Brain Stem Volume Reduction Revealed by Voxel-Based Morphometry in a Patient with REM Sleep Behavior Disorder and Synucleinopathy

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Abstract
A 72-year-old Japanese man was clinically diagnosed as having idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) without any evidence of cognitive impairments for his characteristic behavior disorders at night. ⁹⁹mTc-ethyl cysteinate dimer and ¹²³I-metaiodobenzylguanidine single photon emission computed tomography studies supported the presence of α-synucleinopathy in the patient. A single-subject voxel-based morphometry of white matter revealed a possible volume reduction of the brain stem that may be associated with an axonal degeneration of REM-on glutamatergic neurons or the glycinergic/GABAergic premotoneurons presumed to be present in RBD.

ABBREVIATIONS
REM: Rapid Eye Movement; RBD: REM Sleep Behavior Disorder; VBM: Voxel-Based Morphometry; VSRAD: Voxel-Based Specific Regional Analysis System For Alzheimer’s Disease

INTRODUCTION
Idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) is a late onset parasomnia that is often associated with α-synucleinopathies and may be present as a prodromal condition for them [1]. We report a case with RBD, clinically defined α-synucleinopathy and a single-subject voxel-based morphometry (VBM) finding about the brain stem that is presumed responsible for the motor control of skeletal muscles during REM sleep [2].

CASE PRESENTATION
A 72-year-old Japanese man visited the psychiatric clinic in our university hospital. His chief complaints were frequent nightmares chased and stabbed by someone else. He had recognized the nightmares at age 69 and developed behavior disorders concurrently with them at age 71, such as screaming, punching and walking around the bed. His wife could make him awake easily and he could recall the contents of nightmares. Consequently, the patient’s behavior disorders could be explained as a response action to the terrible dreams. He was hospitalized for detailed examination and treatment. A routine physical examination and blood screen did not show significant findings of serious physical illnesses. In neuropsychiatric assessments, he had no major symptoms suggesting psychotic, mood, cognitive or motor disorders. Persistent visual hallucinations and extra pyramidal signs were negative throughout the entire clinical course. The Mini-Mental State Examination was 28/30 and five cognitive domains of the Repeatable Battery for the Assessment of Neuropsychological Status were all beyond average levels, suggesting intact cognitive functions. Magnetic resonance imaging studies and electroencephalography revealed no abnormalities suggesting any neurological conditions. The patient has never been received any other psychotropic medications which may induce parasomnias. Although polysomnographic evidence was not available at the initial assessment, his parasomnia was clinically diagnosed as idiopathic RBD.

The treatment team decided to try clonazepam in accordance with the existing evidence for the treatment of idiopathic RBD. The effects of clonazepam were remarkable. When the patient gradually discontinued etizolam, he reported an increase of terrible dreams and motor activity with psychological distress. By
contrast, the patient reported a significant decrease of the dreams and a marked improvement in behavior disorders in the first sleep after he took 0.5 mg clonazepam before going to bed. For two months since the hospital discharge, the patient continued to take clonazepam at night regularly and report satisfactory sleep status. Under the condition of taking clonazepam, behavior disorders were not evident in an overnight polysomnography although REM sleep without atonia was infrequently observed.

The results of further examinations for the etiology of his RBD were as follows. 99mTc-ethyl cysteinate dimer single photon emission computed tomography (SPECT) revealed mild hypoperfusion in occipital cortices and 123I-metaiodobenzylguanidine SPECT showed a significant decrease in heart to mediastinum ratio (early image, 1.48; delayed image, 1.18), both strongly indicating α-synucleinopathy as an underlying pathology [3]. The patient scored significantly lower than normal Japanese populations (correct trials/total trials, 2/12) in the Odor Stick Identification Test for the Japanese, which showed α-synucleinopathy-related disorders of sense of smell too [4]. Finally, a volume reduction of the brain stem possibly associated with RBD was significantly demonstrated with the Voxel-Based Specific Regional Analysis System for Alzheimer’s Disease (VSRAD) [5] for the segmented white matter tissues of this case (Figure 1), while there were no significant volume reduction in medical temporal regions of interest for Alzheimer’s disease (AD).

**DISCUSSION**

There are a limited number of VBM studies to report the volume changes in the brain stem of idiopathic RBD. Compared with the age-matched controls, the patients with idiopathic RBD had significant gray matter volume reduction in tegmental portion of the pons as well as in the anterior lobes of the cerebellum and left para hippocampal gyrus [6]. As to the white matter of idiopathic RBD, to our knowledge no VBM studies are available. However, using segmented white matter images from the same VSRAD as ours to dementia with Lewy bodies (DLB), the DLB patients showed specific atrophy in the midbrain, pons, and cerebellum in comparison with AD [5].

![Figure 1](image-url)
More direct evidence for axonal damages of the brain stem in RBD patients is from diffusion tensor imaging (DTI) studies. The patients with idiopathic RBD had significant increases in radial diffusivity can be observed in the fornix and the olfactory region, and a significant decrease in the axial diffusivity can be seen in the pons [7]. In another DTI study, the patients with idiopathic RBD had significant decreases of fractional anisotropy in the tegmentum of the midbrain and rostral pons and increases of mean diffusivity within the pontine reticular formation overlapping with a cluster of decreased fractional anisotropy in the midbrain [8].

Regarding neuronal basis within brain stem possibly corresponding to the above mentioned macroscopic findings, Pierre-Hervé et al in their recent review have proposed that RBD appears based on a specific degeneration of REM-on glutamatergic neurons localized in the caudal pontine sublaterodorsal tegmental nucleus or the glycinergic/GABAergic pre motoneurons localized in the medullary ventral gigantocellular reticular nucleus [9]. These anatomical positions of the nuclei within brain stem appear consistent with the probabilistic maps to show a relative decrease in the dorsal brain stem possibly indicating white matter shrinkage of the case. However, it is unclear that the present findings obtained from the segmented white matter tissues indicate a specific degeneration of the axonal fibers of neurons mentioned above yet. Further VSRAD study with more RBD cases is needed to confirm the clinical utility of this technology for exploring brain stem pathology of RBD.

REFERENCES

1. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med. 2013; 14: 744-748.


