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RESEARCH

Cerebellum white matter reductions in restless legs syndrome are associated with psychiatric symptom severity

Huzursuz bacak sendromunda serebellar beyaz cevher kaybı psikiyatrik semptom düzeyiyle bağlantılıdır

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Abstract

Purpose: Various imaging techniques were used to examine putative changes in restless legs syndrome (RLS), in which the central nervous system and peripheral nervous system play a role by using many biochemical pathways and neurotransmitters. In this study, the cerebellar volumes of drug-naive patients with RLS were examined and compared with healthy control groups. Additionally, the relationship between psychiatric symptom severity and cerebellar white matter (WM) volume was examined.

Materials and Methods: The current study included 44 RLS patients and 53 age- and gender-matched healthy controls. The symptom severity of RLS group was assessed by using the International Restless Legs Syndrome Study Group Rating Scale (RLSRS) and the Symptom Checklist-90-Revised (SCL-90-R). Brain magnetic resonance imaging (MRI) volumes were calculated with Volbrain software.

Results: The patient group consisted of 24 males and 20 females, while the control group included 29 males and 24 females. The mean age in the patient cohort was 36.23±5.43 years, compared to 34.20±5.22 years in the control cohort. The right cerebellum WM (1.10±0.26) and left cerebellum WM (0.90±0.23) percentages of the patient group were significantly lower than the healthy control group (right cerebellum WM=1.27±0.31; left cerebellum WM=1.03±0.26). The right cerebellum WM (15.41±4.03) and left cerebellum WM (12.63±3.05) volumes of the patient group were significantly lower than those of the healthy control group (right cerebellum WM=17.49±4.12; left cerebellum WM=14.25±3.53). In the RLS group, a

Öz

Amaç: Huzursuz bacak sendromunda (HBS), merkezi sinir sistemi ve periferik sinir sisteminin çok sayıda biyokimyasal yolak ve nörotransmitter aracılığıyla etkili olduğu olası değişiklikleri araştırmak amacıyla çeşitli görüntüleme yöntemleri uygulanmıştır. Bu çalışmada, HBS'li tedavi almamış hastaların serebellar hacimleri incelendi ve sağlıklı kontrol grubuyla karşılaştırıldı. Ek olarak, psikiyatrik semptom şiddeti ile serebellar beyaz cevher (BC) hacmi arasındaki ilişki incelendi.

Gereç ve Yöntem: Bu çalışmaya 44 HBS hastası ve yaş ve cinsiyete göre eşleştirilmiş 53 sağlıklı kontrol dahil edildi. HBS grubunun semptom şiddeti Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu Derecelendirme Ölçeği (HBSDÖ) ve Belirti Kontrol Listesi-90-Revize (BKL-90-R) kullanılarak değerlendirildi. Beyin manyetik rezonans görüntüleme (MRG) hacimleri Volbrain yazılımı ile hesaplandı.

Bulgular: Hasta grubunda 24 erkek ve 20 kadın, sağlıklı kontrol grubunda 29 erkek ve 24 kadın vardı. Hasta grubunda ortalama yaş 36,23±5,43 yıl, sağlıklı kontrol grubunda ise 34,20±5,22 yıl olarak bulundu. Hasta grubunun sağ serebellum BC (1.10±0.26) ve sol serebellum BC (0.90±0.23) yüzdeleri sağlıklı kontrol grubundan (sağ serebellum BC=1.27±0.31; sol serebellum BC=1.03±0.26) anlamlı olarak düşüktü. Hasta grubunun sağ serebellum BC (15.41±4.03) ve sol serebellum BC (12.63±3.05) hacmi sağlıklı kontrol grubundan (sağ serebellum BC=17.49±4.12; sol serebellum BC=14.25±3.53) anlamlı olarak düşüktü. HBS grubunda serebellum BC hacim ve yüzdeleri ile BKL-90-R ve HBSDÖ skorları arasında anlamlı negatif korelasyon bulundu.

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significant negative correlation was found between cerebellum WM volumes and percentages and SCL-90-R and RLSRS scores.
Conclusion: This study demonstrates that drug-naive RLS is associated with significant cerebellar WM volume reductions, which may indicate early structural brain abnormalities. The observed correlation between cerebellar WM changes and psychiatric symptom severity highlights the need for further research into the neurological and psychiatric interplay in RLS.
Keywords:. White matter, cerebellum, restless legs syndrome, magnetic resonance imaging

Sonuç: Bu çalışma, tedavi almamış HBS'nin önemli derecede serebellar BC hacim kaybı ile ilişkili olduğunu ve bunun erken yapısal beyin anormalliklerine işaret edebileceğini göstermektedir. Serebellar BC değişiklikleri ile psikiyatrik semptom şiddeti arasındaki korelasyon, HBS'deki nörolojik ve psikiyatrik etkileşimin daha ayrıntılı araştırılması gerektiğini vurgulamaktadır.

Anahtar kelimeler: Beyaz cevher, serebellum, huzursuz bacak sendromu, manyetik rezonans görüntüleme

INTRODUCTION

Restless legs syndrome (RLS) is a prevalent neurological disorder characterized by key features such as an overwhelming urge to move the legs, partial or complete symptom relief through movement, symptom onset during periods of rest, and a marked evening predominance[1]. Proposed underlying pathophysiological mechanisms include primary subcortical disturbances within the dopaminergic and opioidergic systems, abnormalities in the sensorimotor circuitry, and dysregulation of cerebral iron homeostasis[2,3]. Various neuroimaging modalities have been employed to investigate hypothesized alterations in RLS, with both the central and peripheral nervous systems contributing through complex biochemical pathways and neurotransmitter dynamics[4]. Several advanced techniques have been developed to examine structural brain alterations, most of which utilize high-resolution magnetic resonance imaging (MRI). The volume and shape of specific subcortical structures can be assessed through volumetric and shape analysis. To detect subtle structural changes that may lead to inconsistent and often contradictory findings, MRI examinations employing quantitative structural approaches have been conducted in RLS patients[2]. Studies indicate that, in addition to regions such as the basal ganglia, motor and somatosensory cortex, thalamus, hypothalamus, substantia nigra, dopaminergic A11 cell group, spinal cord, red nucleus, inferior olive, and brainstem nuclei, the cerebellum also plays a crucial role in the pathophysiology of RLS[5]. Furthermore, the cerebellum's involvement in sleep regulation and its connection to RLS-related sleep disturbances underscore the need for further research into its potential role in RLS[6].

The cerebellum integrates inputs from neuromodulatory systems that regulate arousal and the sleep-wake cycle while sending projections to multiple brain regions involved in the control of arousal and sleep states[6]. Its role in motor control during sleep includes the regulation of movement, posture, and muscle tone. Cerebellar abnormalities observed in sleep disorders include altered water diffusion in congenital central hypoventilation syndrome, reduced cerebral perfusion in obstructive sleep apnea, cerebellar atrophy in fatal familial insomnia, and decreased gray matter (GM) volume in insomnia. The cerebellum has also been investigated in RLS patients with sleep disturbances[7]. Chang et al.[8] identified significant regional reductions in GM volume among RLS patients, specifically in the left hippocampal gyrus, bilateral parietal lobes, medial frontal regions, and the cerebellum. In contrast, Belke et al.[2] reported no GM alterations in RLS. However, cerebellar white matter (WM) changes in RLS have not been adequately investigated. Belke et al.[2] used diffusion tensor imaging and identified regions of altered fractional anisotropy bilaterally in subcortical WM, predominantly in the temporal lobes, as well as in the right internal capsule, the pons, and the right cerebellum. Conversely, a recent study by Park et al.[9] found no significant differences in cerebellar volume or its subdivisions between RLS patients and healthy controls. These inconsistencies in the literature highlight the need for further studies to clarify the role of cerebellar structural changes in RLS.

Although discussions of brain anatomy often focus on GM, WM also plays a crucial role in information processing. WM in the brain consists of myelinated axons that facilitate the rapid transmission of neural signals. Its primary function is to establish connections between different brain regions, enabling coordinated communication and integration of information. Damage to WM in the brain or spinal

cord can impair movement, sensory perception, and the ability to respond to external stimuli. Patients with WM damage often exhibit deficits in reflexive responses. Additionally, reduced WM volume has been linked to impairments in attention, declarative memory, executive functioning, intelligence, and academic performance[10,11]. It is possible that the symptoms of RLS are associated with WM abnormalities. However, findings from studies investigating WM in RLS remain inconsistent. These discrepancies may be attributed to technological limitations in earlier research, variations in post-processing techniques, differences in magnetic field strength, sample size variability, and the presence of potential concomitant sleep disorders[12].

In addition to sleep disorders, several psychiatric conditions, such as anxiety disorder and major depressive disorder, are also commonly observed in RLS. Moreover, even in the absence of a diagnosable psychiatric condition, individuals with RLS often experience significant psychological distress and functional limitations[13]. Studies have shown that the prevalence of depression and anxiety disorders in RLS patients is 2.1 to 5.3 times higher than in the general population[14]. One study reported that RLS patients exhibit higher levels of neuroticism compared to individuals without RLS[15]. Scholz et al.[16] found increased severity of somatization, compulsive behaviors, depression, and anxiety in RLS patients, as measured by the subscales of the Symptom Checklist-90-Revised (SCL-90-R). Another study reported a higher frequency of chronic pain and somatoform disorders in individuals with RLS[17].

To the best of our knowledge, no studies have specifically examined cerebellar WM in drug-naive RLS patients. This study aimed to compare WM volumes between drug-naive RLS patients and healthy controls and to investigate the correlation between these brain volumes and psychiatric symptom severity. Our hypothesis is that cerebellar WM is already affected in RLS patients at their first hospital admission and that there is a significant relationship between cerebellar WM alterations and psychiatric symptomatology.

MATERIALS AND METHODS

Sample and General Information

The present study included 44 patients diagnosed with primary restless legs syndrome (RLS) and 53 age- and gender-matched healthy controls. Ethical approval was obtained from the Adıyaman University Ethics Committee (Protocol number: 2023/2-16; Date: 24/10/2023). Informed consent was obtained from all participants.

Individuals diagnosed with neurological disorders other than RLS were excluded from the study. Patients with secondary RLS were also not included. Additionally, those using any active medication were excluded. Patients with a history of alcohol or illicit drug use (e.g., methamphetamine, heroin, marijuana, cocaine) were not eligible for participation. Individuals with chronic organic diseases such as hypertension or diabetes mellitus, or those using medications for these conditions, were also excluded. In the healthy control group, individuals with a history of RLS, any medical disease, or medication use were not included. Furthermore, both patients and healthy controls with intellectual disabilities were excluded from the study. The data of all participants, including both patients and healthy controls, were verified through the national hospital record system (e-Nabız).

A total of 140 individuals were initially approached for participation in this study. In the RLS group, 22 individuals were excluded due to the presence of neurological disorders other than RLS (8 participants), current medication use (5 participants), history of alcohol or illicit drug use (3 participants), chronic medical conditions such as hypertension or diabetes (4 participants), and mental retardation or cognitive impairment (2 participants). In the HC group, 21 individuals were excluded due to the presence of medical conditions (7 participants), history of RLS or undiagnosed sleep disorders (6 participants), use of any medication affecting the nervous system (5 participants), and cognitive impairment or history of psychiatric disorders (3 participants). After these exclusions, the study included 44 drug-naive RLS patients and 53 healthy controls.

Procedure

RLS patients were recruited from the neurology outpatient clinics at Adıyaman Training and Research Hospital and were diagnosed by a neurologist based on the International Restless Legs Syndrome Study Group criteria, using structured clinical interviews[18]. Healthy controls were selected from individuals who visited the neurology clinic for reasons such as headache and dizziness, had no diagnosed diseases, and had normal brain MRI findings. The severity of

RLS symptoms was assessed using the International Restless Legs Syndrome Study Group Rating Scale (RLSRS) and the Symptom Checklist-90-Revised (SCL-90-R).

At our hospital, MRI is routinely performed in RLS patients to exclude organic brain diseases. Additionally, a detailed medical history and psychometric assessment findings for all patients are systematically recorded in patient files. All patients and healthy controls were right-handed, as determined by the short version of the Edinburgh Handedness Inventory[19]. The RLSRS and SCL-90-R assessments were conducted by a trained clinical neurologist and a trained clinical psychiatrist. MRI scans were performed immediately on patients who were stable and cooperative. In this study, disease duration refers to the period following an RLS diagnosis, rather than the initial onset of symptoms.

Measures

International Restless Legs Syndrome Study Group Rating Scale

The RLSRS, developed by the International Restless Legs Syndrome Study Group in 2003, is widely used today to assess RLS severity. This scale plays a crucial role in clinical evaluation and has been translated into multiple languages, contributing to both treatment approaches and scientific research on RLS. The scale consists of 10 questions, with the first five assessing symptom severity and the remaining five evaluating daily living activities and quality of life. Each question is rated by the patient on a 0–4 scale: "not at all," "mild," "moderate," "severe," or "very severe." The total score, ranging from 0 to 40, reflects the severity of the disease. Based on this score, RLS severity is classified as follows: mild (1–10), moderate (11–20), severe (21–30), and very severe (31–40)[20].

Symptom Checklist-90-Revised (SCL-90-R)

The SCL-90-R is a widely used self-report instrument designed to assess a broad range of psychological and psychiatric symptoms. It evaluates nine primary symptom dimensions, including somatization, obsessive-compulsive tendencies, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. This tool enables the assessment of an individual's subjective psychopathological experiences without requiring direct evaluation by a mental health professional. The validity and reliability of the Turkish version were established by Kılıç[21].

Image Acquisition

MRI scans were acquired using a Philips Achieva MR system (Philips Medical Systems, Best, Netherlands) with a 1.5 Tesla magnetic field strength and a head coil. The imaging parameters were as follows: time to repeat (TR): 1665 ms, time to echo (TE): 20 ms, field of view (FOV): 220 × 230 mm, slice thickness: 5 mm, matrix size: 292 × 214, number of signal averages (NSA): 1, slice gap: 1 mm, voxel size: 0.75 × 1.07 × 5 mm, and 24 slices per section. To prevent bias and ensure blinding, cerebellar volume measurements were conducted independently by physicians, with patients and controls anonymized during the analysis.

Volume Measurement

Brain MRI segments of the participants were uploaded to VolBrain (VB) software (https://www.volbrain.upv.es/) for volumetric analysis. The MRI examinations were evaluated by two radiologists with 7 and 16 years of experience, respectively. To prevent bias, cerebellar volume measurements were conducted blindly, ensuring that patients and controls remained unidentified during the analysis. VB is an automated software tool designed for brain volume computation. DICOM images were converted to NIFTI format using the MRIcron program before being processed in VB. The segmentation of brain structures in VB is illustrated in Figure 1.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables and descriptive data were expressed as mean ± standard deviation, while categorical variables were summarized as frequencies and percentages. The chi-square test was used to analyze categorical data, and the Kolmogorov-Smirnov test was applied to assess the normality of the data distribution. Group comparisons were conducted using the independent samples t-test to identify statistically significant differences. The diagnostic efficacy of MRI parameters was evaluated through receiver operating characteristic (ROC) curve analysis. Within the patient cohort, Pearson's correlation analysis was used to assess relationships between variables, and Cohen's d was calculated to quantify effect sizes. A p-value < 0.05 was considered statistically significant.

To the best of our knowledge, no other study in the literature has been designed similarly to this one to measure cerebellar white matter (WM) volume, including mean and standard deviation data. Therefore, for power analysis, a study that included both RLS and healthy control groups and examined the cerebellum was considered. In a study conducted by Belke et al.[2] using voxel-based morphometry, cerebellar diffusivity was found to differ significantly between RLS and healthy control groups ($p < 0.0001$). Belke et al.[2] included 12 subjects in their study. Based on their findings, it was determined that each group in the present study should include more than 12 participants to ensure adequate statistical power.

RESULTS

The patient cohort consisted of 24 males (54.54%) and 20 females (45.46%), while the healthy control group included 29 males (54.71%) and 24 females (45.29%). The mean age of the patient group was 36.23 ± 5.43 years, compared to 34.20 ± 5.22 years in the control group, with no statistically significant differences in age ($p = 0.162$) or gender distribution ($p = 0.987$) between the groups. The mean disease duration in the patient group was 3.65 ± 1.12 years, reflecting the interval from symptom onset to neurological evaluation, as all participants were drug-naïve RLS patients.

Cerebellar WM metrics were compared between the groups. The percentage of right cerebellar WM ($p = 0.006$) and left cerebellar WM ($p = 0.009$) was significantly lower in the patient group compared to healthy controls. Similarly, volumetric analysis revealed significantly lower right cerebellar WM volume ($p = 0.014$) and left cerebellar WM volume ($p = 0.019$) in the patient group (Table 1).

Table 1. Comparison of the Cerebellum Parameters of the Patient and Healthy Control Groups

Parameters	RLS (n=44) (mean±SD)	Control (n=53) (mean±SD)	p value	Cohen's *d*
Age (years)	36.23±5.43	34.20±5.22	0.162	0.38
Cerebellum Total, cm^3	131.19±15.22	133.11±15.86	0.548	0.12
Cerebellum Total, %	9.49±0.90	9.61±0.63	0.488	0.14
Cerebellum WM Total, cm^3	28.04±7.10	31.74±7.63	0.059	0.38
Cerebellum WM Total, %	2.00±0.50	2.31±0.56	0.047*	0.41
Cerebellum R, cm^3	65.26±7.66	66.35±8.05	0.501	0.13
Cerebellum R, %	4.72±0.46	4.79±0.32	0.440	0.17
Cerebellum R-WM, cm^3	15.41±4.03	17.49±4.12	0.014*	0.51
Cerebellum R-WM, %	1.10±0.26	1.27±0.31	0.006*	0.59
Cerebellum L, cm^3	65.93±7.70	66.76±7.89	0.603	0.10
Cerebellum L, %	4.77±0.45	4.82±0.31	0.554	0.12
Cerebellum L-WM, cm^3	12.63±3.05	14.25±3.53	0.019*	0.49
Cerebellum L-WM, %	0.90±0.23	1.03±0.26	0.009*	0.52
Cerebellum GM Total, cm^3	103.15±8.17	101.37±8.16	0.718	0.09
Cerebellum GM Total, %	7.49±0.42	7.30±0.10	0.421	0.17
Cerebellum Asymmetry	-1.01±3.28	-0.66±2.45	0.546	0.12
SCL-90-R	1.18±0.72	0.25±0.11	<0.001*	1.82
Somatization	1.28±0.34	0.35±0.12	<0.001*	1.10
Obsessive-Compulsive	0.44±0.20	0.34±0.16	0.564	0.66
Interpersonal Sensitivity	0.68±0.28	0.40±0.18	0.080	0.68
Depression	1.22±0.46	0.28±0.14	<0.001*	1.15
Anxiety	1.46±0.54	0.30±0.16	<0.001*	1.20
Hostility	0.48±0.12	0.12±0.06	0.322	0.82
Phobic Anxiety	0.56±0.22	0.20±0.08	0.040*	0.56
Paranoid Ideation	0.26±0.14	0.16±0.10	0.310	0.92
Psychoticism	0.22±0.16	0.12±0.08	0.176	0.66
RLS Rating Scale	20.88±7.26			

***p<0.05;** Independent-samples t-test was used; **Abbreviations:** RLS: Restless Legs Syndrome, SD: Standard Deviation, WM: White Matter, GM: Gray Matter, R: Right, L: Left; SCL-90-R: Symptom Checklist-90-Revised; **Notes:** All the volumes are presented in absolute value (measured in cm^3) and in relative value (measured in relation to the intracranial volume).

Correlation analyses, adjusted for age, demonstrated a significant inverse relationship between cerebellar WM parameters and SCL-90-R and RLSRS scores within the patient group. A negative and significant correlation was found between WM parameters and the depression, anxiety, and somatization subscale scores. Furthermore, a strong negative correlation was observed between disease duration and cerebellar WM volumes and percentages, emphasizing the impact of disease progression on cerebellar integrity (Table 2).

Table 2. Correlation of various parameters with SCL-90-R and RLS controlling for the effect of age

	Cerebellum R-WM, cm^3 (r, p)	**Cerebellum R-WM, % (r, p)**	**Cerebellum L-WM, cm^3 (r, p)**	**Cerebellum L-WM, % (r, p)**
RLSRS	-0.367, 0.015*	-0.409, 0.006*	-0.374, 0.013*	-0.377, 0.013*
Disease Duration	-0.541, <0.001*	-0.672, <0.001*	-0.324, 0.030*	-0.386, 0.011*
SCL-90-R	-0.511, <0.001**	-0.531, <0.001**	-0.337, 0.027*	-0.440, 0.003*
Somatization	-0.366, 0.012*	-0.392, 0.006*	-0.376, 0.008*	-0.401, <0.001**
Obsessive-Compulsive	0.080, 0.416	0.102, 0.386	-0.266, 0.218	-0.218, 0.266
Interpersonal Sensitivity	-0.166, 0.466	-0.202, 0.116	-0.186, 0.284	-0.176, 0.302
Depression	-0.446, <0.001**	0.422, <0.001**	-0.326, 0.032*	-0.390, 0.024*
Anxiety	-0.536, <0.001**	-0.566, <0.001**	-0.422, <0.001**	0.446, <0.001**
Hostility	0.116, 0.665	0.122, 0.502	0.086, 0.776	0.080, 0.702
Phobic Anxiety	-0.206, 0.102	-0.216, 0.116	-0.280, 0.089	-0.276, 0.092
Paranoid Ideation	-0.118, 0.466	-0.126, 0.402	-0.166, 0.208	-0.178, 0.212
Psychoticism	0.164, 0.386	0.182, 0.401	0.187, 0.366	0.199, 0.604

***p<0.05;** Pearson correlation analysis was used; **Abbreviations:** SCL-90-R: Symptom Checklist-90-Revised; RLSRS: International Restless Legs Syndrome Group Rating Scale; WM: White Matter; R: Right; L: Left

The ROC curve analysis was performed based on the entire cohort of 44 patients and 53 healthy controls (Table 3). For right cerebellar WM percentage, the optimal threshold was 20.77, with sensitivity and specificity of 20.8% and 95.5%, respectively. For left cerebellar WM percentage, the optimal cut-off was 17.26, with sensitivity of 20.8% and specificity of 97.7%. Regarding volumetric metrics, the optimal cut-off for right cerebellar WM volume was 1.41, with sensitivity and specificity of 39.6% and 93.2%, respectively. For left cerebellar WM volume, the cut-off was 1.24, achieving sensitivity of 22.6% and specificity of 97.7% (Figure 2).

Table 3. ROC curve analysis of various parameters

Parameters	**Area Under the ROC Curve**	**Std. Errora**	**p value**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	Upper Bound
Cerebellum R-WM, cm^3	0.640	0.056	0.018*	0.530	0.750
Cerebellum L-WM, cm^3	0.625	0.057	0.035*	0.513	0.736
Cerebellum R-WM, %	0.669	0.056	0.004*	0.561	0.778
Cerebellum L-WM, %	0.637	0.056	0.020*	0.527	0.748

***p<0.05;** ROC curve analysis was used; **Abbreviations:** ROC: Receiver Operating Characteristic; WM: White Matter; R: Right; L: Left

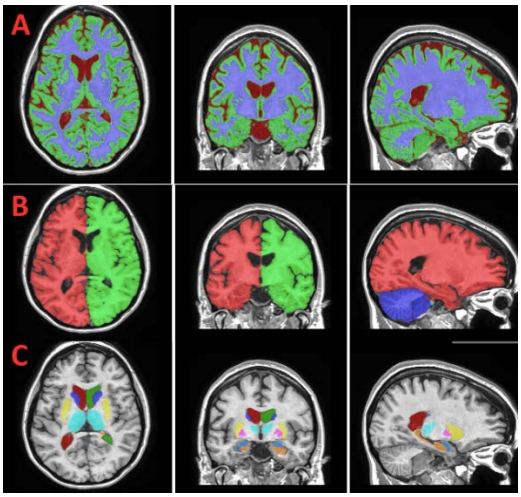

Figure 1. Illustration of brain structures

(A: Tissue Classification, B: Macrostructures, C: Subcortical Structures).

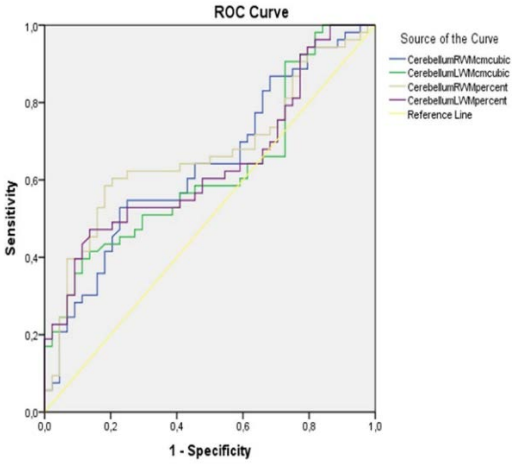

Figure 2. ROC curve analysis of cerebellum white matter parameters.

DISCUSSION

This study compared cerebellar WM volume between drug-naive RLS patients and healthy controls. The findings demonstrated that the proportion and volume of cerebellar WM were significantly lower in the patient group compared to healthy controls. Additionally, a significant inverse correlation was observed between cerebellar WM volume and both SCL-90-R and RLSRS scores.

Using resting-state functional MRI, Zhang et al.[22] conducted a comparative analysis between RLS patients and healthy controls, revealing increased neural activity in the left parahippocampus and right cerebellum among RLS patients. Additionally, these patients exhibited enhanced functional connectivity between the right cerebellum and regions such as the left basal ganglia, left postcentral gyrus, and right precentral gyrus. A strengthened effective connectivity from the right cerebellum to the left postcentral gyrus was identified, distinguishing RLS patients from healthy controls. The authors suggested that the neuropathological basis of RLS might involve an aberrant circuit between the cerebellum, basal ganglia, and sensorimotor cortex. They emphasized that the right cerebellum plays a critical role in RLS development and that precision therapy might be able to target this region. Similarly, our study found significantly lower cerebellar WM volumes in RLS patients, along with a correlation between cerebellar changes and psychiatric symptom severity. The worsening of RLS symptoms at night can potentially be explained by these cerebellar changes, given its role in the sleep-wake cycle[23]. Recent research has also highlighted the cerebellum's involvement in perception, attention, emotion, and cognition, in addition to its motor functions[24]. Moreover, cerebellar abnormalities have been reported in depression and anxiety disorders[25,26].

Demyelination has been identified in post-mortem studies of RLS patients[27]. This is further supported by the role of iron deficiency in the etiology of RLS[28], its importance in myelin synthesis[29], and the higher prevalence of RLS in patients with multiple sclerosis[30]. Although our study did not find direct evidence of demyelination on MRI, which is critical for WM structure, more detailed studies are needed to investigate the structural causes of WM volume changes. We hypothesize that the increased severity of somatization, depression, and anxiety observed in the SCL-90-R subscale scores of RLS patients may be associated with the higher prevalence of psychiatric disorders in demyelinating diseases[31].

The possible role of the cerebellum in RLS has led researchers to investigate the structural implications of this functional association. Park et al.[9] examined cerebellar volume alterations in RLS patients using three-dimensional T1-weighted MRI. Their study found no significant differences in cerebellar volume or its subdivisions between RLS patients and healthy controls. However, they observed significant

alterations in the intrinsic cerebellar network of RLS patients. Furthermore, total cerebellar volume exhibited a negative correlation with sleep quality, insomnia severity, and RLSRS scores. These findings indicate that further volumetric studies are necessary. While no structural differences (i.e., volume changes) were detected between RLS patients and healthy controls, functional alterations were evident, suggesting that structural changes may lag behind functional changes. Some studies on cerebellar GM have reported significant findings in RLS patients compared to healthy controls[8]. Our study, which aimed to explore cerebellar WM changes in RLS, produced meaningful findings, demonstrating that cerebellar WM volume and percentages were significantly lower in RLS patients compared to healthy controls. However, no significant differences in cerebellar GM volumes were observed between the groups. In a study conducted by Belke et al.[2] using voxel-based morphometry, no significant differences were found in GM volume between RLS patients and healthy controls. The variability in findings across studies is likely due to differences in methodology (e.g., imaging techniques, age, disease duration, gender, disease severity, and disease stage). Additionally, differences in analysis methods, statistical thresholds, sample heterogeneity, and clinical characteristics contribute to discrepant results in structural studies[32].

Further studies are required to determine whether WM volume reduction is a cause or consequence of RLS. This study is valuable as it provides evidence that WM reduction is present even at the first admission of RLS patients.

The cerebellum receives inputs from neuromodulatory systems involved in arousal and the sleep-wake cycle, including cholinergic, noradrenergic, serotonergic, histaminergic, and orexin/hypocretin pathways[6]. The cerebellum's relationship with these neurotransmitter systems and their role in psychiatric disorders may provide a new perspective on the origins of psychiatric comorbidities in RLS. Additionally, sleep disturbances are linked to various diseases affecting the cerebellum, though the exact role of the cerebellum in these disorders remains unclear[7,33]. Studies have also reported structural abnormalities in the WM of the frontocerebellar pathway in RLS patients[34]. Evidence of frontocerebellar involvement has been observed in acute-onset RLS following cerebrovascular events[35]. Stefani et al.[36] reported reductions in pre- and post-central WM volumes in RLS patients, along with decreased fractional anisotropy values in the internal capsule. The internal capsule carries motor fibers from the prefrontal cortex to the cerebellum, forming the frontocerebellar pathway[37]. This pathway is thought to be involved in the leg withdrawal reflex, and abnormalities in this reflex may contribute to RLS symptoms[38]. The reduced cerebellar WM volume observed in our study may indicate frontocerebellar pathway involvement in RLS pathophysiology.

The early recognition of the strong association between RLS and psychiatric disorders is evident in the original description of RLS as anxietas tibiarum. Although the exact mechanism underlying this relationship remains unclear, a bidirectional cause-and-effect interaction is likely[13,39]. Patients may be more susceptible to psychiatric disorders due to sleep disturbances, discomfort from leg dysesthesia, and symptom anticipation[40,41]. Conversely, mental health conditions may increase sensitivity to RLS symptoms and prolong wakefulness during the night, when symptoms are most pronounced[13]. This study further supports the significant relationship between cerebellar volume changes in RLS and psychiatric symptoms, reinforcing existing literature. Additionally, anxiolytic and antidepressant medications may exacerbate RLS symptoms. However, since our patient group was drug-naïve, such an effect is unlikely in this study. A comprehensive understanding of psychiatric comorbidities is essential for the effective management of RLS. Clinicians should be prepared to provide appropriate psychiatric support and consider the complex interactions between RLS medications, psychiatric drugs, and the clinical progression of both conditions.

This study provides valuable insights into the underlying pathophysiological mechanisms of RLS, contributing to a deeper understanding of the disorder. Since detailed medical history is often sufficient for RLS diagnosis, our findings do not directly impact diagnostic procedures. Instead, the ROC analysis was performed to demonstrate brain changes caused by RLS through detailed statistical analysis.

The primary limitation of this study is its retrospective and cross-sectional design. Future studies comparing volumetric MRI findings at baseline and after treatment in drug-naïve RLS patients would help further interpret our results.

Additionally, the absence of control measures for validating MRI in detecting neuronal degeneration is another limitation. Future research should incorporate alternative neuroimaging techniques and control for dietary habits, BMI, smoking status, and RLS characteristics. Further studies are required to address these limitations and clarify unanswered questions.

Future studies should focus on longitudinal assessments to determine whether cerebellar WM volume reductions in RLS patients progress over time or improve with treatment. Advanced neuroimaging techniques, such as diffusion tensor imaging and functional MRI, could provide deeper insights into microstructural and functional connectivity changes in the cerebellum and its interaction with other brain regions implicated in RLS. Additionally, investigating the effects of iron metabolism, neuroinflammation, and genetic predisposition on cerebellar WM alterations may help clarify the underlying pathophysiology. Given the significant correlation between psychiatric symptom severity and cerebellar WM changes, multidisciplinary approaches integrating neurology, psychiatry, and sleep medicine are essential for a more comprehensive understanding of the disorder. Future research should also explore potential therapeutic implications, such as whether treatments targeting cerebellar dysfunction through neuromodulation or pharmacological interventions can alleviate both motor and psychiatric symptoms in RLS. Expanding the sample size and including diverse patient subgroups, such as individuals with varying disease durations, familial RLS cases, and those with psychiatric comorbidities, will further enhance the generalizability of findings.

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