Introduction: Narcolepsy has recently been suggested to be primarily caused by the hypocretin deficiency. Structural changes in hypothalamus, where the hypocretin-producing neurons are located, have also been suspected in patients with narcolepsy. However, previous voxel-based morphometry (VBM) studies on narcolepsy have not reported consistent findings. Therefore, a study with more well-defined subjects and more sensitive imaging method is highly recommended. The objective of this study was to explore gray matter volume changes and their clinical meanings in young adults with a sole diagnosis of narcolepsy, using a 3 Tesla magnetic resonance (MR) scanner and an optimized VBM technique.

Methods: Seventeen narcoleptic patients (13 men / 4 women; 26.6 ± 5.2 years old) and 17 healthy comparison subjects (13 men / 4 women; 24.6 ± 4.9 years old) were recruited. Inclusion criteria for narcoleptic patients include presence of cataplexy, HLA allele DQB1 *0602, and two or more sleep-onset rapid eye movement sleep in multiple sleep latency test. Exclusion criteria include age over 35 years and comorbid sleep disorders or major psychiatric/medical disorders. Clinical severity of narcolepsy was assessed by polysomnographic findings and subjective reports including Ullanlinna narcolepsy scale. An optimized VBM study using a 3 Tesla MR scanner was conducted in order to assess changes in gray matter volume. In addition, gray matter volumes in voxel of interest (VOI) at bilateral hypothalamus were also calculated. Cognitive functions were assessed by a battery of neuropsychological tests.

Results: Relative to healthy comparison subjects, narcoleptic patients had lower gray matter volumes in the right hypothalamus, brainstem, bilateral putamen, left thalamus, bilateral uncus, bilateral cingulate cortex, bilateral posterior cingulate cortex, bilateral superior frontal cortex, bilateral middle occipital cortex, right insula, and left lingual cortex (all p<0.001). Gray matter volume of VOI at right and left hypothalamus was decreased in narcoleptic patients relative to healthy comparison subjects (10.4 % decrease, t= -5.53, p<0.0001; 6.9 % decrease, t= -3.56, p=0.001, respectively). Narcoleptic patients have shown a lower rate of correct responses in paced auditory serial addition (2.4 s) and digit symbol tests (beta= -0.33, p=0.04; beta= -0.38, p=0.02, respectively). In narcoleptic patients, gray matter volume of both right and left hypothalamus correlated with the Ullanlinna narcolepsy scale score (r=-0.53, p=0.03; r=-0.52, p=0.03, respectively).

Conclusion: Current findings suggest that narcoleptic patients have structural changes of hypothalamic gray matter, which correlate with the symptom severity of narcolepsy. The hypothalamic gray matter changes might play an important role in the pathophysiology of narcolepsy with cataplexy. It could be related to loss of hypocretin-containing neurons in affected area. It is also shown that the most impaired cognitive function in narcoleptic patients is the impaired attention.

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