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Mills syndrome with dementia:

Broadening the phenotype of FTD/MND

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Sirs: The syndrome of progressive ascending or descending hemiplegia without significant sensory involvement reported by Mills in 1900 [1, 11] is of uncertain nosological status [4, 7, 10]. We report a patient with Mills syndrome and dementia, with a pathological substrate typical of motor neurone disease (MND).

A 60-year old right-handed lady presented with a two-year history of cognitive and motor problems. She retired early, aged 58, because of difficulty adapting to new routines. Her husband noted progressive loss of social graces and interest in usual activities, sexual disinhibition, and predilection for chocolate with subsequent weight gain. She had become "a different person". She had falls for no apparent reason, on one occasion fracturing her nose. Family history was negative for cognitive or motor disorder.

On examination there was no aphasia, apraxia or myoclonus. MMSE score was 26/30 (3 points lost for orientation). Palmomental, pout and jaw reflexes were brisk. There was left-sided upper motor neurone facial weakness, spastic catch and pyramidal distribution weakness (MRC grade 4/5), with bilateral hyperreflexia and upgoing plantars. Sensory examination was normal; there was no sensory inattention.

Structural brain imaging (CT, MRI) showed asymmetric frontotemporal atrophy (right > left). Functional imaging (^{99m}Tc-HM-PAO-SPECT) showed asymmetric frontotemporal hypoperfusion. In a retrospective audit of SPECT imaging [2], 5/5 observers blind to clinical details rated this scan abnormal and suggestive of frontotemporal dementia (FTD). EEG was normal. CSF was normal aside from slightly elevated protein (0.73 g/l). Neuropsychological assessment was limited by poor attention, disinhibition, concrete interpretation and perseverative tendencies, for example in tests of verbal fluency. A clinical diagnosis of FTD was made [12].

MMSE fell to 20/30 over six months. Speech output was reduced to monosyllables but she still recognised friends and could write multiplication tables [15]. The left arm hung by her side, she dragged the left leg; there was no right sided weakness. She died 3 years after disease onset. At postmortem, macroscopically the brain showed severe, "knife-edge", frontotemporal atrophy. Microscopically there was no spongiform change. Immunocytochemistry was negative for Aβ, tau, α-synuclein and prion proteins, but positive for ubiquitin, showing small inclusions in some layer 2 cortical neurones, hippocampal dentate granule cells, and hypoglossal nerve nucleus neurones. Spinal cord was not examined. A pathological diagnosis of MND inclusion dementia was made [16].

In this case, progressive spastic hemiparesis of unknown cause, reminiscent of the syndrome described by Mills [11], accompanied FTD. The neuropathological substrate was typical of MND, namely ubiquitinated inclusions in cortical neurones and hypoglossal nucleus motor neurones, establishing a diagnosis of FTD/MND [16]. Some cases of Mills syndrome may be hemiplegic forms of motor neurone disease with exclusively upper motor neurone signs [4, 7, 10] although this clinical picture falls outside proposed diagnostic criteria for primary lateral sclerosis (progressive symmetric spinobulbar spasticity) [14].

The syndrome of FTD/MND, also known as MND dementia, is rare (on average one new case per year in our clinic [8]). Typically the cognitive syndrome precedes motor dysfunction of amyotrophic (lower motor neurone) type although brisk reflexes and extensor plantar responses may be noted [16]. Our case had no lower motor neurone signs, hence EMG was not performed. We are not aware of prior reports of FTD with Mills syndrome, although FTD/MND presenting as cortical-basal ganglionic degeneration has been reported [5].

The different initial manifestations of MND inclusion pathology (dementia ± upper and/or lower motor neurone features) presumably reflects the predominant neuroanatomical locus of pathology, which may differ even in familial cases [13]. This is analogous to Alzheimer's disease, which may present with isolated amnesia, agnosia, aphasia, apraxia, or combinations thereof [3]; and Lewy body disease, which may present with isolated parkinsonism, dementia, autonomic failure, or combinations thereof [6, 9].

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