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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 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

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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.

Keywords

Cognitive Disorders; Dementia; corticobasal degeneration; genetics; PET; Parkinson's disease/ Parkinsonism

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 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, with astrocytic plaques[7] being the lesion that is 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

Genealogical investigations

Phone calls and interviews with surviving family members were conducted.

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.

Neuroimaging studies

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

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 grams, 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.

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 Columbia/ 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 (Figure 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 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. His face was hypomimic. 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. An individual, **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 maternal grandmother (**I-2**) was reported to have had a slowly progressive neurodegenerative disorder. The mother (**II-1**) was reported to have had progressive difficulties with speech and gait beginning around age 85 years. The maternal aunt (**II-3**) was reported to have ALS and died in her early sixties. The maternal aunt (**II-4**) was reported to have language difficulties 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)

¹¹C-DTBZ PET and ¹⁸F-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 mild decrease of neuromelanin pigmentation. Microscopically, there was subpial gliosis and spongiosis in the neocortical layer II of the mid-frontal (Figure 1A), parietal, and temporal lobes. Ballooned neurons were detected mainly in the fifth and sixth layer of the mid-frontal (Figure 1A), parietal, temporal, motor, cingulate cortexes, and amygdala. The subthalamic nucleus had mild neuronal loss (Figure 1B). The substantia nigra had neuronal loss and gliosis (Figure 1C). Immunohistochemistry for tau showed oligodendroglial inclusions and coiled bodies in the mid-frontal, motor, parietal, and temporal cortexes (Figure 1D), subcortical regions (Figure 1E), and the basal ganglia. Tau-immuno positive astrocytic plaques were prominent in the mid-frontal (Figure 1D) and parietal cortexes, as well as the amygdala. Pretangles were numerous in the dentate gyrus of the hippocampus (Figure 1F). 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 (Figure 1G), whereas tau immunohistochemistry with 3R tau antibody showed only rare extracellular tangles (Figure 1H). Neurofilament-positive ballooned neurons were prominent in the mid-frontal cortexes (Figure 1I) 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 and 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 α -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 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 or 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 motor neuron disease. While motor cortex and corticospinal tract pathology are common, lower motor neuron disease is not a feature of CBD. Intriguingly, globular glial tauopathy (GGT), which is a 4-repeat tauopathy in the same family of tauopathies as CBD, has been reported to occasionally have lower motor neuron disease [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 ^{18}F -FDG and ^{11}C -DTBZ ligands in three potentially affected family members. PET with ^{18}F -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 phenotypes [3, 22]. ^{18}F -FDG PET of corticobasal syndrome patients displays a contralateral hypometabolism in the frontal and parietal cortexes, as well as subcortical regions including the striatum and thalamus [3, 4]. ^{11}C -DTBZ is a presynaptic marker for dopaminergic terminals. ^{11}C -DTBZ PET can detect presynaptic dysfunction earlier than PET utilizing other radioligands [23, 24]. Presynaptic dopaminergic imaging reflects striatal dopamine synthesis, dopamine storage and dopamine transport [23]. The imaging generally shows reduced uptake of radioligands in the striatum in patients with corticobasal syndrome compared with neurologically normal individuals. The three potentially affected individuals showed no detectable abnormalities on PET with ^{18}F -FDG and ^{11}C -DTBZ. Given that PET with ^{11}C -DTBZ for pathologically confirmed CBD cases has never been reported, the reason for the negative studies remains to be resolved. One possible reason for the result is that these individuals were affected by non-inherited forms of parkinsonism, such as drug-induced parkinsonism, non-organic parkinsonism [23], and parkinsonism caused by disconnectivity in the brain as suggested in hereditary diffuse leukoencephalopathy with spheroids [25].

To date, few families in which the proband has pathologically confirmed CBD have been reported (Table 2). Maeda and colleagues[26] described a CBD family, which was updated by Uchihara and Nakayama [11]. Three affected patients were autopsied, and the brain showed typical pathological features of CBD. Interestingly, all three patients had early symptomatic disease onset and short disease duration, which is indicative of strong genetic effects; however, DNA of the patients was unavailable for genetic analysis. Three families have been reported to present familial forms of CBD. Tuite and colleagues[12] reported a seven-generation autosomal dominant family in which 22 individuals suffered from Parkinsonian disorders, including CBD, PSP, and parkinsonism. Two patients who were clinically diagnosed as having corticobasal syndrome were autopsied, and one of them was pathologically diagnosed as having CBD. Jung and colleagues[10] described a three-generation family in which three individuals suffered from neurodegenerative diseases. The proband was clinically and pathologically diagnosed as having CBD, and the proband's mother was clinically diagnosed as having Parkinson's disease, but pathologically was diagnosed with CBD. The sister of the proband was clinically diagnosed as having had primary progressive aphasia, but no autopsy was available. Fekete and colleagues [9] identified a three-generation family in which two individuals were reported to be affected by CBD. Exome sequencing performed in this family revealed mutations leading to possible structural changes in the *MRS2* and *ZHX2* genes, but the pathogenicity of these mutations is still unclear. To date, mutations in several genes have been identified to be associated with patients clinically manifesting corticobasal syndrome or pathologically confirmed CBD. The MAPT G389R mutation[27] was reported to cause corticobasal syndrome; however, there

are no autopsies available. The *PGRN* [28], *LRRK2* [29], and *C9ORF72* [30] mutations have been reported to cause a corticobasal syndrome phenotype. The pathology seen in the cases with *PGRN* mutations is consistently TDP-43 pathology, and an autopsy of the case with the *LRRK2* mutation that clinically presented with corticobasal syndrome has never been reported. The MAPT N410H mutation has recently been discovered in autopsy-proven CBD [2]. We excluded mutations in *MAPT*, *PGRN*, *LRRK2*, *C9ORF72* for this study.

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.

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References

1. Corticobasal degeneration. [cited 2014 2/4] Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=278.
2. Kouri N, Whitwell JL, Josephs KA, Rademakers R, Dickson DW. Corticobasal degeneration: a pathologically distinct 4R tauopathy. *Nat Rev Neurol*. 2011 May; 7(5):263–272. [PubMed: 21487420]
3. Zhao P, Zhang B, Gao S. 18F-FDG PET study on the idiopathic Parkinson's disease from several parkinsonian-plus syndromes. *Parkinsonism Relat Disord*. 2012 Jan; 18(Suppl 1):S60–S62. [PubMed: 22166456]
4. Klaffke S, Kuhn AA, Plotkin M, Amthauer H, Harnack D, Felix R, et al. Dopamine transporters, D2 receptors, and glucose metabolism in corticobasal degeneration. *Move Disord*. 2006 Oct; 21(10):1724–1727.
5. Sawle GV, Brooks DJ, Marsden CD, Frackowiak RS. Corticobasal degeneration. A unique pattern of regional cortical oxygen hypometabolism and striatal fluorodopa uptake demonstrated by positron emission tomography. *Brain*. 1991 Feb; 114(Pt 1B):541–556. [PubMed: 1900728]
6. Blin J, Vidailhet MJ, Pillon B, Dubois B, Feve JR, Agid Y. Corticobasal degeneration: decreased and asymmetrical glucose consumption as studied with PET. *Move Disord*. 1992 Oct; 7(4):348–354.
7. Feany MB, Dickson DW. Widespread cytoskeletal pathology characterizes corticobasal degeneration. *Am J Pathol*. 1995 Jun; 146(6):1388–1396. [PubMed: 7778678]
8. Komori T, Arai N, Oda M, Nakayama H, Mori H, Yagishita S, et al. Astrocytic plaques and tufts of abnormal fibers do not coexist in corticobasal degeneration and progressive supranuclear palsy. *Acta Neuropathol*. 1998 Oct; 96(4):401–408. [PubMed: 9797005]
9. Fekete R, Bainbridge M, Baizabal-Carvallo JF, Rivera A, Miller B, Du P, et al. Exome sequencing in familial corticobasal degeneration. *Parkinsonism Relat Disord*. 2013 Nov; 19(11):1049–1052. [PubMed: 23867865]

10. Jung HH, Bremer J, Streffer J, Virdee K, Spillantini MG, Crowther RA, et al. Phenotypic variation of autosomal-dominant corticobasal degeneration. *Eur Neurol*. 2012; 67(3):142–150. [PubMed: 22261560]
11. Uchihara T, Nakayama H. Familial tauopathy mimicking corticobasal degeneration an autopsy study on three siblings. *J Neurol Sci*. 2006 Jul 15; 246(1–2):45–51. [PubMed: 16540122]
12. Tuite PJ, Clark HB, Bergeron C, Bower M, St George-Hyslop P, Mateva V, et al. Clinical and pathologic evidence of corticobasal degeneration and progressive supranuclear palsy in familial tauopathy. *Arch Neurol*. 2005 Sep; 62(9):1453–1457. [PubMed: 16157754]
13. Kouri N, Carlomagno Y, Baker M, Liesinger AM, Caselli RJ, Wszolek ZK, et al. Novel mutation in MAPT exon 13 (p.N410H) causes corticobasal degeneration. *Acta Neuropathol*. 2013 Oct.:12.
14. Nandhagopal R, Kuramoto L, Schulzer M, Mak E, Cragg J, Lee CS, et al. Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. *Brain*. 2009 Nov; 132(Pt 11):2970–2979. [PubMed: 19690093]
15. Jacova C, Hsiung GY, Tawankanjanachot I, Dinelle K, McCormick S, Gonzalez M, et al. Anterior brain glucose hypometabolism predates dementia in progranulin mutation carriers. *Neurology*. 2013 Oct 8; 81(15):1322–1331. [PubMed: 24005336]
16. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013 Jan 29; 80(5):496–503. [PubMed: 23359374]
17. Ahmed Z, Doherty KM, Silveira-Moriyama L, Bandopadhyay R, Lashley T, Mamais A, et al. Globular glial tauopathies (GGT) presenting with motor neuron disease or frontotemporal dementia: an emerging group of 4-repeat tauopathies. *Acta Neuropathol*. 2011 Oct; 122(4):415–428. [PubMed: 21773886]
18. Fu YJ, Nishihira Y, Kuroda S, Toyoshima Y, Ishihara T, Shinozaki M, et al. Sporadic four-repeat tauopathy with frontotemporal lobar degeneration, Parkinsonism, and motor neuron disease: a distinct clinicopathological and biochemical disease entity. *Acta Neuropathol*. 2010 Jul; 120(1): 21–32. [PubMed: 20140439]
19. Josephs KA, Katsuse O, Beccano-Kelly DA, Lin WL, Uitti RJ, Fujino Y, et al. Atypical progressive supranuclear palsy with corticospinal tract degeneration. *J Neuropathol Exp Neurol*. 2006 Apr; 65(4):396–405. [PubMed: 16691120]
20. Bigio EH, Lipton AM, Yen SH, Hutton ML, Baker M, Nacharaju P, et al. Frontal lobe dementia with novel tauopathy: sporadic multiple system tauopathy with dementia. *J Neuropathol Exp Neurol*. 2001 Apr; 60(4):328–341. [PubMed: 11305868]
21. Kaji R, Izumi Y, Adachi Y, Kuzuhara S. ALS-parkinsonism-dementia complex of Kii and other related diseases in Japan. *Parkinsonism Relat Disord*. 2012 Jan; 18(Suppl 1):S190–S191. [PubMed: 22166431]
22. Coulier IM, de Vries JJ, Leenders KL. Is FDG-PET a useful tool in clinical practice for diagnosing corticobasal ganglionic degeneration? *Movement Disord*. 2003 Oct; 18(10):1175–1178. [PubMed: 14534923]
23. Cummings JL, Henchcliffe C, Schaefer S, Simuni T, Waxman A, Kemp P. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. *Brain*. 2011 Nov; 134(Pt 11):3146–3166. [PubMed: 21810889]
24. de la Fuente-Fernandez R, Schulzer M, Kuramoto L, Cragg J, Ramachandiran N, Au WL, et al. Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. *Ann Neurol*. 2011 May; 69(5):803–810. [PubMed: 21246604]
25. Sundal C, Fujioka S, Van Gerpen JA, Wider C, Nicholson AM, Baker M, et al. Parkinsonian features in hereditary diffuse leukoencephalopathy with spheroids (HDLS) and CSF1R mutations. *Parkinsonism Relat Disord*. 2013 Oct; 19(10):869–877. [PubMed: 23787135]
26. Maeda S, Yokoi S, Isaka K, Numabe T. [Type of familial extrapyramidal disease--cortico-striato-pallido-nigral degeneration (author's transl)]. *Seishin Shinkeigaku Zasshi*. 1973 Oct; 75(10):657–672. [PubMed: 4798818]
27. Rossi G, Marelli C, Farina L, Laura M, Maria Basile A, Ciano C, et al. The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. *Movement Disord*. 2008 Apr 30; 23(6): 892–895. [PubMed: 18307268]

28. Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Grafman J, et al. Corticobasal syndrome associated with the A9D Progranulin mutation. *J Neuropathol Exp Neurol*. 2007 Oct; 66(10):892–900. [PubMed: 17917583]
29. Chen-Plotkin AS, Yuan W, Anderson C, McCarty Wood E, Hurtig HI, Clark CM, et al. Corticobasal syndrome and primary progressive aphasia as manifestations of LRRK2 gene mutations. *Neurology*. 2008 Feb 12; 70(7):521–527. [PubMed: 17914064]
30. Lindquist SG, Duno M, Batbayli M, Puschmann A, Braendgaard H, Mardosiene S, et al. Corticobasal and ataxia syndromes widen the spectrum of C9ORF72 hexanucleotide expansion disease. *Clin Genet*. 2013 Mar; 83(3):279–283. [PubMed: 22650353]

Highlights

- We performed genealogical, clinical, neuroimaging, pathological, and molecular genetic studies on a Family in which the affected individuals are suffered from neurodegenerative disorders.
- The proband of the family had corticobasal degeneration, and the other affected family members had various progressive clinical phenotypes including parkinsonism, dementia, and motor neuron disease.
- Genetic sequencing of DNA from the proband excluded mutations in *MAPT*, *PGRN*, *LRRK2*, and *C9ORF72*.
- We identified a novel familial form of parkinsonism, dementia, and motor neuron disease without known gene mutations.

Figure 1. Pedigrees of a family with atypical parkinsonism and dementia

Standard pedigree symbols were used. Round symbols indicate females; squares indicate males; and diagonal lines indicate that the individual is deceased. Diamonds were used to disguise gender. + indicates individuals with blood specimen were available for DNA sequencing. Numbers within the diamonds indicate the number of siblings. The solid arrowhead indicates the proband. * indicates autopsy patients.

Figure 2. Pathological features of the proband

H&E staining shows moderate loss and gliosis in the mid-frontal cortex (A) and substantia nigra (B), and mild gliosis in the subthalamic nucleus (C). A few ballooned neurons were detected in the frontal cortex (A) with H&E staining. Tau immunohistochemistry with 4-repeat tau antibody revealed neurofibrillary tangles (NFT), astrocytic plaques, as well as ballooned neurons in the temporal cortex (E), coiled bodies and numerous tau-positive threads in the white matter of the temporal lobe (F), many pretangles and some NFT in the dentate gyrus of the hippocampus (G), and many intracellular and extracellular tangles and numerous tau-positive threads in the CA3 section of the hippocampus (H). Whereas, tau immunohistochemistry with 3-repeat tau antibody showed a few extracellular tangles and threads (I). Immunohistochemistry for neurofilament detected ballooned neurons in the frontal cortex (J).

Table 1

Summary of demographics and clinical features of the affected patients in the family V

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

L=left; PET=positron emission tomography; R=right; SPECT=single photon emission computed tomography; DTBZ=dihydrotetabenazine and FDG=fluorodeoxyglucose.

* The individuals did not notice any subjective symptoms;

[‡]=proband.

Table 2
Summary of previously published autopsy-proven genetic form of corticobasal degeneration

Patients whom known mutations were excluded or genetic tests were not performed							
References	Number of autopsied CBD	Suggested mode of inheritance	Gender	AAO (years)	DD (years)	Clinical diagnosis of the other affected family members (pathological Diagnosis,)/ Number of patients	Excluded possible causative gene
Maeda, et al. Uchihara, et al.	3	AD	Female	40	2	Parkinsonism/1	Not performed
			Male	34	3		
			Male	40	3		
Tuite, et al.	1	AD	Female	57	8	CBS (PSP)/1, Parkinsonism/19, PSP/3	<i>MAPT</i>
Jung, et al.	2	AD	Female	54	5	PPA/1	<i>MAPT</i> , <i>PGRN</i>
			Female	61	12		
			Female	68	6		
Fekete, et al.	2	AD	Male	75	5	None	<i>MAPT</i> , <i>PGRN</i> , <i>LRRK2</i>
			Female	64	6		
Present study	1	AD	Female	64	6	Parkinsonism/2, dementia/1, ALS/1, others [*] /2	<i>MAPT</i> , <i>PGRN</i> , <i>LRRK2</i> , <i>C9ORF72</i>
Patients whom known mutations were identified							
References	Number of autopsied CBD	Suggested mode of inheritance	Gender	AAO (years)	DD (years)	Clinical diagnosis of the other affected family members	Causative gene mutation
Kouri, et al.	1	Sporadic	Female	63	4	None	<i>MAPT</i> N410H

AAO=age at onset; AD=autosomal dominant; ALS=amyotrophic lateral sclerosis; CBD=corticobasal degeneration; CBS=corticobasal syndrome; DD=disease duration; PPA=primary progressive aphasia; PSP=progressive supranuclear palsy.

* –patients who presented with progressive disorders, but clinical details were unavailable.