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Orbitofrontal Hemorrhage and Mild Cognitive Impairment Associated with Othello Syndrome

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Dear Editor,

Content-specific delusions (CSDs) are delusions that have a specific theme; for example, Othello syndrome (OS)[1] is another name for delusion of infidelity. CSDs are often caused by identifiable neurological diseases. We report a patient who had experienced OS over 5 years, which seemed to have developed from multidomain amnestic mild cognitive impairment (MCI) due to Alzheimer's disease (AD) accompanied by an old orbitofrontal hemorrhage.

A 62-year-old right-handed female was brought to the dementia clinic presenting with a persistently mistaken belief about her husband. She was illiterate, but could perform her activities of daily living (ADL) as a housewife without problems. Five years prior to this visit she had begun to have morbid suspicions about his infidelity. This delusion increased to the level of physical violence. She did not report any hallucination. Her motor, sensory functions, and reflexes were normal. She scored 19 out of 30 on the Mini Mental State Examination (MMSE). A battery of neuropsychological tests was performed, although this was restricted by her illiteracy. The tests showed marked decrements in memory and naming, with the patient being at the 4.85th percentile for delayed recall in the verbal learning test and at the 14.30th percentile in the Boston Naming Test. Normal findings were obtained in frontal/executive function tests including the contrasting program, go/no-go test, fist-edge-palm test, digit symbol coding, and Controlled Oral Word Association Test. Her global Clinical Dementia Rating (CDR) was 0.5 and CDR-Sum of Boxes was 2.

Brain magnetic resonance imaging revealed an encephalomalacic change in the left orbitofrontal cortex, which suggested an old hemorrhagic stroke (Fig. 1A-D). Mild cortical atrophy was evident in the frontal and parietal lobes, whereas the gross findings for hippocampal atrophy were unremarkable (Fig. 1E and F). There were no cerebral microbleeds. ^{18}F-flutemetamol amyloid positron-emission tomography (PET) was performed. Early dynamic brain images acquired 10 min after injecting ^{18}F-flutemetamol showed decreased uptake in the bilateral parietal and left dorsolateral prefrontal/orbitofrontal areas (Fig. 1G).[2,3] Delayed images obtained 90 min after the injection revealed amyloid deposition in the right frontal lobe (Fig. 1H).

The cognitive defects of this patient had gone unnoticed by her family, but she had multidomain amnestic MCI due to AD. She denied any attack of severe headache, but an old orbitofrontal hemorrhage was found incidentally in the absence of cerebral microbleeds, and this did not seem to be associated with amyloid pathology. Therefore, the final diagnosis was made of multidomain amnestic MCI due to AD accompanied by orbitofrontal hemorrhage, both of which seemed to contribute to the development of her OS. The patient was prescribed olanzapine (15 mg), escitalopram (10 mg), and donepezil (5 mg), but her delusion persisted. Over the following year her ability to perform ADL deteriorated. She scored 18 on MMSE, 1 on global CDR, and 5 on CDR–Sum of Boxes. She was judged to have converted to AD dementia. Memantine was added to her medications, and 14 months later she no

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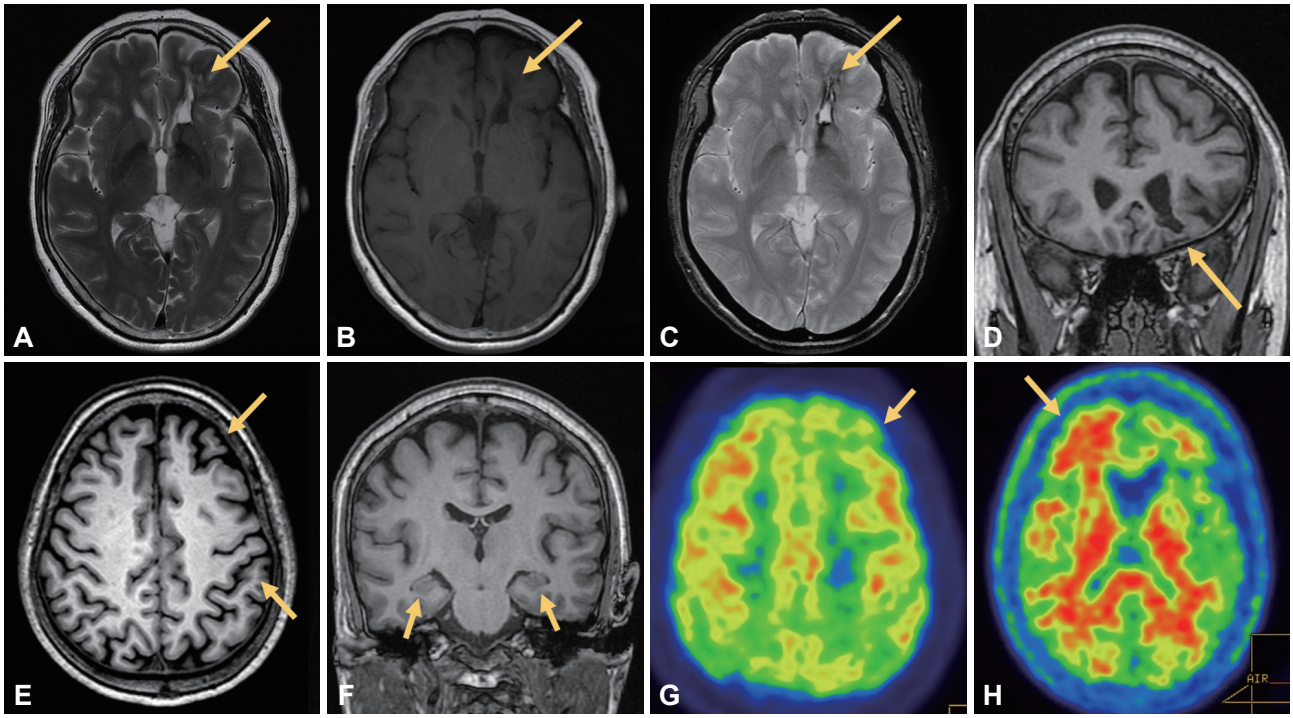

Fig. 1. Brain magnetic resonance imaging (MRI) (A-F) and ^{18}F-flutemetamol amyloid positron-emission tomography (PET) (G and H). Brain MRI showed encephalomalacic changes in the left orbitofrontal cortex, suggesting an old hemorrhagic stroke (A-D). Mild cortical atrophy was evident in the frontal and parietal lobes, whereas hippocampal atrophy was grossly unremarkable (E and F). Early dynamic brain ^{18}F-flutemetamol amyloid PET images acquired 10 min after injecting ^{18}F-flutemetamol reveal decreased uptake in the bilateral parietal and left dorsolateral prefrontal regions as well as in the damaged left orbitofrontal region (G). Delayed brain images obtained 90 min after the injection reveal amyloid deposition in the right frontal lobe (H).

longer exhibited OS.

Delusions begin to develop when unpredicted sensory events are detected but are evaluated in an abnormal manner. Midbrain dopamine neurons respond to unpredicted stimuli, and the detected error signals are conveyed to the striatum, limbic system, and frontal cortex. The right lateral prefrontal cortex is a hub for these mesocorticolimbic projections, and impaired circuitry critically involving this hub leads to delusion. Using voxel-based morphometry analyses, a previous study found greater gray-matter loss predominantly in the dorsolateral frontal lobe in patients with OS.[4] Case reports have indicated that structural lesions in the frontal lobes including orbitofrontal lesions[5,6]—such as in the present case—and in the right hemisphere are critical to the development of OS.[7] Furthermore, a recent lesion network mapping study proposed that the underlying pathobiology of poststroke delusions was not the lesion location itself but rather the disruption of functional connectivity of a network involving the right frontal cortex.[8] Our patient exhibited decreased uptake in the dorsolateral prefrontal/orbitofrontal areas during the early phase of ^{18}F-flutemetamol amyloid PET accompanied by an old orbitofrontal hemorrhage, which matched previous reports. This case shows that an orbitofrontal hemorrhage causing disruption of the functional connectivity of a network involving the frontal cortex, combined with neurodegenerative dysfunction in the dorsolateral prefrontal area can synergistically contribute to the development of OS. Like in the present case, delusions can occur during the early to middle stages of degenerative dementia, and disappear when the cognitive deficits become severe.[9] However, the lesions in our patient were on the left side, which contrasts with most previous reports. We could not conclude from this single case whether a right-side-dominant hemisphere or left-sided lesions would cause disruption of the functional connectivity of a network involving the right frontal cortex that would lead to the development of OS.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methology: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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