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

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A B S T R A C T

**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 11C-dihydrotetrabenazine and 18F-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.

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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
diagnose CBD. Neuroimaging, such as 18F-fluorodeoxyglucose (FDG) PET, can be a useful diagnostic tool in CBD, which usually shows involvement of the frontal and parietal cortices, 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 11C-dihydroetabenzazine (DTPB) and 18F-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, SP). 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. Paraaffin-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 (L5B09, 1:200; Zymed, San Francisco, CA, USA). Sections of the frontal lobe, parietal, and amygdala were processed for neurofilament immunohistochemistry (2F11, 1:75; DAKO, Carpinteria, CA, USA). Sections of the frontal, parietal, and occipital lobes, hippocampus, and amygdala were processed for β-amyloid immunohistochemistry (6F3D, 1:10 dilution; Novacastra Vector Labs, Burlingame, CA, USA). The density and distribution of neurofilibrillary 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, PONR and LRRK2, was performed. CS08F72 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 tremor. 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 phenomena, 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 99mTc-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 (II-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
maternal grandmother (I-2) was reported to have had a slowly progressive neurodegenerative disorder. The proband’s mother (II-1) was reported to have had progressive difficulties with speech and gait beginning around age 85 years. The maternal aunt (II-4) was reported to have language problems and cognitive impairment that developed when she was in her eighth decade of life. The proband’s older brother (III-1) was reported to have a parkinsonian disorder and language problems that developed when he was in his sixties. He died aged 79 years. The proband’s younger brother (III-6) was reported to have parkinsonism in his early sixties.

3.3. Neuroimaging studies (PET)

$^{11}$C-DTBZ PET and $^{18}$F-FDG PET revealed normal tracer uptake in three family members (IV-12, IV-13, and IV-14).

Demographics, clinical features, and radiological findings of the affected patients are summarized in Table 1.

3.4. Pathological studies

Macroscopically, the fixed brain had moderate general atrophy that was prominent in the anterior temporal, frontal, and parietal lobes. The substantia nigra showed a mild decrease of neuromelanin pigmentation. Microscopically, there was subpial gliosis and spongiosis in the neocortical layer II of the mid-frontal lobe. Ballooned neurons were prominent in the mid-frontal cortexes and in the amygdala. The substantia nigra had mild neuronal loss (Fig. 2B). The substantia nigra had neuronal loss and gliosis (Fig. 2C). Immunohistochemistry for tau showed oligodendrogial inclusions and coiled bodies in the mid-frontal, motor, parietal, and temporal cortexes (Fig. 2D), subcortical regions (Fig. 2E), and the basal ganglia. Tau-immuno positive astrocytic plaques were prominent in the mid-frontal (Fig. 2D) and parietal cortexes, as well as the amygdala. Pretangles were numerous in the dentate gyrus of the hippocampus (Fig. 2F). Neurofibrillary tangles and pretangles were detected in the subthalamic nucleus and substantia nigra. In the CA3 section of the hippocampus, tau immunohistochemistry with 4R tau antibody revealed many pretangles and NFT (Fig. 2G), whereas tau immunohistochemistry with 3R tau antibody showed only rare extracellular tangles (Fig. 2H). Neurofilament-positive ballooned neurons were prominent in the mid-frontal cortexes (Fig. 2I) and also in the parietal, temporal, motor, and cingulate cortexes and in the amygdala. Argyrophilic grains were detected in the medial temporal lobe. No plaques but a few neurofibrillary tangles in the neocortex, hippocampus, subiculum, and entorhinal cortex were detected with the Bielschowsky silver stain. A mild to moderate degree of amyloid angiopathy was detected in the leptomeninges, which was greater than in parenchymal vessels. There were no immunopositive lesions with x-synuclein immunohistochemistry. The pathologic diagnosis was CBD with concomitant Alzheimer’s pathology (Braak neurofibrillary tangle stage III), as well as argyrophilic grains and mild to moderate amyloid angiopathy.

3.5. Molecular genetic studies

Neither mutations in MAPT, PGRN, and LRRK2 nor repeat expansion in C9orf72 were found in the proband. Exome

Table 1

<table>
<thead>
<tr>
<th>Affected individuals</th>
<th>Gender</th>
<th>Age at onset (years)</th>
<th>Clinical features or disease course</th>
<th>PET/SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-2</td>
<td>Female</td>
<td>NA</td>
<td>Slowly progressive neurodegenerative disease</td>
<td>Not performed</td>
</tr>
<tr>
<td>II-1</td>
<td>Female</td>
<td>85</td>
<td>Progressive speech difficulty</td>
<td>Not performed</td>
</tr>
<tr>
<td>II-3</td>
<td>Female</td>
<td>NA</td>
<td>Progressive motor neuron dysfunction</td>
<td>Not performed</td>
</tr>
<tr>
<td>II-4</td>
<td>Female</td>
<td>80’s</td>
<td>Language difficulties and cognitive impairment</td>
<td>Not performed</td>
</tr>
<tr>
<td>III-1</td>
<td>Male</td>
<td>Late 60’s</td>
<td>Parkinsonism, language problem</td>
<td>Not performed</td>
</tr>
<tr>
<td>III-4</td>
<td>Female</td>
<td>64 years</td>
<td>Language problems, eye movement problems, parkinsonism, hyperreflexia</td>
<td>99mTc-HMPAO SPECT: reduced uptake $L &gt; R$ hemisphere</td>
</tr>
<tr>
<td>III-6</td>
<td>Male</td>
<td>Early 60’s</td>
<td>Parkinsonism</td>
<td>Not performed</td>
</tr>
<tr>
<td>III-12</td>
<td>Male</td>
<td>53</td>
<td>Parkinsonism, memory impairment (subjective), several falls</td>
<td>Not performed</td>
</tr>
<tr>
<td>IV-12</td>
<td>Male</td>
<td>-a</td>
<td>Parkinsonism and language problems at age 57</td>
<td>$^{11}$C-DTBZ/$^{18}$F-FDG PET: normal</td>
</tr>
<tr>
<td>IV-13</td>
<td>Male</td>
<td>-a</td>
<td>Mild tremor and postural instability at age 58</td>
<td>$^{11}$C-DTBZ/$^{18}$F-FDG PET: normal</td>
</tr>
<tr>
<td>IV-14</td>
<td>Female</td>
<td>-a</td>
<td>Mild rigidity at age 57</td>
<td>$^{11}$C-DTBZ/$^{18}$F-FDG PET: normal</td>
</tr>
</tbody>
</table>

1. left; PET – positron emission tomography; R – right; SPECT – single photon emission computed tomography; DTBZ – dihydrotetrabenazine and FDG – fludeoxyglucose.
2. The individuals did not notice any subjective symptoms.
3. proband.
sequencing in the proband and an additional affected family member excluded mutations in known FTD and ALS-related genes.

4. Discussion

We describe a family with a progressive neurodegenerative disorder presenting with a spectrum of clinical phenotypes. The proband presented with cognitive impairment and asymmetrical levodopa-unresponsive parkinsonism that was accompanied by pyramidal signs. The clinical features were consistent with CBD, and the case fulfills clinical criteria for possible CBD [16]. The brain of the proband showed pathological features consistent with that of CBD, including numerous threads in gray and white matter, ballooned neurons and astrocytic plaques. There were some unusual features, including mild-to-moderate tau pathology in the motor cortex and basal ganglia, regions that are usually severely affected in CBD. The clinical phenotypes of the other affected patients, except for one individual (II-3), were characterized by parkinsonism, cognitive impairment or both. All the cases had an insidious onset and a gradually progressive disease course, which is suggestive of a neurodegenerative process; however, they did not fulfill criteria for specific neurodegenerative disorders based upon the available information, some of it obtained retrospectively.

One of the affected family members (II-3) by history had clinical features of corticospinal tract pathology, which is not a feature of CBD. Intriguingly, globular glial tauopathy (GGT), which is a specific clinical syndrome of GGT is a 3R+4R tauopathy [17–20]. Patients with GGT are clinically heterogeneous and can present with frontotemporal dementia, motor neuron disease, atypical parkinsonism, or a combination of these syndromes. One of the characteristic pathological features of GGT is the presence of tau immunopositive globular oligodendroglial inclusions, which were absent in our case. The combination of the clinical phenotypes of ALS, parkinsonism, and cognitive impairment in this family is also reminiscent of the ALS-parkinsonism/dementia complex of Guam, which is a 3R+4R tauopathy [21]. In addition to the different biochemical composition abnormal tau, the distribution of tau pathology in Guam disease is also different from that seen in our patient. Given that there are genetic factors underlying the conditions of all of the affected family members in this family and taking diversity of clinical phenotypes of CBD patients into account, tauopathy could potentially be the common underlying pathology for this family, but additional autopsies are needed to verify this hypothesis.

We performed PET studies utilizing the 18F-FDG and 11C-DTBZ ligands in three potentially affected family members. PET with 18F-FDG can assess regional glucose metabolism in the brain and can be helpful to physicians in discriminating among patients presenting with corticobasal syndrome from patients manifesting the other parkinsonian syndromes [3,22]. 18F-FDG PET of corticobasal syndrome patients displays a contralateral hypometabolism in the frontal and parietal cortices, as well as subcortical regions including the striatum and thalamus [3,4]. 11C-DTBZ is a presynaptic marker for dopaminergic terminals. 11C-DTBZ PET can detect

Fig. 2. Pathological features of the proband
H&E staining shows moderate loss and gliosis in the mid-frontal cortex (A) and substantia nigra (C). A few ballooned neurons were detected in the frontal cortex (A) with H&E staining. Tau immunohistochemistry with 4-repeat tau antibody revealed neurofilament tangles (NFT), astrocytic plaques, as well as ballooned neurons in the temporal cortex (D), coiled bodies and numerous tau-positive threads in the white matter of the temporal lobe (E), many pretangles and some NFT in the dentate gyrus of the hippocampus (F), and many intracellular and extracellular tangles and numerous tau-positive threads in the CA3 section of the hippocampus (G). Whereas, tau immunohistochemistry with 3-repeat tau antibody showed a few extracellular tangles and threads (H). Immunohistochemistry for neurofilament detected ballooned neurons in the frontal cortex (I).
In conclusion, we identified a novel familial form of parkinsonism, dementia, and motor neuron disease without a known genetic cause. CBD is a rare condition and underlying mechanisms have yet to be elucidated. Identification of new families and discovery of causative genes for these families will advance our understanding of the molecular mechanisms of the disease and eventually will help discover curative therapy. We are further investigating this family by utilizing whole exome sequencing, with the hope that this will uncover the causative gene mutations or genetic risk factors for this family.

Financial disclosure/conflict of interest

Nothing to disclose.

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