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Dementia Accompanying Motor Neuron Disease – 7 Cases

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Frontal lobe dementia · Motor neuron disease · Neuropathology · Psychopathology · Epidemiology

Abstract
Seven typical cases of dementia with motor neuron disease (D-MND) are reported. Among 1,000 dementia cases, D-MND was more frequent than Pick's disease, Lewy body disease or Creutzfeldt-Jakob disease. D-MND accounted for 30.4% of all forms of frontal lobe dementia (FLD) including FLD and Pick's disease. These data support that this combined syndrome may be more frequent than previously reported. As the subcortical neuropathology of D-MND is identical with MND, D-MND is rather the cortical manifestation of MND than a new disease entity.

Introduction

Ziegler [1] and Wechsler and Davidson [2] described psychiatric symptoms in amyotrophic lateral sclerosis [motor neuron disease (MND)]. Von Poppe and Trennstedt [3] were the first to publish the coincidence of dementia and MND. In subsequent studies, this syndrome was only reported in a few cases [4, 5]. In an epidemiological survey, dementia was found in 4% of the MND cases in Japan [6]. Jokelainen [7] and Gubbay et al. [8] also reported that only 2–6% of MND patients were demented. There is an ongoing discussion whether MND-associated frontal lobe dementia (FLD) is a variant of MND [9, 10], a variant of FLD [11] or a new disease entity [5]. In this study, we report 7 cases of dementia with MND (D-MND) and discuss the prevalence of D-MND among patients with dementia and particularly with FLD.

Case Report

A 68-year-old male engineer developed personality changes and subsequent dementia at the age of 63 years. There was no history of mental illness in his family. According to his wife, the intellectual decline had begun approximately 4 years previously, when she noted behavioral disturbances, emotional lability, paranoid ideation and a loss of spontaneous speech. Three years later, the initial examination revealed mild dementia. The Mini-Mental-State Examination (MMSE) score [12] was 24. EEG and MRT were normal. Probable Alzheimer's disease (AD) was suspected. Treatment with tacrine provided no benefit. In 1994, the patient developed muscle wasting and bulbar symptoms. Because of dysphagia, he lost 20 kg in 2 months and was admitted to our clinic for the first time. At that time, he had

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mild to moderate dementia with memory impairment, intellectual deterioration, complete lack of insight and poor judgment. Apraxia, agnosia or visual/spatial problems were not apparent. The neurological examination showed muscle wasting with fasciculation predominant in the upper limbs as well as bulbar symptoms including dysphagia and dysarthria. No extrapyramidal symptoms were found. Electromyography was typical of myotrophic lateral sclerosis and D-MND was diagnosed. During the subsequent months, his speech became increasingly incomprehensible as dysphasia rapidly worsened. His vocabulary diminished until he finally became completely mute. Dysarthria and dysphagia progressed. He became incontinent and bedridden and died from bronchopneumonia on December 3, 1994, 4 years after first symptoms had been noticed.

The fresh brain weighed 1,320 g. There was mild frontal lobe brain atrophy. Nonspecific cortical neuronal loss was predominant in layers 2 and 3. Spongiform changes in the cerebral cortex were found in addition to subcortical gliosis, neuronal loss of pigmented cells in the substantia nigra, loss of hypoglossal nuclei, cortico-spinal tract degeneration, anterior horn cell loss and neurogenic muscle atrophy. Senile plaques, Alzheimer's neurofibrillary tangles, Lewy bodies, Pick's argentophilic bodies or vascular degeneration were not found.

Seven Cases of Dementia with MND

To determine the prevalence of dementia with MND in our outpatient clinic for cognitive disorders, we screened the clinical records of 1,000 patients who had been evaluated between 1985 and 1995. 76.6% of these were diagnosed with AD, and 15.2% were diagnosed with vascular dementia (VD) or VD + AD (table 1). 8.2% were non-AD and non-VD dementia cases. 0.7% suffered from dementia with MND (table 2). In these 7 patients, no family history of dementia or MND was reported except for 1 male patient whose father was disorientated at the age of 88. The average onset of dementia was 54.4 years (table 4), which clearly demonstrates the presenile nature of the illness. All patients had frontal lobe symptomatology including personality changes, apathy and progressive aphasia. None of them had apraxia, agnosia or visual/spatial disturbances. Dementia was mild to moderate as reflected by an average MMSE score of 25 (21–29). All patients developed neurological symptoms after an interval of 28 (7–54) months after first symptoms had been noticed. Neurogenic muscle atrophy and bulbar symptoms were apparent in all cases. One patient had hypersalivation and urinary incontinence. No extrapyramidal symptoms were found. Electromyography was typical for MND. The EEG was normal. All patients had cranial CT or MRI scans. Four showed mild frontal atrophy, while 3 had normal brain images. SPECT was performed in 1 female patient, who showed reduced cerebral blood flow in the superior frontal area. Length of survival was dra-

Table 1. Dementia cases (n = 1,000)

Total	1,000
DAT	766
VD and VD + DAT	152
Non-DAT, non-VD cases	82

Table 2. Non-DAT and non-VD cases (n = 82)

Parkinson's disease	18
FLD	10
Korsakoff's syndrome	8
D-MND	*7*
Normal pressure hydrocephalus	7
Pick's disease	6
Huntington's disease	6
Encephalitis	5
CJD	4
Lewy body	3
Others (frequency < 3)	14

Table 3. FLD cases (n = 23)

FLD	43.5%
D-MND	30.4%
Pick's disease	26.1%

Table 4. D-MND (n = 7)

Male:female	3:4
Age at onset, years	54.4 (45–63)
Age at diagnosis, years	57.0 (47–68)
Age at death, years	58.9 (49–68)
Interval between dementia and neurologic symptoms, months	28 (7–54)
MMSE (time of diagnosis)	25 (21–29)

Figures in parentheses are ranges.

Table 5. Epidemiology of related diseases

	n	Sex ratio	Age at onset	Age at diagnosis	MMSE
D-MND [5]	7	0.75	54.4 ± 6.9	57.0 ± 7.1	25.0 ± 9.0
Pick's disease + FLD [11]	16	0.8	55.0 ± 9.0	59.0 ± 9.0	21.0 ± 8.0
DAT [32]	766	0.4	71.8 ± 8.2	75.5 ± 8.3	15.3 ± 6.8

matically reduced in all cases due to progressive MND. The age of death was 58.9 (49–68) years, with total duration from the onset of disease to death being 4.5 years. Compared with Pick's disease and FLD cases within the patient sample, no significant differences were found with regard to gender, age at onset of disease and age at diagnosis (table 5). D-MND patients were less severely demented compared with patients with dementia of the Alzheimer type (DAT), FLD or Pick's disease according to MMSE scores. Compared with DAT cases, D-MND patients were significantly younger and less demented. Neuropathological examination was performed in the case mentioned above, data of the other cases were extracted from files. Ubiquitin-immunoreactive dye was not available at this time. Neuronal loss and degeneration characterized by simple atrophy in the upper layers of the frontal lobe were the main pathological features in the cortex.

Discussion

In the clinical data of the 7 patients reported here, presenile age at onset, interval between onset of dementia and neurologic symptoms, and duration of the illness are comparable with findings of Mitsuyama [5] who reviewed the majority of cases reported in the literature. EEG remained normal and CT/MRT imaging was normal in 3 of 4 cases, comparable with the results of Gustafson [13]. SPECT showed reduced cerebral blood flow in the superior-frontal area. Miller et al. [14] described reduced cerebral blood flow in SPECT as highly characteristic in separating patients with FLD from D-MND [15].

30.4% of all FLD cases in our study (Pick's disease, FLD, D-MND) were associated with MND (table 3). In this selected sample from the outpatient clinic of our university, D-MND was more frequent than Pick's disease, or Creutzfeldt-Jakob disease (CJD) (table 2). This could indicate that dementia in MND might occur much more frequently than previously reported [6–8]. Considering an estimated prevalence of MND of 2.9/100,000 [16], frontocortical pathology in MND seems to be common. This assumption appears to be supported by Caselli et al. [17], who found cognitive impairment in 8 out of 9 patients with primary lateral sclerosis on neuropsychological tests sensitive to frontal lobe functions. Neuropsychological and PET studies [18] indicate cognitive impairment of predominantly 'subcortical' frontal lobe type in early sporadic MND. Further neuropsychological testing with tests sensitive to frontal lobe and subcortical function may be useful in helping to establish a cortical involvement in patients with MND. Lopez et al. [4] suggested that slowing of cognitive processes associated with selective motor speed and attentional tasks were more frequent than deficits in planning and conceptualization. As these impaired cognitive processes have been associated with subcortical functioning, they could be of major interest to distinguish D-MND from FLD and Pick's disease before neurological symptoms will be apparent.

Psychopathological symptoms in our patients were suggestive of Pick's disease or FLD rather than AD. Five cases of DAT with MND have been reported [3, 19, 20] in the literature. While the frequency of senile plaques shows a continuum between nondemented and demented people [21], only 1 case had a number of neurofibrillary tangles which could not be interpreted as related to age. The only known pathoanatomically proven case of AD related to MND might have occurred by coincidence, as AD is the most common cause of dementia [22].

According to clinical [13] and epidemiological (table 4) findings, dementia in MND is very similar to that of FLD and Pick's disease. But there are clear-cut pathoanatomical differences [23] between dementia in MND, Pick's disease and FLD. A positive heredity in FLD is reported in 60% [13] compared with 14% in D-MND [11]. In our 7 patients, we found no conclusive data indicating heredity as an additional parameter for D-MND. As MND can occur in CJD, an infective origin of dementia in MND was discussed [24]. The transmission experiments by Salazar et al. [25] were negative. Morita et al. [26] and Mitsuyama [5] reviewed Japanese cases. Although the neuro-

logical findings were identical to MND, they regarded the clinicopathologic findings as indicative of an atypical spinal progressive muscular atrophy and suggested a new disease entity.

There is a growing body of evidence that the neurodegenerative process underlying MND may present itself as FLD with characteristic inclusions in the nonmotor cortex [10]. Chang et al. [27] found hematoxylin and eosin staining revealed eosinophilic, granular, central cytoplasmatic clearing in most neurons of the substantia nigra and in anterior horn cells. Electron microscopy showed that these neurons contained a central cytoplasmic zone cleared of neuromelanin and normal cytoplasmic organelles containing small mitochondria with matrix inclusions and randomly orientated filamentous material. They suggested a mitochondrial dysfunction or defective transport of mitochondria into axonal processes as a potential cause for the coassociation of MND and dementia.

Ferrer et al. [28] found that the density of calbindin D-28k immunoreactive cells is reduced in MND with and without dementia. The density of parvalbumin immunoreactive cells is reduced only in MND with FLD. These neurons are located in the upper cortical layers and preserve the integrity of the major inhibitory intracortical circuits. Two gene defects leading to D-MND have recently been detected: Rosen et al. [29] found mutations in the Cu/Zn superoxide dismutase gene associated with familial MND and Lynch et al. [30] described autosomal dominant FLD with MND and parkinsonism bound to chromosome 17q21–23. Inclusions in motor neurons and nonmotor cortex can also be detected by antiubiquitin. The origin of the inclusions based on filaments remain uncertain, but they are specific to MND. These ubiquitin-immunoreactive inclusions can be seen in neurons in the frontal cortex in D-MND and it seems to be a common pathological substrate of FLD and MND [9]. As ubiquitin-immunoreactive filament inclusions are also seen in nondemented MND patients [31], MND is not simply a disease of motor neurons and a concept of a multisystem degeneration should be considered.

Among 1,000 dementia patients of an outpatient clinic for cognitive disorders, D-MND was more frequent than Pick's disease or CJD and accounted for 30.4% of all forms of FLD. According to the relatively high frequency of D-MND, frontal lobe and subcortical pathology seems to be common in MND and might be detected by neuropsychological and PET examinations. As the subcortical neuropathology of D-MND is identical with MND, D-MND represents the cortical manifestation of MND rather than a new disease entity.

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Erratum

We have been informed by the authors about a calculation error in the paper by Wimo et al. 'An Economic Evaluation of Donepezil in Mild to Moderate Alzheimer's Disease: Results of a 1-Year, Double-Blind, Randomized Trial' (Dement Geriatr Cogn Disord 2003;15:44-54). The numbers reported of hours of caregiver time reflect the sum of average hours per day for each quarterly visit rather than the average hours per day for the entire study period. The correct figure for the difference in caregiver time was 83 hours on a yearly basis favouring donepezil (NS). The results, however, do not change the primary cost analysis at all or the conclusions of the study.