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A familial form of parkinsonism, dementia, and motor neuron disease: A longitudinal study

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ABSTRACT

Objective: To describe the clinical, positron emission tomography (PET), pathological, and genetic findings of a large kindred with progressive neurodegenerative phenotypes in which the proband had autopsy-confirmed corticobasal degeneration (CBD).
Methods: Five family members, including the proband, were examined neurologically. Clinical information from the other family members was collected by questionnaires. Three individuals underwent PET with ^{11}C-dihydrotetrabenazine and ^{18}F-fludeoxyglucose. The proband was examined post-mortem. Genetic studies were performed.
Results: The pedigree contains 64 individuals, including 8 affected patients. The inheritance is likely autosomal dominant with reduced penetrance. The proband developed progressive speech and language difficulties at the age of 64 years. Upon examination at the age of 68 years, she showed non-fluent aphasia, word-finding difficulties, circumlocution, frontal release signs, and right-sided bradykinesia, rigidity, and pyramidal signs. She died 5 years after disease onset. The neuropathology was consistent with CBD, including many cortical and subcortical astrocytic plaques. Other family members had progressive neurodegenerative phenotypes – two were diagnosed with parkinsonism and behavioral problems, two with parkinsonism alone, one with amyotrophic lateral sclerosis alone, one with dementia, and one with progressive gait and speech problems. PET on three potentially affected individuals showed no significant pathology. Genetic sequencing of DNA from the proband excluded mutations in known neurodegenerative-related genes including *MAPT*, *PGRN*, *LRRK2*, and *C9ORF72*.
Conclusions: Families with such complex phenotypes rarely occur. They are usually associated with *MAPT* mutations; however, in this family, *MAPT* mutations have been excluded, implicating another causative gene or genes. Further genetic studies on this family may eventually disclose the etiology.

1. Introduction

The term "tauopathy" encompasses several different neurodegenerative disorders, including corticobasal degeneration (CBD), progressive supranuclear palsy, argyrophilic grain disease, and Pick disease. CBD is a relatively rare tauopathy, and its prevalence is estimated to be 1–9 per 100,000 [1]. The clinical phenotype of CBD is heterogeneous and includes progressive asymmetric rigidity and apraxia (corticobasal syndrome), progressive supranuclear palsy (Richardson syndrome), behavioral variant frontotemporal dementia (bvFTD), and primary progressive aphasia [2]. Antemortem diagnostic accuracy is poor, and no biomarker is available to

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diagnose CBD. Neuroimaging, such as ^{18}F-fluorodeoxyglucose (FDG) PET, can be a useful diagnostic tool in CBD, which usually shows involvement of the frontal and parietal cortexes, as well as the striatum and thalamus [3–6]. Pathological hallmarks of CBD are 4-repeat tau-immunopositive neuronal and glial inclusions in neocortical and subcortical areas; astrocytic plaques [7] are the lesions closest to being pathognomonic [8].

Familial forms of CBD have only rarely been reported [9–12]. The first causative mutation in the *MAPT* gene was recently identified in an autopsy-proven sporadic CBD patient [13]. Here we report a family in which the proband suffered from CBD, and the other affected family members had various progressive clinical phenotypes.

2. Methods

2.1. Genealogical investigations

Phone calls and interviews with surviving family members were conducted.

2.2. Clinical studies

Study participants were evaluated utilizing standardized medical history and Neurologic Examination forms, including the Unified Parkinson's Disease Rating Scale, Mini–Mental State Examination, and Hoehn–Yahr Stage.

2.3. Neuroimaging studies

PET studies were performed using ^{11}C-dihydrotetrabenazine (DTBZ) and ^{18}F-FDG as ligands, as previously reported [14,15].

2.4. Pathological studies

The brain of the proband was available for neuropathological examination. Neuropathological evaluations were performed at the Mayo Clinic in Rochester, MN, (JEP), with additional studies, including 3R and 4R tau immunohistochemistry, done at the Mayo Clinic in Jacksonville, FL (DWD, SF). The whole brain of the proband, which weighed 1090 g, was fixed in formalin and sampled for histology according to a standardized protocol. Tissue sections were embedded in paraffin, and 5 μm thick sections were mounted on glass slides for histological studies and immunohistochemistry. The areas sampled were frontal, cingulate, temporal, parietal and occipital neocortices, hippocampus, amygdala, basal nucleus of Meynert, caudate nucleus, putamen, thalamus, subthalamic nucleus, midbrain, pons, medulla, cerebellum, and spinal cord. Paraffin-embedded sections were stained with hematoxylin and eosin. Most sections were also studied with tau immunohistochemistry (AT8, 1:1000; Innogenetics, Alpharetta, GA, USA). Sections from the frontal and parietal lobes, hippocampus, and amygdala were stained with Okazaki modified Bielschowsky silver stain. Sections of the temporal lobe, hippocampus, amygdala, caudate nucleus, and putamen were processed for immunohistochemistry for 3R tau antibody (RD3, 1:5000, Millipore, Temecula, CA, USA), and 4R tau antibody (RD4, 1:5000, Millipore, Temecula, CA, USA). Sections of the cingulate gyrus, amygdala, midbrain, pons, and the spinal cord were processed for α-synuclein immunohistochemistry (LB509, 1:200; Zymed, San Francisco, CA, USA). Sections of the frontal lobe, parietal lobe, and amygdala were processed for neurofilament immunohistochemistry (2F11, 1:75; DAKO, Carpinteria, CA, USA). Sections of the frontal, parietal, and the occipital lobes, hippocampus, and amygdala were processed for β-amyloid immunohistochemistry (6F/3D, 1:10 dilution; Novacastra Vector Labs, Burlingame, CA, USA). The density and distribution of neurofibrillary tangles (NFT) on Bielschowsky stain were used to assign a Braak NFT stage.

2.5. Molecular genetic studies

DNA was extracted from peripheral leukocytes from the proband, and direct sequencing of all exons of *MAPT*, *PGRN* and *LRRK2*, was performed. *C9ORF72* was screened for the causal expanded repeat, and other FTD and amyotrophic lateral sclerosis (ALS)-related genes were screened by exome sequencing.

The project was approved by the ethics committee of the Mayo Clinic and the University of British Colombia/Vancouver Coastal Health, and informed consent was received from all participants, except for one autopsied case. In this case, the consent was obtained from next-of-kin.

3. Results

3.1. Genealogical investigations

The family tree contains 64 family members spanning five generations (Fig. 1). Genealogic studies identified seven affected individuals. The mode of inheritance is suggestive of an autosomal dominant pattern with reduced penetrance.

3.2. Clinical studies

The proband (**III-4**) was a right-handed female who developed her symptoms at age 64 years. She had slowly progressive speech and language difficulties, which were characterized by nonfluent aphasia, word-finding difficulties, and circumlocution. She also initially suffered from apraxia, reading and writing difficulties, visual perceptual dysfunction, delusions, and hallucinations. Neurological examination at age 68 years showed her to be alert and attentive but quite anxious. She attempted to exit the room at the end of interview. She exhibited psychomotor retardation and decreased speech output. She had mild saccadic extraocular movement and a moderately decreased upgaze. She had right-sided hemi-parkinsonism characterized by facial masking, mild bradykinesia, and mild rigidity. There was neither postural instability nor tremors. Her gait was slow with decreased arm swing on the right side. Deep tendon reflexes were exaggerated in the right upper and lower extremities with flexor plantar reflexes bilaterally. She did not have limb apraxia, alien limb phenomenon, dystonia, stimulus sensitive myoclonus, cortical sensory loss, or muscle fasciculations. She scored 19 in the Part III of the UPDRS. Brain MRI showed moderate non-localized cerebral atrophy. A ^{99m}Tc-HMPAO SPECT scan revealed mild to moderate diffuse reduced blood flow, which was slightly more severe in the left hemisphere. She was clinically diagnosed as having focal asymmetric cortical degeneration with parkinsonism. She was treated with high-dose vitamin E, donepezil, and carbidopa/levodopa without significant improvement. She died aged 70 years.

The maternal cousin (**III-12**) of the proband was a right-handed male who developed reduced left arm swing and left hand tremor at the age of 53 years. His symptoms were progressive. To treat his parkinsonism, he underwent surgery three times, including a right posterior ventral pallidotomy/thalamotomy at age 57 years. He also underwent a left stereotactic mini-pallidotomy and the implantation of a deep brain stimulator electrode into the thalamus at age 61 years. He was put on carbidopa/levodopa therapy without any benefit. He developed dyskinesia, and the therapy was discontinued. He experienced memory impairment, excessive salivation, and micrographia. He had balance problems and fell on several occasions. Neurological examination at age 64 years showed him to be fully oriented and cooperative. His speech was slow and hypophonic. He had hypomimia. He had rigidity in both the neck and appendicular muscles. He showed intermittent resting tremor of the chin. His posture was stooped, but his postural stability was preserved. His arm swing was bilaterally reduced when walking. He scored 28 out of 30 on the Mini Mental State Examination. He scored 17.5 in the Part III of the UPDRS. He died aged 79 years.

Three individuals (**IV-12**, **IV-13**, and **IV-14**) had no complaints; however, they had subtle neurological signs upon neurological examination, but they did not fulfill any of the diagnostic criteria for neurodegenerative disorders. One of these individuals, **IV-12**, who was aged 57 years at the examination, had minimal rigidity in his right upper extremity, mild impairment of finger tapping, mild impairment of hand movements, and hypophonia; **IV-13**, who was 58-years-old at the examination, had mild hand tremor in his right hand and postural instability; **IV-14**, who was 57-years-old at the examination, showed mild rigidity in her limbs and her neck.

The medical histories of the other family members were notable for progressive neurological disorders. The proband's