Psychotic Symptoms in Dementia Associated With Motor Neuron Disease: A Pathophysiological Hypothesis

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Three patients with neuropathologically confirmed frontotemporal dementia, motor neuron disease type, manifested hallucinations. In this dementia, the superficial layers of the frontal and temporal cortices are predominantly affected. Hallucinations may emerge as release phenomena secondary to selective laminar cortical involvement.

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Frontotemporal dementia, motor neuron disease type (FTD-MND), belongs to the spectrum of FTD.[1] The clinical picture of FTD is characterized by early behavioral and personality changes. Hallucinations are not included in the clinical diagnostic features.[1] Neuropathological changes affect mainly the frontal and anterior temporal lobes and are characterized by a slight status spongiosus, neuronal loss, and gliosis of cortical layers I-III, in addition to cell loss in the hypoglossal nucleus and anterior horns of the spinal cord.[1,2]

Three patients with FTD-MND who manifested hallucinations are described.

CASE REPORTS

Case 1. A 58-year-old male bricklayer manifested motor sluggishness, soon followed by hallucinatory episodes, lasting for hours, during which he saw and talked with a deceased friend. Progressively, he developed cognitive decline, aggressive behavior, dysarthria, dysphagia, weakness of the arms, and muscle wasting of the hands and tongue. The hallucinatory episodes spontaneously remitted after a few months. Previous psychotic symptoms or family history of dementia were absent.

Eighteen months after the initial manifestations, neurological examination revealed a severe dementia with prominent signs of bulbar and spinal MND. Reflexes were brisk in the upper limbs and absent in the lower limbs.

Electroneuromyography (ENMG) revealed signs of lower motor neuron involvement. CSF and EEG were normal.

The patient died from ventilatory failure 20 months after the beginning of symptoms. Neuropathological examination revealed global atrophy, with spongy state, neuronal loss, and glial proliferation in the transition of the second to the third cortical layers, more prominent in the frontal lobes but also affecting the temporal and parietal lobes. Neuronal loss and gliosis were also found in the putamen, thalamic nuclei, and substantia nigra. Spongy degeneration of the corticospinal tracts at the level of the cerebral peduncles and pyramids and severe motor neuron loss in the spinal cord were also observed.

Case 2. A 44-year-old male school bus driver began to go to funerals to comfort unknown people. He became aggressive, and visual hallucinations emerged, during which he saw persons inside his house and was afraid of them. A few months later, he developed a progressive atrophy of the upper limbs. Persecutory delusions became frequent. Previous psychotic symptoms or family history of dementia were absent.

Neurological examination revealed generalized weakness, muscular atrophy, and fasciculations with deep arreflexia in the four limbs. The patient showed excessive and inappropriate hilarity and verbal and gestural stereotypies. He had severe attention and abstraction deficits. Visual perception, left-right orientation, and spatial abilities were intact.

ENMG demonstrated signs of lower motor neuron involvement. CSF and EEG were normal. MRI of the brain demonstrated cortical atrophy predominating in the frontal and anterior temporal lobes. SPECT revealed frontal lobe hypoperfusion.

The psychotic symptoms remitted spontaneously as his condition deteriorated. He died from ventilatory failure 5 years after the onset of symptoms.

Neuropathological examination showed a diffuse atrophy, more prominent in the frontal lobes, with neuronal loss and status spongiosus affecting mainly the II and III cortical layers of the frontal and anterior temporal lobes. The substantia nigra and the anterior horns of the spinal cord showed a profound loss of nerve cells.

Case 3. A 51-year-old woman started to complain of seeing monsters in clouds, in shaded places, and in corners of her home. When this occurred, she asked for God's protection. She said that she sometimes saw Jesus in her room and talked with him. Persecutory delusions were also frequent.

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These symptoms increased slowly but progressively. Three years later she showed lack of motivation, confusion, insomnia, and affective indifference to her relatives. She started to neglect her household chores, to talk to strangers in the street, and to say whatever she thought without inhibition. Previous psychotic symptoms or family history of dementia were absent.

Four years after the emergence of the hallucinations, progressive weakness and atrophy of the hands appeared. Neurological examination revealed weakness in the hands, hyperactive tendon jerks, atrophy, and fasciculations in the hands, arms, and tongue; sucking reflex was present. During the examination, the patient showed inattention and disinhibited behavior. Memory, visual perception, and spatial abilities were intact.

CSF and EEG were normal. ENMG showed signs of MND. MRI showed cortical atrophy, mainly in the frontal and anterior temporal lobes. SPECT showed frontal lobe hypoperfusion.

One year later, her condition had deteriorated, she was more apathetic, the hallucinations had become very rare, and she had dysphagia and dyspnea. She died from ventilatory dysfunction 6 years after the hallucinations had started.

Neuropathological examination showed atrophy with neuronal loss, astrogliosis, and spongiosis, more prominent in the superficial cortical layers of the frontal and temporal lobes. A few senile plaques were seen in the presubiculum. The spinal cord was not examined.

DISCUSSION

Hallucinations are considered rare in FTD.[3] Our findings and data from the literature reveal that hallucinations and delusions are not so uncommon in FTD-MND, and that they may be the initial manifestations in some patients.[4–6] These patients may constitute a subgroup in the FTD spectrum.

Hallucinations from temporal lobe seizures can be reproduced by electrical stimulation of the temporal isocortex, amygdala, hippocampus, and parahippocampal gyrus. According to Gloor,[7] electrical stimulation of temporal lobe structures or temporal lobe epileptic discharge can induce the elaboration of patterns of excitation and inhibition in widely distributed neuronal networks, some of which are capable of forming a specific matrix representing the substrate of a given experience.

According to Damasio,[8] recall of an experience depends on a time-locked multiregional retroactivation that binds together related fragments of information contained within different association areas. This retroactivation reconstitutes a pattern of neural activity that was present during the processes of perception and encoding of this experience. Corticocortical feedback projections, initiated from any point of this network, but especially from the heteromodal, paralimbic, and limbic cortices, can reconstitute this pattern of neural activity.[8–10]

In nonhuman primates, corticocortical feedback projections arise predominantly from cells in infragranular (V-VI) layers[11–13] and terminate mainly in layer I.[12,13] The feedback projections from the limbic, paralimbic, and heteromodal association cortices of the temporal lobe apparently follow this general pattern of laminar specificity.[11,14]

The involvement of the supragranular layers of the temporal lobes in FTD-MND may release the infragranular layers from some kind of inhibitory or regulatory control. Without this control, feedback projections originating from infragranular layers of the temporal lobes can activate heteromodal and unimodal association cortices in an abnormal fashion that is responsible for the emergence of hallucinations.

Why do psychotic symptoms not occur in all patients with FTD-MND? The answer is unknown. Our hypothesis is that in the patients with psychotic symptoms, the temporal lobes are affected earlier.

The laminar selectivity of the cortical involvement, predominantly affecting the supragranular layers of the temporal cortex, may be responsible for hallucinations in FTD-MND. This mechanism may also contribute to the occurrence of psychotic symptoms in other types of dementia.

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References

1. Brun A, Englund B, Gustafson L, et al: Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 1994; 57:416–418
2. Neary D, Snowden JS, Mann DMA, et al: Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry 1990; 53:23–32
3. Lopez OL, Gonzalez MP, Becker JT, et al: Symptoms of depression and psychosis in Alzheimer's disease and frontotemporal dementia. Neuropsychiatry Neuropsychol Behav Neurol 1996; 9:154–161
4. Thiel A, Pilichowska ME, Hemmerlein B, et al: Demenz und psychotische Symptome bei der amyotrophen Lateralsklerose [Dementia and psychotic symptoms in amyotrophic lateral sclerosis]. Nervenarzt 1993; 64:618–622
5. Horoupian DS, Thal L, Katzman R, et al: Dementia and motor neuron disease: morphometric, biochemical, and Golgi studies. Ann Neurol 1984; 16:305–313
6. Dickson DW, Horoupian DS, Thal LJ, et al: Klüver-Bucy syndrome and amyotrophic lateral sclerosis: a case report with biochemistry, morphometrics, and Golgi study. Neurology 1986; 36:1323–1329

7. Gloor P: Experiential phenomena of temporal lobe epilepsy: facts and hypotheses. Brain 1990; 113:1673–1694
8. Damasio AR: Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. Cognition 1989; 33:25–62
9. Mesulam MM: Neurocognitive networks and selectively distributed processing. Rev Neurol (Paris) 1994; 150:564–569
10. Van Hoesen GW: The parahippocampal gyrus: new observations regarding its cortical connections in the monkey. Trends Neurosci 1982; 5:345–350
11. Galaburda AM, Pandya DN: The intrinsic architectonic and connectional organization of the superior temporal region of the rhesus monkey. J Comp Neurol 1983; 221:169–184
12. DeLacoste MC, White CL: The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system. Neurobiol Aging 1993; 14:1–16
13. Hof PR, Morrison JH: The cellular basis of cortical disconnection in Alzheimer disease and related dementing conditions, in Alzheimer Disease, edited by Terry RD, Katzman R, Bick KL. New York, Raven, 1994, pp 197–229
14. Pandya DN, Yeterian EH: Architecture and connections of cortical association areas, in Cerebral Cortex, vol 4, edited by Peters A, Jones EG. New York, Plenum, 1985, pp 3–61