Neuroimaging of Narcolepsy and Kleine-Levin Syndrome

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KEYWORDS

• Narcolepsy • Kleine-Levin syndrome • MRI • SPECT • PET

KEY POINTS

- Numerous neuroimaging studies have been performed to characterize the pathophysiology and various clinical features of narcolepsy.
- Brain MRI and various functional imaging tools revealed structural and functional abnormalities located in the hypothalamus, in agreement with a loss of hypocretinergic neurons in narcolepsy.
- In Kleine-Levin syndrome (KLS), subtracted single-photon emission CT (SPECT) showed significant hypoperfusion in the left hypothalamus, bilateral thalami, basal ganglia, bilateral medial and dorsolateral frontal regions, and left temporal lobe during the symptomatic period.
- Brain imaging is a useful tool to investigate and understand the neuroanatomic correlates and brain abnormalities of narcolepsy and other hypersomnias.

Narcolepsy is characterized by excessive daytime sleepiness (EDS), a disruption of sleep-wake behavior, cataplexy (sudden loss of muscle tone provoked by emotional stimuli), and other rapid eye movement (REM) sleep phenomena, such as sleep paralysis and hypnagogic hallucination. Hypocretin-containing neuron numbers are reduced in the hypothalamus of the narcolepsy brain.[1] The neuropeptide hypocretin seems to play a critical role in the neurobiology of narcolepsy.[2–4] Narcolepsy patients suffer from cognitive or emotional problem besides sleep-wake disturbances. To investigate the responsible neuroanatomic substrates for those problems, neuroimaging studies have been actively performed.

STRUCTURAL IMAGING IN NARCOLEPSY

Voxel-Based Morphometry

Differences in brain morphology that are not identifiable by routine visual inspection of individual brain MRI[5–8] can be investigated using voxel-based morphometry (VBM). VBM allows between-group statistical comparisons of tissue composition (gray matter and white matter [WM]) across all brain regions, based on high-resolution scans. Previous VBM studies reported equivocal results in narcolepsy patients.

One study insisted that there were no structural changes in brains of patients with hypocretin-deficient narcolepsy,[9] whereas all other studies reported significant regional decreases in gray matter volumes (GMVs) or gray matter concentration (GMC).[10–14] Two of these studies reported decreases of GMC[10] or GMV[11] in the hypothalamus of narcolepsy patients. These findings suggest that neuronal losses may affect hypocretinergic structures (ie, hypothalamus) as well as some major sites of hypocretin projections (ie, nucleus accumbens). Two other studies found decreases of GMV in 12 narcolepsy patients in inferior temporal/frontal[12] and right prefrontal/frontomesial regions,[13] possibly contributing to cognitive impairments, such as attentional deficits experienced by narcolepsy patients.[15] A recent VBM study revealed that 29 narcolepsy patients showed reduced

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GMC in bilateral thalami, left gyrus rectus, bilateral frontopolar gyri, bilateral short insular gyri, bilateral superior frontal gyri, and right superior temporal and left inferior temporal gyri compared with 29 normal controls and, furthermore, small volume correction revealed GMC reduction in bilateral nuclei accumbens, hypothalami, and thalami (Fig. 1).[14] In particular, reduced GMC in the hypothalamus and nucleus accumbens in the author and colleagues' study, may support the prior hypothesis that these reductions are associated with EDS and cataplexy in narcolepsy patients. The author and colleagues' result suggests that those areas with decreased GMC may serve possible roles in wake-sleep controls, attention, or memory. Discrepancies of results among several VBM studies might be due to differences in the analysis processes used (eg, the SPM version, modulated or unmodulated, grand mean scaling, absolute or relative thresholding, and sample size) and clinical characteristics of study patients (hypocretin deficiency, disease duration, medical treatment, and so forth). The patients' characteristics are variable from one study to another. More than half of

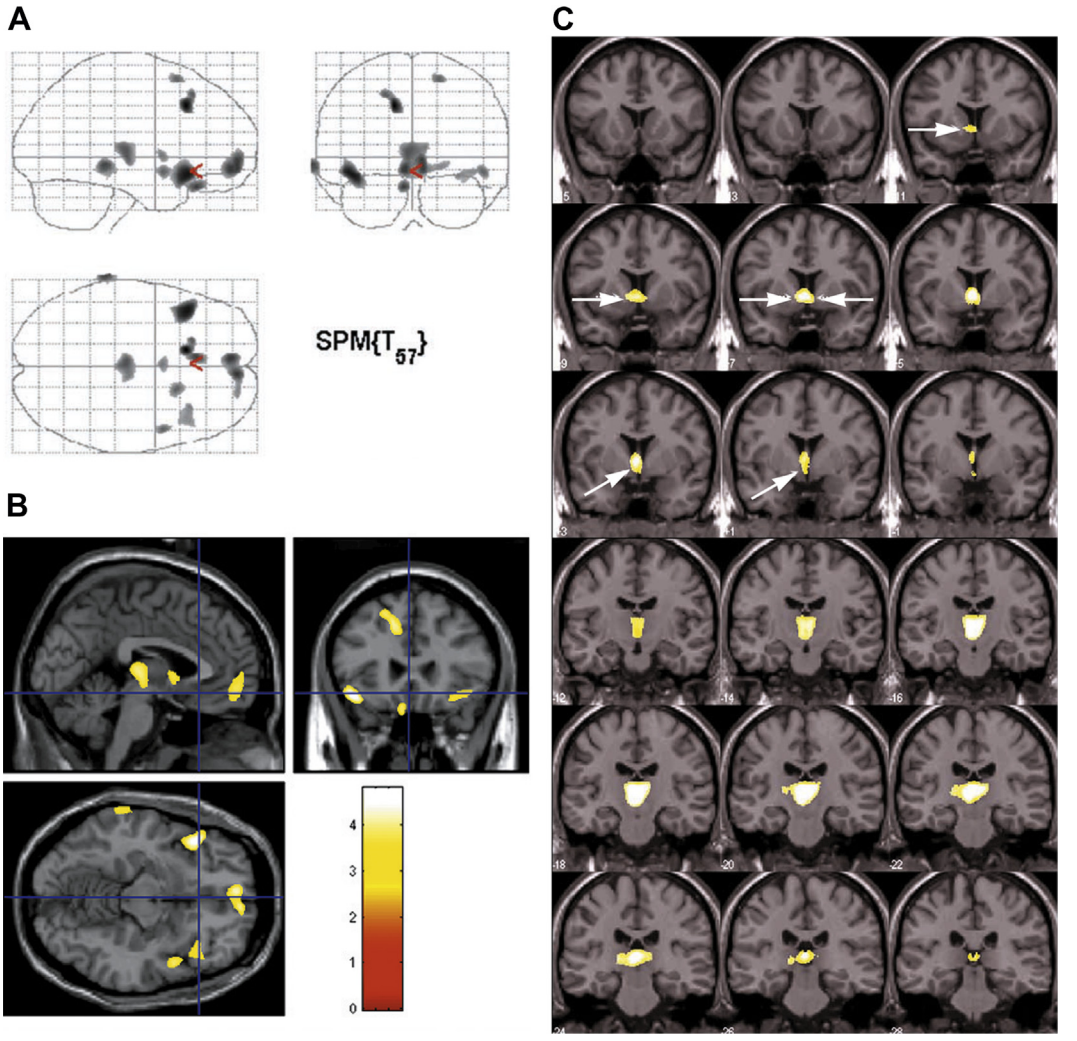

Fig. 1. GMC abnormality in brains of narcolepsy patients. Overall areas showing reduced GMCs are shown in glass brain view (*A*). Decreased gray matter concentrations in narcolepsies with cataplexy in left gyrus rectus, bilateral thalami, bilateral frontopolar gyri, bilateral short insula gyri, bilateral superior frontal gyri, right superior temporal gyrus, and left inferior temporal gyrus are shown as T1 template overlaid MRI at the level of uncorrected *P*<.001 (extent threshold *k*E <100 voxels) (*B*). Bilateral nuclei accumbens (*dotted arrows*), bilateral hypothalamus (*solid arrows*), and bilateral thalami (*arrowhead*) showed reduced GMCs at the level of false discovery rate corrected *P*<.05 with small volume correction (*C*). Superior to inferior panels are arranged in anterior to posterior direction in coronal images. (*Adapted from* Joo EY, Tae WS, Kim ST, et al. Gray matter concentration abnormality in brains of narcolepsy patients. Korean J Radiol 2009;10:555; with permission.)