	0.019[b]	1.752 (1.112–2.762)	0.016[b]
History of smoking, yes/no	2.346 (1.106–4.976)	0.026[b]	3.4343 (1.477–7.986)	0.004[b]
Currently smoking, yes/no	3.652 (1.234–10.805)	0.019[b]	5.634 (1.735–18.292)	0.004[b]
Pack-years	1.641 (1.073–2.509)	0.022[b]	1.725 (1.096–2.715)	0.019[b]
ICD symptoms, yes/no	4.219 (1.884–9.452)	<0.001[b]	4.014 (1.766–9.121)	<0.001[b]
MMSE	1.004 (0.583–1.727)	0.989	1.079 (0.614–1.893)	0.792
Education	0.812 (0.464–1.418)	0.463	0.897 (0.495–1.626)	0.720
BIS-11	1.142 (0.725–1.799)	0.568	1.181 (0.726–1.921)	0.503
HADS	0.983 (0.656–1.473)	0.983	1.090 (0.709–1.674)	0.695

Note: The significance level is set at $p < 0.05$.

Abbreviations: BIS-11, Barratt Impulsiveness Scale; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ICD, impulse control disorder; IRLS, International Restless Leg Scale; LED, levodopa equivalent dose; MMSE, Mini-Mental State Examination; OR, odds ratio; TAS-20, Toronto Alexithymia Scale.

[a]Adjusted for age and gender.

[b]Statistically significant.

taken into account in this study. Although not statistically significant, RLS patients with augmentation had lower education than those patients without. It is possible that a larger sample size would have also revealed group differences in schooling. Moreover, there was a partial overlap of patients included in the current and a previous study [4].

Finally, this study was carried out in a tertiary referral centre for RLS patients, and therefore patients with severe augmentation may be overrepresented.

CONCLUSIONS

Longer disease duration, a past history of smoking, currently smoking, more excessive smoking, alexithymia, higher RLS severity scores, ICD symptoms, and higher doses of dopaminergic medication seem to be important risk factors for developing augmentation in patients with RLS. The results of this study may help clinicians to screen and treat patients with these associated factors more carefully to avoid the challenging side effect of augmentation in RLS.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

editing (equal). **Melanie Bergmann:** Project administration (equal), resources (equal), writing–review & editing (equal). **Elisabeth Brandauer:** project administration (equal), resources (equal), writing–review & editing (equal). **Klaus Seppi:** Conceptualization (equal), formal analysis (equal), methodology (equal), supervision (equal), writing–review & editing (equal). **Birgit Högl:** Resources (equal), supervision (equal), validation (equal), writing–review & editing (equal). **Atbin Djamshidian:** Conceptualization (lead), data curation (equal), formal analysis (equal), methodology (equal), resources (equal), supervision (lead), visualization (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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