Neuroimaging in Restless Legs Syndrome

Federica Provini, MD, PhD[a,b,*], Giacomo Chiaro, MD[a]

KEYWORDS

• Restless legs syndrome • Willis-Ekbom disease • Neuroimaging • MRI • PET
• Single-photon emission computed tomography • Voxel-based morphometry
• Diffusion tensor imaging

KEY POINTS

- RLS pathophysiology excludes structural neurodegenerative processes, as shown by structural neuroimaging and autoptic studies.
- Both structural and functional neuroimaging studies showed that RLS is probably associated with changes in thalamus, sensorimotor cortical areas, and cerebellum.
- MRI and ultrasonography studies are consistent with a central iron deficiency in patients with RLS, mostly located in the SN.
- Functional studies point at a subcortical dopaminergic hypoactivity, which can be found in the striatum at both presynaptic and postsynaptic levels in patients with RLS.

INTRODUCTION

The pathophysiology of restless legs syndrome (RLS) still represents a puzzle of multiple interacting mechanisms involving cortical and subcortical brain structures, the spinal cord, the peripheral nervous system, and multiple biochemical pathways and neurotransmitters.

Over the last few years, various neuroimaging techniques have been used to study putative alterations in patients with RLS. Structural brain abnormalities in RLS have been studied by means of MRI in the form of voxel-based morphometry (VBM), diffusion tensor imaging (DTI), relaxometry, and transcranial ultrasonography (TCS) (**Table 1**). The neural mechanisms underlying RLS dysfunctions in central pathways have been investigated by means of functional MRI (fMRI), proton magnetic resonance spectroscopy (H-MRS), PET, and single-photon emission computed tomography (SPECT) imaging studies (**Table 2**).

Specifically, research attention focused on iron metabolism and the dopaminergic system. More recently, several radiographic studies have broadened the acknowledged pathophysiologic boundaries to other systems, including the serotoninergic, glutamatergic, and opiatergic circuitry. The few published works available have yielded different and sometimes inconsistent results, thus leaving open opportunities for further observations. This overview provides a critical literature review of all neuroimaging studies conducted on RLS, highlighting the most relevant findings.

BRAIN MRI

MRI studies showed no structural brain lesions in patients with RLS. Regarding iron concentration, although a universal agreement has not been reached yet, most studies are consistent with the view that a central iron deficiency plays a role in

Funding Sources: None.
Conflict of Interests: None.
[a] Department of Biomedical and Neuromotor Sciences, Bellaria Hospital, University of Bologna, Via Altura 3, Bologna 40139, Italy; [b] IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy
* Corresponding author. Department of Biomedical and NeuroMotor Sciences, Bellaria Hospital, University of Bologna, Via Altura 3, Bologna 40139, Italy.
E-mail address: federica.provini@unibo.it

Sleep Med Clin 10 (2015) 215–226
http://dx.doi.org/10.1016/j.jsmc.2015.05.006
1556-407X/15/$ – see front matter

Table 1
Structural neuroimaging of RLS

Results	Imaging Technique	No. Patients/Control Individuals	International RLS Study Group Rating Scale (Mean Score; Severity)	Medication	Author
GM and WM Volume Changes					
GM increase in dorsal thalamus	MRI/VBM	51/51	29; S	Y	Etgen et al,[13] 2005
GM increase in hippocampus and orbitofrontal gyrus	MRI/VBM	14/14	26; S	N	Hornyak et al,[14] 2007
GM decrease in primary sensorimotor cortex	MRI/VBM	63/40	27; S	Y	Unrath et al,[15] 2007
GM decrease in left hippocampus, parietal lobes, medial frontal areas, lateral temporal areas, and cerebellum	MRI/VBM	46/46	27; S	13/46	Chang et al[16]
GM anomalies in ACC	MRI/VBM	34/18	20; S	N	Pan et al,[21] 2014
WM changes near sensorimotor and thalamic areas	MRI/DTI	45/30	28; S	Y	Unrath et al,[22] 2008
WM decrease in corpus callosum, ACC, precentral gyrus Myelin decrease	MRI/VBM Autopsy Myelin WB	23/23	24; S	—	Connor et al,[11] 2011