Frontotemporal Dementia and Motor Neuron Disease: Report of 3 Cases in Taiwan and Literature Review

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Abstract-

Purpose: Case reports and a review of literature of the coexistence of motor neuron disease (MND) and frontotemporal dementia (FTD).

Case Report: All three patients demonstrated generalized lower motor neuron signs and very few upper motor neuron signs. In the level of patterns of cognitive impairments, neuropsychological studies do not distinguish between patients with onset of weakness from bulbar palsy and patients with onset of weakness from limbs. All patients of FTD had their onset of MND or amyotrophic lateral sclerosis symptoms within a two-year interval which is similar to previous reports. FTD combined with MND may shorten the survival to less than three years shorter than cases with FTD only. Respiratory failure occurred one to two years after onset of the behavioral symptoms in all patients.

Conclusion: We reported three patients of FTD with MND to remind clinicians that these two disorders may occur together on the same patient and that these two disorders may belong to one broad spectrum neurodegenerative disease.

Key Words: motor neuron disease, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar degeneration

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INTRODUCTION

Motor neuron disease (MND) comprises a group of conditions with progressive motor neuron loss. Clinically, MND produces progressive weakness, muscle wasting, fasciculation, spasticity, dysarthria and ventilation problem with a survival of 3 to 5 years in 50% of the patients. Amyotrophic lateral sclerosis (ALS) is the most common form of presentation, and is characterized by the progressive loss of both upper (UMN) and lower motor neurons (LMN). Other variants include progressive muscular atrophy, primary lateral sclerosis and progressive bulbar palsy [1]. However, a clear pathophysiology of the disease is still not known.

Frontotemporal dementia (FTD) is a focal, non-Alzheimer form dementia, characterized by behavioral or language dysfunctions with a high clinical, genetic, and neuropathological heterogeneity [2]. In 1994, the

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Lund and Manchester group proposed clinical and neuropathological criteria for the classification of FTD: frontal lobe degeneration type, Pick-type, and MND type[3]. In 1998, Neary et al proposed the concept of frontotemporal lobar degeneration (FTLD) to facilitate diagnosis and provide diagnostic criteria to classify FTLD into FTD, progressive non-fluent aphasia, and semantic dementia[2]. In 2001, an international group of clinical and basic scientists participated in the Frontotemporal Dementia and Pick's Disease Criteria Conference to reassess clinical and neuropathological criteria for the diagnosis of FTD[4]. In 2007, Cairns et al. proposed another version of the criteria for pathological diagnosis of the neurodegenerative group of diseases termed as FTLD on the basis of the recent advances in molecular genetic, biochemical, and neuropathological studies[5].

Recently neurologists have noticed that MND involves not only the motor system but also cognitive dysfunctions especially those related to the fronto-temporal cortex. Definite ALS was also diagnosed in FTD patients[6]. Evidence from clinical observation may redefine association between these two diseases and consider them as a generalized degenerative disease. This study reports on three cases of FTD combined with MND.

CASES REPORT

Case 1. AB

AB was a male patient who worked in a bank before the disease. He denied previous systemic disease and none of his family members was diagnosed with dementia or motor neuron disease. At the age of 51, his job performance declined and he had difficulty in communicating with his colleague. He often quarreled with them over trivial matters. He made frequent errors at work after the onset of his behavior symptoms. He became listless at work and eventually quit his job without notifying his family. His family noted that he was apathetic and uncommunicative. He behaved inappropriately doing things such as closing and opening windows repetitively, asking his wife to come home while she was at work. His family also reported bursts of spontaneous laughing and crying.

His wife consulted a psychiatrist who diagnosed him as having depression for which he was prescribed an antidepressant. However, at the age of 52, he started to have difficulty in holding his bowl and in using chopsticks. He had trouble in dressing himself and in performing personal hygiene. He became dependent on others in performing daily activities because of bilateral upper limb weakness.

At the age of 53, he began to have dysphagia and choked when drinking. He consequently lost 10 kilograms body weight. There was also bilateral muscle atrophy in the bilateral lower limbs, especially the quadriceps femoris. Neurological examination revealed that the patient was in a state of clear consciousness. Cranial nerve examination showed fasciculation of the tongue and an increased jaw jerk. He displayed mild weakness on a manual muscle test, scoring 4+ /5 in the proximal muscles of the four extremities, 3+ /5 in bilateral hands, and 4/ 5 in bilateral feet. Muscle wasting, especially in the intrinsic muscles of the bilateral hands, was noted. There were decreased deep tendon reflexes with equivocal Babinski sign on the right side. His score on the Mini Mental State Examination (MMSE) was 20/30 and his clinical dementia rating (CDR) was 1. Surveys of Vitamin B12, VDRL, and HIV were within normal range. The nerve conduction velocity study (NCV) showed absence or reduced amplitude in compound muscle action potentials (CMAP) in the right median and ulnar nerves, prolonged distal motor latencies in the right ulnar and peroneal nerves, but preserved amplitudes and normal conduction velocities in all sampled sensory nerves. Electromyography (EMG) showed positive waves and reduced recruitment in the right abductor digiti minimi, giant waves in right rectus femoris, biceps brachii, and left anterior tibialis, and neurogenic polyphasic waves in all sampled muscles. Brain magnetic resonance imaging (MRI) showed no obvious signal changes or structural lesions but marked bilateral frontotemporal lobe atrophy (Figure). Single photon emission computed tomography (SPECT) showed bilateral frontal and anterior temporal and medial parietal lobe hypometabolism. A neuropsychological

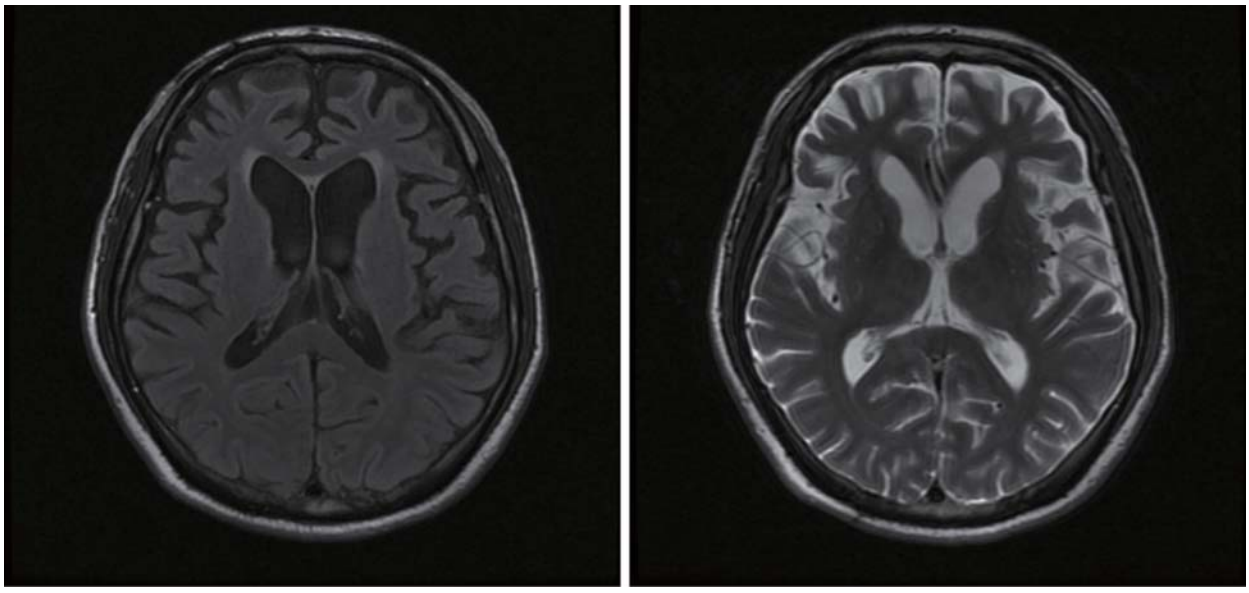

Figure. FLAIR and T2WI MRI of head in case 1 shows severe cortex atrophy in bilateral fronto-temporal area, without obvious signal changes

test was performed which showed impairments of memory, both semantic memory and episodic memory; spatial-constructional apraxia; naming difficulty, difficulty in following complex verbal commands; and dysexecutive function, such as deficits of category fluency, and concept formation (7 non-perseverative errors) and mental shifting (34 perseverative errors) in Wisconsin Card Sorting Test (WCST). Psychopatho- logical manifestations included inflexibility, personal neglect, disorganization, inattention, loss of insight, impulsivity, and restlessness which were represented by a Frontal Behavior Inventory (FBI) of 22/36 for negative behavior score and 7/36 for positive disinhibition score. The clinical picture of this patient matched the criteria for frontotemporal lobar degeneration, behavior variant form (bvFTD) with MND. A few months later, he had an episode of pneumonia and severe CO2 retention. He required intermittent Bi-level positive airway pressure (BiPAP) ventilator support. He died due to pneumonia at the age of 54.

Case 2. CD

CD was a college graduate and a manager in his workplace. He then set up a recycling company at the age of 50. He denied previous systemic disease and none of his family members was diagnosed dementia or motor neuron disease. At the age of 52, his occupational and social performance gradually deteriorated. He could not concentrate on his work. He had dysphoric mood and irritability. He had a very poor appetite, which resulted in a weight loss of 20 kilograms in two years. He became socially withdrawn and had disturbing behaviors, such as stealing food from stores, and had poor personal hygiene. He was taken into custody for theft several times. He would wander around outside all day alone. He was no longer able to do his job and usually stayed home most of the time. Laboratory surveys found that thyroid function, Vitamin B12, VDRL, and HIV were all normal. Brain MRI showed some non-significant signal changes on FLAIR at the right frontal white matter without obvious cortical atrophy.

He scored 27/30 on the MMSE and 90/100 on the Cognitive Abilities Screening Instrument with impairment in short-term memory, naming, and abstract thinking.

One year later, he became apathetic and displayed decreased social interaction.

Stereotyped behaviors, poverty of thoughts, repetitive questioning, and verbal perseverations were noted

by his family. A neuropsychological test revealed mental rigidity and inflexibility, emotional blunting, and stereotyped speech. He could speak only simple sentences and had much difficulty in understanding what others said. SPECT images showed moderately decreased perfusion at the bilateral frontal, parietal and temporal lobes. Neurological examination revealed decreased muscle power and atrophy of distal muscles in the four extremities. There was generalized hyporeflexia. EMG showed positive waves, fibrillation, and neurogenic polyphasic waves in the upper extremities and middle thoracic paraspinal muscles. Giant waves up to 4 mV were also recorded. He was therefore diagnosed FTD with MND. One year later, he had choking and consequent respiratory failure and septic shock. He received tracheotomy and artificial ventilation, and then was transferred to respiratory care ward for long-term care.

Case 3. JD

JD had a history of benign prostate hyperplasia, neurosis, and insomnia. He denied any of his family members being diagnosed dementia or motor neuron disease. At the age of 54 years, he suffered from an insidious onset of left upper limb weakness and left hand muscle atrophy. Although he had no apparent choking, dysphagia or dysarthria, he had a 6-kilogram weight loss within two years. Progressive bilateral upper limb weakness and atrophy also occurred within two years. He also had poor impulse control. Neurological examination revealed decreased muscle power and distal muscle atrophy in the four extremities. Examination of tendon reflexes revealed generalized hyporeflexia. There were positive sucking reflex, and motor perseveration. Psychopathological manifestations of evident negative behavior symptoms (24/36 negative score of FBI), and obsessive-compulsive behavior (17/36 disinhibition score of FBI) were noted. Significant deterioration from estimated premorbid intellectual level was found. A neuropsychological test also showed a low average of verbal comprehension; and deficits of memory function including defected semantic memory and impaired delayed recall of verbal memory; and impaired core linguistic function. The executive dysfunction function was manifested as deficits of concept formation (11 non-perseverative errors) and mental shifting (22 perseverative errors) in WCST. The NCV study showed reduced CMAP amplitudes in the bilateral median and ulnar nerves and mild slowing of motor conduction velocity in the right median nerve. Prolonged minimal F-waves in the right median and left ulnar nerves, and an absence of F-waves in the left median nerve were also noted. A waves were seen in the right ulnar, peroneal and tibal nerves. The EMG study showed neurogenic polyphasic and giant waves in all sampled muscles, including thoracic paraspinal muscles. He was prescribed riluzole since then. Two years later, he was hospitalized for aspiration pneumonia and was discharged with a nasogastric tube for feeding. In six months, he had gradually developed disturbed consciousness due to hypercapnic respiratory failure for which he received a Bi-PAP ventilator support.

DISCUSSION

ALS is increasingly recognized as a complex multisystem disorder in levels of pathobiology and in the breadth of non-motor manifestations [7]. The prevalence of the frontal lobe cognitive dysfunction in MND patients ranges from 5% to 50% [6,8,9]. Symptoms associated with FTD and may precede, co-occur, or follow the development of motor deficits [10].

Because of the extensive spectrum of behavioral and cognitive impairments in ALS patients, most of these patients do not fulfill the Hodge [11] or the Neary criteria [2] for typical FTD (Table). Therefore, a consensus of clinical diagnosis for FTD and MND was proposed by an international workshop in 2007 which consists of four axes [12]. The first axis is the clinical diagnosis of motor neuron diseases focusing on ALS. In the second axis, behavioral and cognitive impairments are defined. The third axis consists of additional descriptions of other non-motor manifestations, such as cerebellar symptoms and extrapyramidal signs. The fourth axis includes the presence of disease modifiers such as age of onset, site of disease onset, disease duration and gender [12].

According to consensus of the clinical diagnosis, three different clinical types can be identified. First, the

Table. *Neary FTLD (FTD, PNA, SD) criteria 1998 for FTD*
Adapted from Neurology. 1998;51:1546-54.

Frontotemporal dementia
Core diagnostic feature
A. Insidious onset and gradual progression
B. Early decline in social interpersonal conduct
C. Early impairment in regulation of personal conduct
D. Early emotional blunting
E. Early loss of insight
Supportive diagnostic feature
A. Behavioral disorder
B. Speech and language
C. Physical signs
D. Investigations
Diagnostic exclusion features
A. Historical and clinical
B. Investigations: predominant postcentral structural or functional deficit; multifocal lesions on CT or MRI; Laboratory tests indicating brain involvement of metabolic or inflammatory disorder.
Relative diagnostic exclusion features
A. Typical history of chronic alcoholism
B. Sustained hypertension
C. History of vascular disease (e.g., angina, claudication)

ALS-behavioral impairment, patients have to meet at least two non-overlap supportive diagnostic features from either the Neary [2] or the Hodge [11] criteria. Second, the ALS-cognitive impairment, patients have to demonstrate cognitive impairment in at least two distinct cognitive tests sensitive to executive functions compared to their age and education matched control. Third, the ALS-comorbid dementia, patients must have a dementia other than FTD.

Although behavioral and psychiatric symptoms are the characteristics of FTD [13], episodic memory impairment was documented in pathologically proven bvFTD patients [14], and some patients may have memory problems as their onset symptoms [15]. Reasons for episodic memory impairment in patients with FTD may be multiple but the linguistic core function deficits can contribute to impairment of both semantic function and delayed recall of verbal memory.

Several important findings were observed in this case series. All patients demonstrated generalized LMN signs and very few UMN signs. In level of patterns of cognitive impairments, neuropsychological studies do not distinguish between patients with onset of weakness from bulbar palsy and patients with onset of weakness from limbs. However, the Neary FTD criteria[2] includes muscular wasting and fasciculation, which indicates LMN symptoms which suggests LMN manifestation may be the earliest signs of MND in these patients. All patients of bvFTD had their onset of MND or ALS symptoms within a two-year interval which is similar to previous reports [16]. The average survival time of ALS patients is about two to three years [16] while FTD patients survive for about 6-10 years [17,18]. Several studies demonstrated that FTD combined with ALS (28.2 months) may shorten the survival to less than three years compared to FTD alone (68.5 months) [18]. Respiratory failure occurred one to two years after onset of the behavioral symptoms in all patients.

There are some difficulties in diagnosing cognitive impairment in patients with ALS/MND because motor deficits may interfere with cognitive testing from their hand weakness (for writing and drawing) and dysarthria for replying in oral language. Differential diagnosis could be confounded by bulbar muscle weakness in ALS patients which may be wrongly coded as non-fluent aphasia [19], and patients could be depressive due to the incurable disease, which might be mistaken for “abulia” or “apathy” [19]. To define FTD in MND/ALS patients, a complete neuropsychological test should be performed when the patient is first diagnosed with MND/ALS. At that time they are still capable of doing neuropsychological test. Early screening could help clinicians decrease the confounding effect from dysarthria and depression in

the evaluation of frontotemporal dysfunction. A single evaluation is likely to miss many patients who are in the process of losing motor neuron functions because of the progressive nature of both diseases

Even though there is no effective biomarker for ALS/MND [20], diffusion tensor tractography of MRI can detect early degeneration of the pyramidal tract, which could demonstrate a decrease of fractional anisotropy in FTD patients and early ALS [21]. SPECT and positron emission tomography demonstrated similar hypometabolism in the frontal and temporal lobes in both FTD and ALS-FTD patients [22]. Triggs et al. applied transcranial magnetic stimulation, which is a non-invasive technique, to examine 121 patients with possible MND and found that an increased threshold of motor evoked potential was the most sensitive parameter. Progressive inexcitability of the central motor pathways and the loss of the normal cortical silent period provided additional diagnostic value [23].

In conclusion, we reported three patients of FTD with MND to remind clinicians that these two disorders may occur together on the same patient and that they may belong to one broad spectrum neurodegenerative disease.

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