Clinical-pathologic study of biomarkers in FTDP-17 (PPND family with N279K tau mutation)


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Abstract

The objective of this clinical-pathologic study was to identify biomarkers for a pallidopontonigral degeneration (PPND) kindred of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) harboring the N279K tau mutation. Five affected subjects, one at-risk who later became symptomatic, and one at-risk asymptomatic mutation carrier, had abnormal 18fluorodeoxyglucose PET demonstrating asymmetric temporal lobe hypometabolism. All except the asymptomatic mutation carrier had abnormal brain MRI. Parkinsonism, myoclonus, anosmia, insomnia, speech, and autonomic dysfunction were identified. Autopsy of six affected subjects showed frontotemporal degeneration with extensive tauopathy. Further studies of FTDP-17 patients are needed to replicate these findings.

Keywords: Clinical-pathologic; Biomarker; FTDP-17; Genetics; Dementia; Parkinsonism; Neuroimaging; Positron emission tomography; Neurodegeneration; Tauopathy

1. Introduction

Tau is an intraneuronal microtubule-binding protein that plays an important role in microtubule assembly and stabilization, axonal transport, the integrity of neuronal function, and neuronal survival [1]. Although originally described as a familial disease with abnormal tau [2], the term tauopathy now refers to a large group of

Abbreviations: EEG, electroencephalographic, electroencephalography; FD, 6-[18F]fluoro-L-dopa; FDG, 18fluorodeoxyglucose; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; MSLT, multiple sleep latency test; MRI, magnetic resonance imaging; ND, not done; PET, positron emission tomography; PPND, pallidopontonigral degeneration; REM, rapid eye movement; sEMG, combined EEG-surface electromyographic recording

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neurodegenerative disorders [3], sporadic as well as familial, in which functional abnormalities of the tau protein are thought to be central to the pathogenesis of these conditions. Recent advances in the understanding of some familial forms of tauopathy may have implications for improved treatments for the more common sporadic tauopathies [4]. Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is a familial form of tauopathy that is linked to mutations in the MAPT gene on chromosome 17. This study focuses on one of the most common and well-studied forms of FTDP-17, pallidopontonigral degeneration (PPND), a familial autosomal dominant neurodegenerative disease with complete penetrance, caused by the N279K mutation [5,6]. PPND presents with insidious onset of parkinsonism and dementia in adults who are typically in their fourth decade of life. It is a multisystem disorder, with neurodegeneration thought to begin about a decade before symptoms become apparent on clinical examination [7].

Given the increasing number of persons with neurodegenerative disorders, finding biomarkers for these diseases is important. Identification of an ideal biomarker would improve patient care by facilitating early diagnosis [8]. In practice, however, predicting who will eventually develop symptoms among persons at risk for developing neurodegenerative disease remains difficult. This is true even for familial forms of neurodegeneration, as many genetic mutations have yet to be identified and their mode of inheritance remains unclear. To our knowledge, no single nongenetic biomarker of FTDP-17 has been recognized. In this clinical-pathologic study of affected and at-risk subjects from a family with PPND, we aim to identify biomarkers of disease in unaffected at-risk subjects.

2. Methods

2.1. Subjects

Ten subjects were identified from a well-described family affected by PPND [5]. Five affected family members and five (of 74 potentially available) unaffected at-risk family members volunteered to undergo detailed evaluations for research purposes. All subjects for this study were selected on the basis of genealogic characteristics (specifically, only persons who were family members of this particular family were considered for inclusion on this study) and not genetic characteristics (persons were not included based on whether or not they had a particular genetic mutation). This approach was used in order to respect the family members who did not wish to know of their mutation carrier status.

The Mayo Foundation Institutional Review Board approved the study protocol. All subjects signed an informed consent document to participate in this study. Permission for brain autopsy at time of death was obtained.

2.2. Clinical evaluations

All ten subjects underwent clinical evaluations in 2000 at Mayo Clinic, which included a structured history and physical examination, with emphasis on the neurologic examination. Each subject was examined in person by subspecialty neurologists, including two movement disorder neurologists (R.J.U. and Z.K.W.), a dementia neurologist (Z.A.), an autonomic neurologist (W.P.C.), and a clinical electrophysiologist (J.N.C.), as well as a psychiatrist and sleep specialist (S.C.L.).

Standardized clinical tests, scales, and staging tools were used for each subject. Motor assessment included the Unified Parkinson Disease Rating Scale [9], a modified Hoehn and Yahr Staging Scale [10], and the Schwab and England Scale [10]. Cognitive status was assessed by neuropsychological testing, including the Mini-Mental State Examination [11], an abbreviated version of the Boston Naming Test [12], a frontal lobe assessment battery [13], and a modified version of the Hachinski Scale [14], and has been described elsewhere [15a]. Mood was assessed with the Beck Depression Inventory-II. A standard speech and voice sample [15b] was recorded digitally for acoustic and perceptual analysis (J.M.L.). Finally, subjects underwent standardized olfactory testing [16], with 40 different stimuli used.

The mean age of symptom onset was 43 years, with a range of 32–58 years, and mean disease duration was 8 years [17]. Study subjects were classified into four clinical stages [18]. Briefly, patients with stage 1 present with mild to moderate parkinsonism (particularly bradykinesia and rigidity), mild cognitive impairment, and personality, behavioral, or mood (depression) changes. Stage 2 is characterized by worsening symptoms of parkinsonism with development of postural instability, progression of cognitive impairment, and other signs, including pyramidal signs and eye movement abnormalities. Stage 3 involves progression of these features, with dysphagia and weight loss. Stage 4, the terminal stage, is defined by severe parkinsonism with loss of mobility, contractures, severe dementia, urinary incontinence, and complete loss of independence. Patients with no evidence of PPND were categorized as stage 0.

2.3. Brain imaging

All subjects underwent magnetic resonance imaging (MRI) on a GE Medical Systems Horison LX 1.5-T scanner, with axial three-dimensional spoiled-gradient-recalled-echo, 22-cm field of view, 256 × 256 acquisition matrix, 3/35 TE/TR, and 45° flip angle (GE Medical Systems, Waukesha, Wisconsin). MRI acquisition allowed for anatomic co-registration with positron emission tomographic (PET) images. Five affected and four at-risk subjects had PET scans with 18fluorodeoxyglucose (FDG). Subjects were in a fasting state, with eyes open, in a quiet, moderately lit room. Approximately 5 mCi of FDG (PETnet Pharmaceutical Services, Inc, Knoxville, Tennessee) was injected and allowed to circulate for 45 min before imaging.

Image analysis was accomplished using Analyze AVW 3.0 software (Mayo Foundation for Medical Education and Research, Rochester, Minnesota) running on a Sun Sparc II Solaris 2.5.1 (Sun Microsystems, Santa Clara, California) Unix system (The Open Group, San Francisco, California) workstation. MRI and PET datasets were transferred via a digital imaging system (DICOM, National Electrical Manufacturers Association, Rosslyn, Virginia) to the Unix workstation. Data sets were imported into Analyze, reformatted, and aligned. Axial, sagittal, and coronal coregistered slices were qualitatively evaluated for alignment of MRI and PET data. Cerebellar regions of interest for each subject were placed, allowing tissue–cerebellar ratios to be calculated. Cerebellar ratios were compared with a control population who were undergoing whole-body PET imaging for non-central nervous system reasons and had no evidence of central nervous system disease by history. All scans were interpreted by the same neuroradiologist (R.J.W.).

2.4. Neurophysiologic testing

All subjects underwent electroencephalography (EEG) and polysomnography [19], and the results were reviewed by a sleep specialist (S.C.L.). Further, all underwent detailed autonomic testing, including thermoregulatory sweat testing, quantitative sudomotor axon reflex test, sympathetic skin response, heart rate response to deep breathing, and Valsalva maneuvers [20]. Combined EEG-surface electromyographic recording (sEMG) was performed (by J.N.C.) during rest and various muscle activation tasks.
2.5. Genetic testing and mutation carrier status

All subjects provided blood samples for genetic testing. Testing for the N279K mutations on the MAPT gene on chromosome 17 was performed (by M.L.H.) as previously described [6]. The MAPT haplotype [21] and apolipoprotein E genotyping [22] were determined, using standardized techniques.

Before the affected subjects were invited to participate in this study, mutation carrier status was confirmed by clinical genetic testing, which was then confirmed by additional research testing. For at-risk subjects, the examiners were blinded to carrier status before conducting the evaluations and analyses of data. Later, the carrier status of at-risk subjects were unblinded to the examiners. To respect the wishes of the at-risk subjects not to be informed of their mutation carrier status, the sex and age of each subject has not been provided in this report, and some ages have been provided as ranges (Table 1).

2.6. Neuropathological data

Six subjects enrolled in the study (cases 1–6) died by the time of this manuscript preparation, and all underwent a brain autopsy. A standardized detailed neuropathological assessment (by D.W.D.) included routine histological examination (with H&E and thioflavin-S fluorescent microscopy), as well as immunostaining with a phospho-tau monoclonal antibody (CP13 from Peter Davis, PhD, Albert Einstein College of Medicine, NY). In selected cases, Gallyas–Braak silver staining was also performed.

3. Results

Results concerning the clinical, neuroimaging, neurophysiologic, and genetic data are summarized in Table 1, and neuropathological data are shown in Table 2.

Table 1
Clinical, neuroimaging, neurophysiologic, and genetic features of the ten PPND family members

<table>
<thead>
<tr>
<th>Feature</th>
<th>Affected individuals</th>
<th>At-risk individuals</th>
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<tbody>
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<td></td>
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<td>45</td>
</tr>
<tr>
<td>Disease stage³</td>
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<tr>
<td>UPDRS subscale</td>
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<td>+</td>
</tr>
<tr>
<td>Dystonia</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Eye movements</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dementia</td>
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<td>–</td>
</tr>
<tr>
<td>Personality changes</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Anosmia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Speech changes</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brain FDG PET</td>
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<td>+</td>
</tr>
<tr>
<td>MSLT</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Polysomnogram</td>
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<td>+</td>
</tr>
<tr>
<td>Near reflex</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Autonomic tests</td>
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<td>+</td>
</tr>
<tr>
<td>Myoclonus</td>
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<td>–</td>
</tr>
<tr>
<td>EMG</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Tau haplotype H1/H1</td>
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<td>H1/H1</td>
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</tbody>
</table>

ApoE, apolipoprotein E ε allele; EMG, electromyography; FDG PET, 18fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; MSLT, Multiple Sleep Latency Test; ND, not done; PPND, pallidopontonigral degeneration; UPDRS, Unified Parkinson Disease Rating Scale.

²Age range provided to preserve confidentiality of subjects.

³See Methods for description of clinical stages of PPND.

+ means that the clinical feature is present or a test result is abnormal; – means that the clinical feature is absent or a test result is within normal limits or unremarkable.

3.1. Clinical features

Affected subjects were in stage 1, 2, or 3 of the disease and all had some degree of parkinsonism and cognitive or behavioral changes. Unaffected subjects were asymptomatic at the time of testing and were categorized as stage 0. However, within 8 months of testing, one of these unaffected subjects (case 6) developed initial signs of disease, consisting of bradykinesia, severe depression, and social withdrawal. About 2 months later, she had marked memory impairment resulting in inability to perform her job, and another 2 months later, she was placed on levodopa/carbidopa to control bradykinesia. Over these 4 months, she had clearly converted to stage 1 of PPND. Genetic testing confirmed the presence of the N279K mutation. The disease progressed rapidly, and she died about 1–1/2 years later. A brain autopsy was performed (see below). To date, the other four at-risk subjects, including one mutation carrier, remain asymptomatic.

Neuropsychological testing of affected subjects showed a pattern of early frontal executive dysfunction and three subjects met criteria for dementia, two of whom had a pattern characteristic of a frontotemporal dementia. Cognitive impairment can precede the onset of parkinsonism by two years, and impaired letter fluency may be a useful marker of conversion to disease (case 6) [15a].

Nine of ten subjects could be evaluated for smell perception. Five affected subjects reported anosmia, but in
one subject (case 5), this was determined on the basis of the patient’s history. One unaffected mutation carrier (case 6) reported anosmia, but the other four unaffected subjects, including one mutation carrier (case 9), did not. Analyses of speech samples revealed that affected subjects had impaired voice amplitude control and modulation, with intermittent vocal tremor and high-frequency vocal flutter. Speech was characterized by reduced fundamental frequency variation (monotonicity) in connected speech, reduced voice loudness, speech slowing, and consonant imprecision [15b]. Three asymptomatic subjects presented with abnormal speech findings and two of these subjects were later identified as mutation carriers (cases 6 and 9), suggesting that speech changes may appear very early in the disease.

3.2. Brain imaging

Structural imaging, consisting of brain MRI studies (Fig. 1), showed a similar pattern of atrophy of temporal regions in all affected subjects and one unaffected who shortly thereafter developed the disease (case 6). No incidental findings (e.g., tumor) were noted.

FDG-PET scans were performed in all but one subject (case 10) who missed the appointment and was unable to reschedule it. Functional imaging results were abnormal in all affected subjects and in two of the four unaffected at-risk subjects, both mutation carriers (cases 6 and 9), as shown in Fig. 1. The PET studies showed hypometabolism of the temporal lobe with some asymmetry, and studies of two affected subjects (cases 1 and 2) and two at-risk mutation carriers (cases 6 and 9) showed medial temporal lobe involvement. In addition (Fig. 2), hypometabolism of the frontal lobes was present in all affected subjects and one at-risk subject (case 9) and of the parietal lobes in the most-affected subjects (cases 2–4) and one at-risk (case 9). Other regions were variably involved in the affected subjects (two had left thalamic changes) and in the at-risk subjects (two had basal ganglia changes). Overall, findings suggested that temporal lobe hypometabolism may predate clinical manifestations of the disorder, as two at-risk subjects who were later shown to carry the genetic mutation for PPND had abnormalities on functional imaging.

3.3. Neurophysiology

Sleep studies [19] showed preservation of atonia during rapid eye movement (REM) sleep, and no parasomnias or excessive daytime sleepiness in all 10 subjects. However, non-REM sleep initiation and maintenance were disrupted in all affected subjects. Severe insomnia was noted in two of the most advanced cases. Suboptimal sleep efficiency due to difficulty in sleep initiation and maintenance was observed in one subject who later became symptomatic (case 6). Periodic leg movements were increased in three affected subjects (cases 1-3) and one at-risk subject who had an upper airway resistance syndrome (case 8).

All affected subjects reported autonomic dysfunction, with sialorrhea, hyperhidrosis, urinary frequency or incontinence, thermal intolerance, or dryness of the eyes or mouth, but none reported orthostatic hypotension. Testing showed mild to moderate abnormalities in all affected subjects, in keeping with preganglionic dysfunction: impaired cardiovagal function and abnormal pupillary near-responses were noted. The degree of autonomic dysfunction correlated with disease duration and severity. The three oldest asymptomatic at-risk subjects, two of whom were mutation carriers, had abnormal sudomotor function, suggesting that autonomic testing may be a useful marker of disease onset [20].

Movement disorder neurophysiology [23] showed that myoclonus was present in three affected subjects and one at-risk mutation carrier but not the other (Fig. 1). Affected subjects had predominant upper extremity myoclonus, with small amplitude multifocal action-induced movements.

3.4. Genetic testing

Testing confirmed that all affected subjects had the missense N279K mutation in exon 10 of the MAPT gene. Further, two at-risk subjects, cases 6 and 9, had the same genetic mutation, and case 6 later developed the disease. Results for haplotype H1/H1 and apolipoprotein E genotyping are shown in Table 1.

3.5. Neuropathology

Between 2002 and 2006, the five affected subjects (cases 1–5) and one who was unaffected at the time of the clinical evaluation but became symptomatic about one year later (case 6, see above) died and all underwent a brain autopsy. Neuropathological data are presented in Table 2 and Figs. 3 and 4. In these six subjects, the mean age at death was 52.5 years and mean duration of illness 6.8 years.
Fig. 1. FDG-PET findings, corresponding MRI, and sEMG recording of left wrist extensor muscle activation in subjects with and without PPND (studies were conducted on the same day or the following day). Case 5, an affected subject. (A) Axial PET shows moderately reduced temporal lobe tracer uptake and metabolism (arrows). (B) Moderate to severe atrophy on corresponding MRI (arrows). (C) Difficulty in activation shows low-amplitude activity in the first second of the EMG recording. When activation ensues in the last second, a train of myoclonus EMG discharges is seen. Case 6, an at-risk mutation carrier who converted to affected status 8 months after completion of this study. (D) Axial PET shows mildly reduced temporal lobe tracer uptake and metabolism (arrows). (E) Mild atrophy on corresponding MRI (arrows). (F) Oscillating tremor EMG discharges are seen, and the amplitude of discharges vary. Case 9, an at-risk mutation carrier who remains asymptomatic to date. (G) Axial PET shows mildly reduced temporal lobe tracer uptake and metabolism (arrows). (H) Normal corresponding MRI. (I) Trains of myoclonus EMG discharge interrupt the EMG activation. Case 7, an at-risk subject who was not a mutation carrier. (J) Axial PET image at the level of the temporal lobes shows normal tracer uptake and metabolism (arrows). (K) Normal corresponding MRI. (L) Normal tonic EMG activation.
Findings were similar in all six cases, which all had a pathologic diagnosis in keeping with frontotemporal degeneration with extensive tauopathy (Table 3). On gross examination, there was mild cortical atrophy, most pronounced in medial temporal lobes (Fig. 3A, B), amygdala, thalamus, and subthalamic nucleus. The substantia nigra showed decreased pigmentation. Superficial spongiosis and gliosis at the gray/white matter junction were present in the frontal and temporal lobes (Fig. 4C), and there was neuronal loss and gliosis in the hippocampus, subthalamic nucleus, and substantia nigra (Fig. 4E). Ballooned neurons were seen in frontal, temporal, and parietal lobe. Almost no senile plaques were identified with thioflavin-S fluorescent microscopy, but neurofibrillary tangles were selectively detected with silver stain in the basal nucleus of Meynert (Fig. 4D). The olfactory bulbs showed signs of severe atrophy (Fig. 4G).

Tau immunohistochemistry of the brains and spinal cords revealed granular cytoplasmic staining of neuronal perikarya consistent with pre-tangles, cell processes consistent with...
with neuropil threads (Fig. 4A, B, H), and oligodendroglial cells (coiled bodies). The severe tau burden seen on gross examination of the medial temporal lobe (Fig. 3B) was consistent with atrophy of the same region visible on macroscopy (Fig. 3A) and neuroimaging (Fig. 1). The gross examination of tau immunostained slides of the sensorimotor region revealed a clear demarcation between strong tau immunoreactivity of the motor cortex and weak reactivity of the sensory cortex (Fig. 3C), further confirmed microscopically (Fig. 4B). In the substantia nigra and the locus ceruleus, the tau deposits formed so-called globose tangles (Fig. 4F). Tau pathology was also evident in the spinal cords, especially in the anterior horns (Fig. 4H), however tau deposits were also seen in the posterior horns and intermediolateral nucleus. Although Onuf’s nucleus was unremarkable on routine examination (Fig. 4I), tau immunohistochemistry revealed few positive neurons. Diffuse microglial/macrophage reactivity in the corticospinal tracts of the spinal cord was noted.

4. Discussion

This clinical-pathologic study presents detailed data on members of a family affected by PPND, a common form of FTDP-17. We examined five affected and five asymptomatic at-risk subjects, using clinical, neuroimaging, and neurophysiologic testing. Affected persons have a dementing parkinsonian syndrome, with impairment on neuropsychological tests of frontal lobe function, atrophy of temporal lobes on MRI, physiologically demonstrated increased periodic limb movements in sleep, poor sleep...
efficiency with insomnia, dysarthria, abnormal autonomic function testing, and upper extremity-predominant myoclonus. Six family members, five affected and one at-risk who became symptomatic, died and all had neuropathological evidence of frontotemporal degeneration with extensive tauopathy.

This study provides valuable information concerning potential biomarkers of PPND. In the absence of knowledge about genetic mutation carrier status, FDG-PET studies may identify persons at risk for PPND who later become symptomatic. Two at-risk subjects, who were found to be mutation carriers, one of whom became symptomatic, had FDG-PET studies showing abnormalities in keeping with the findings observed in the affected subjects, with frontotemporal hypometabolism. Other possible markers of disease in at-risk persons include cognitive impairment, anosmia and speech changes, temporal atrophy on the MRI scan, sleep disturbance, sudomotor dysfunction, and myoclonus. The wide range of abnormal test results reflects the multisystem nature of this neurodegenerative disease. An abnormal PET result accompanied by other findings may be useful in identifying a person likely to develop the disease. However, currently, the best single test to predict disease occurrence remains genetic testing.

As the older segment of the population expands [24], the number of persons with neurodegenerative diseases is increasing. Identifying biomarkers of neurodegenerative diseases is a priority [25], especially now that treatment options are becoming available and may be offered earlier in the course of disease. An ideal biomarker would be an in vivo estimate of disease processes, reproducible, noninvasive, safe, and affordable [8]. In addition to facilitating early diagnosis and possibly improving care of persons at risk for disease, the study of biomarkers of genetic diseases, such as PPND, may have wider implications: these biomarkers may be useful for more common neurodegenerative diseases, such as sporadic forms of frontotemporal dementias, or other neurodegenerative disorders, such as Alzheimer’s disease. This and other work may contribute to identifying biomarkers related to neurodegeneration. This identification is particularly relevant, because no genetic or other biomarker tests are currently available for most forms of neurodegeneration.

Neuroimaging, particularly functional imaging, is a plausible biomarker of PPND. A previous study [7] examined 6-[18F]fluoro-L-dopa (FD)-PET studies in 12 asymptomatic at-risk subjects from a PPND family, including cases 1, 4, and 6 from this study (before they became symptomatic), and four symptomatic subjects, including one subject involved in this study (case 5). FD-PET studies were useful to demonstrate reduced dopaminergic function in asymptomatic subjects with positive genetic linkage, with such subjects expected to develop symptomatic disease more than an average of 10 years later. Subsequent studies have confirmed the utility of PET scanning in PPND [26,27]. FDG-PET studies are increasingly used in the evaluation of patients presenting with a progressive dementia syndrome, particularly in cases that are atypical for Alzheimer’s disease. Specifically, functional imaging may be useful in distinguishing Alzheimer’s disease from frontotemporal dementia [28], for which the pattern of abnormality is similar to that seen in PPND, with early, often asymmetric, frontal and temporal hypometabolism [29]. Recently, the cost of PET imaging has been approved for coverage by Medicare when used for the diagnosis or management of suspected cases of frontotemporal dementia. Whether PET imaging can reliably detect asymptomatic carriers of the PPND mutation, and distinguish PPND from other causes of frontotemporal dementia, will need to be examined in future studies.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
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<td>7</td>
<td>8</td>
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<tr>
<td>Tau pathology</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sup/mid-frontal gyrus</td>
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</table>

*Semi-quantitative measure of tau severity: ‘’+’’ is weak, ‘’++’’ is moderate, ‘’+++’’ is strong, ‘’ND’’ is not done.*
A biomarker of neurodegeneration should be validated in cases confirmed by neuropathology [8]. Whether FDG-PET imaging proves to be a useful biomarker of PPND remains to be demonstrated in a study with a larger number of at-risk subjects who undergo brain autopsy. Two at-risk subjects in this study (cases 6 and 9) who were found to be mutation carriers, had abnormal FDG-PET, suggesting that the PET findings correlate with the disease. Further, neuropathologic data became available in six of the 10 subjects presented here, including five subjects affected by PPND (cases 1–5) and one initially asymptomatic at-risk subject who developed the clinical features of the disease (case 6). The neuropathologic examination of these six brains showed findings similar to those previously described in PPND, with ballooned neurons in neocortical and subcortical regions and abundant tau inclusions in neuronal and glial cells [5,30]. The accumulation of abnormally phosphorylated tau appears central to these disorders, now referred to as tauopathies. Other tauopathies include corticobasal degeneration and progressive supranuclear palsy, both of which share clinical and pathologic features with PPND [3,30–32]. In this study of PPND, neuroimaging findings observed on MRI (atrophy) and FDG-PET (hypometabolism) appear to correspond to pathological changes of the disease, particularly in the hippocampus (Figs. 1 and 3) and posterior frontal lobe (Fig. 2), such as shown in case 5. In addition, several clinical features may be attributable to changes found on pathology. Cognitive impairment corresponds to hippocampal and basal nucleus changes, behavioral and language dysfunction to frontal lobe changes, and parkinsonism to substantia nigra and basal ganglia changes. Olfactory bulb atrophy contributes to anosmia. Sleep disturbances may be due to locus ceruleus and other brain stem pathology. The myoclonus may be either cortical (suggested by action myoclonus) or spinal (cervical spinal cord) in origin. Pyramidal signs can be attributed to changes in the spinal cord, possibly secondary to corticospinal tract involvement originating in the motor cortex. Autonomic dysfunction corresponds to intermediolateral nucleus of the spinal cord changes, and urinary incontinence to involvement of Onuf’s nucleus. The thorough neuropathologic examination of these cases allow for a better understanding of the clinical and neuroimaging features of PPND, and contributes to examining the value of potential biomarkers of this disease.

The genetic aspects of frontotemporal dementia are continuing to be explored. In this study of a familial form of frontotemporal dementia, we found that four of the 10 family members, and specifically four of the seven mutation carriers, had one apolipoprotein E ε4 allele. This suggests that this may be an over-representation of this allele compared to the frequency observed in the general population. The frequency in our study sample is similar to that seen in patients with Alzheimer’s disease. Whether or not there is an increased frequency of the apolipoprotein E ε4 allele in persons with PPND will need to be further explored in a larger study sample, and the implications of this remain to be elucidated.

This study has several strengths. It provides detailed clinical, neuroimaging, neurophysiologic, and neuropathologic data in affected and at-risk subjects from a family with PPND. Further, of the at-risk subjects, two were found to be mutation carriers, thus providing a valuable source of data to examine potential predictive biomarkers of symptomatic disease in asymptomatic subjects. In addition, this study identified a potentially useful biomarker of PPND: PET scans are noninvasive and safe and appear to correlate with genetically proven and neuropathologically confirmed cases. FDG-PET imaging, in combination with other clinical tests discussed in this study, may be used in the evaluation of asymptomatic at-risk subjects in whom genetic testing is not available. Finally, this study may provide useful insight into potential biomarkers for non-familial frontotemporal and other dementias.

Our study also has important weaknesses. Only a small number of subjects were tested, raising the possibility that findings were spurious. The utility of FDG-PET scanning as a biomarker in a larger sample of at-risk subjects needs to be examined. In addition, because the genealogically at-risk participants wished to remain blinded to mutation carrier status, we were not able to select asymptomatic subjects who had the genetic mutation as the comparison group. This limited our ability to test for potentially useful biomarkers, as three of the five at-risk subjects remain asymptomatic and are not mutation carriers. Nevertheless, the study benefited from inclusion of at least two at-risk subjects who were mutation carriers, providing useful data on presymptomatic features of the disease.

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References


