Familial Progressive Supranuclear Palsy

Detection of Subclinical Cases Using ¹⁸F-Dopa and ¹⁸Fluorodeoxyglucose Positron Emission Tomography

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Background: Progressive supranuclear palsy (PSP) is generally considered to be a sporadic disease; however, occasional cases of familial PSP have been described. The rarity of reports of familial PSP may be attributed in part to an inability to detect subclinical disease in affected relatives who subsequently die before symptoms clinically develop.

Objective: To study regional cerebral dopaminergic function and glucose metabolism in members of 2 large kindreds with familial PSP to identify subclinical cases.

Methods: Three clinically affected members from the 2 PSP kindreds were scanned with both ¹⁸F-dopa and ¹⁸fluorodeoxyglucose (¹⁸FDG) positron emission tomography (PET). Fifteen asymptomatic first-degree relatives were scanned with ¹⁸F-dopa PET; 10 of them also underwent a second PET study with ¹⁸FDG.

Results: All 3 clinically affected PSP patients showed a significant reduction in caudate and putamen ¹⁸F-dopa uptake along with a significant reduction in striatal, lateral, and medial premotor area and dorsal prefrontal cortex glucose metabolism. In 4 of the 15 asymptomatic relatives, caudate and putamen ¹⁸F-dopa uptake was 2.5 SDs lower than the normal mean. These 4 subjects and a fifth asymptomatic relative with normal ¹⁸F-dopa uptake showed a significant reduction of cortical and striatal glucose metabolism in a pattern similar to that of their affected relatives.

Conclusion: ¹⁸F-dopa and ¹⁸FDG PET allowed us to identify 5 cases with subclinical metabolic dysfunction among 15 subjects (33%) at risk for PSP, suggesting that this approach is useful for characterizing the pattern of aggregation in PSP kindreds.

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PROGRESSIVE supranuclear palsy (PSP) is a late-onset neurodegenerative disease characterized by supranuclear vertical gaze palsy, postural instability, rigidity, bulbar dysfunction, and dementia with the variable presence of pyramidal and cerebellar signs.¹,² It is usually considered a sporadic disorder, even though a few familial, pathologically proven PSP cases have been reported.³ In a recent article concerning PSP kindreds from Europe and North America, 12 probands with typical clinical PSP features have been described.³ Thus, the apparent rarity of familial PSP may reflect the difficulty in recognizing PSP cases in epidemiological surveys. In particular, atypical presentations of PSP cases may hinder accurate phenotypic assignment, and mortality owing to other diseases may be responsible for a censoring effect with subclinically affected relatives dying before symptoms develop.

Positron emission tomography (PET) has proven to be a reliable method for detecting in vivo subclinical dysfunction in degenerative diseases.⁴⁻⁶ ¹⁸F-dopa PET studies have shown that 25% of asymptomatic adult relatives of patients with familial Parkinson disease (PD) and 55% of elderly asymptomatic co-twins of PD patients show subclinical dopaminergic nigrostriatal dysfunction.⁶⁻⁸ ¹¹C-raclopride PET revealed that 50% of asymptomatic adult carriers of the Huntington disease IT15 gene had significant reductions in striatal dopamine D₂ receptor binding.⁹ In this study we used ¹⁸F-dopa and ¹⁸fluorodeoxyglucose (¹⁸FDG) PET to investigate regional cerebral dopaminergic function and glucose metabolism in clinically affected patients and their asymptomatic relatives from 2 kindreds with familial PSP. Our aim was to determine the prevalence of subclinical cases with disease.
SUBJECTS AND METHODS

We studied 2 unrelated kindreds in which PSP was present across several generations. The members of these families were referred to our PET Centre from the Movement Disorder Clinics at the National Hospital for Neurology, Queen Square, London, England (kindred 1) and from the Fundacion Jimenez Diaz, Avenida de los Reyes Catolicos, Ciudad Universitaria, Madrid, Spain (kindred 2). One of the 2 original probands (kindred 2) had died by the time of this study, and postmortem analysis showed typical PSP neuropathological tangle disease. In the antecedent relatives, the diagnosis of PSP was based on review of hospital records.

The diagnosis of possible or probable PSP was made according to the National Institute of Neurological Disorders and Stroke PSP society criteria.° Three affected subjects (2 from kindred 1; 1 from kindred 2) had an akinetic-rigid syndrome poorly responsive to levodopa with onset at age 33, 60, and 70 years, respectively; 2 had a supranuclear down-gaze palsy, whereas the third had slowing of vertical saccades and prominent postural instability. All 3 PSP subjects had axial rigidity, and 2 had a pseudobulbar palsy. Two of the 3 patients had mild to moderate cognitive impairment of frontal type. (For more clinical details see reference 4.) To establish the pattern of dopaminergic and metabolic dysfunction in these families, we studied the 3 clinically affected members with 18F-dopa and 18FDG PET.

All asymptomatic first-degree adult relatives aged 40 years or older were asked to participate in the study. Fifteen subjects agreed to undergo PET scanning with both 18F-dopa and 18FDG. All 15 relatives underwent 18F-dopa PET, and 10 of them also underwent 18FDG PET. Of the other 5 that did not have 18FDG, 3 could not be rescanned for technical reasons, and 2 subjects refused to have a second scan because they experienced claustrophobia during the first scan.

The 15 asymptomatic relatives had no history of neurological illness and had not taken drugs known to affect the dopaminergic system. At the time of scanning, all underwent a full neurological examination. Fourteen subjects had no signs or symptoms of neurological disease, while 1 subject, aged 68 years (kindred 2, III.3), had an isolated postural hand tremor. The characteristics of these 15 subjects are detailed in Table 1B.

SCANNING PROTOCOLS

Permission for these studies was obtained from the Ethics Committee of the Hammersmith Hospitals Trust, London. Approval to administer radio-labeled ligands was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom. Written consent was obtained from all subjects after a full explanation of the procedure.

The PET studies were performed using a camera at the Medical Research Council, Cyclotron Building, Hammersmith Hospital, London (ECAT 953B; CTI Inc, Knoxville, Tenn). This camera acquired data simultaneously from 31 consecutive transaxial planes (slice separation, 3.4 mm with an average in-plane resolution of 6 mm full width at half maximum). Scanning was performed with the orbitomeatal line parallel to the detector rings. A 10-minute transmission scan, using a retractable 68Ga/68Ge ring source, was performed prior to the acquisition of the emission data to correct for tissue attenuation.

18F-Dopa Scans

Prior to 18F-dopa injection, subjects were given oral carbidopa, 100 mg, 1 hour before and 50 mg 5 minutes before the study to block peripheral aromatic amino acid decarboxylase. A mean dose of 4.4 mCi (163 MBq) of 18F-dopa was infused into each subject intravenously over 30 seconds, and the dynamic emission data were acquired in 3-dimensional (D) mode as 25 time-frames over 95 minutes.

18FDG Scans

A mean dose of 4.7 mCi (174 MBq) of 18FDG was administered to each subject by intravenous infusion over 30

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RESULTS

CLINICALLY AFFECTED RELATIVES

18F-Dopa

Mean 18F-dopa caudate and putamen Ki values (0.0051±0.001 min−1 and 0.0049±0.008 min−1) were significantly reduced (P<.001) in the 3 PSP relatives compared with normal subjects (0.010±0.0010 min−1 and 0.0102±0.009 min−1) (Figure 1).

18Fluorodeoxyglucose

The SPM analysis revealed areas of significantly reduced 18FDG uptake in bilateral lateral and medial prefrontal areas (areas 6 and 8) (x, y, z=−4, 20, 8; z score, 4.86), and bilateral striatum (x, y, z=−12, −8, 4; z score, 6.46; and x, y, z=−8, −10, 4; z score, 6.32) (Figure 2) in the PSP patients compared with controls. Increases in 18FDG uptake were not found in any location.

ASYMPTOMATIC MEMBERS

18F-Dopa

Four of the 15 asymptomatic relatives had 18F-dopa caudate and putamen uptake values that were 2.5 SDs lower than the normal mean (Figure 1). One subject was from kindred 1, and 3 subjects were from kindred 2 (Figure 3).

18Fluorodeoxyglucose

The comparison of individual scans for each asymptomatic relative vs the control group identified 5 subjects with areas of significantly decreased regional glucose uptake.
Four of them were also subjects with reduced striatal 18F-dopa K<sub>i</sub> values. In these 4 subjects, we found cortical and subcortical reductions of 18F-FDG uptake similar to those found in their affected relatives. A fifth asymptomatic relative, with normal striatal 18F-dopa uptake, showed a reduction of 18F-FDG uptake in the lateral premotor cortex and dorsal prefrontal cortex (x, y, z = 40, −22, 30; maximal z score, 3.17; and x, y, z = −46, −54, 8; maximal z score, 3.84, respectively).

The voxel-by-voxel analysis applied to these 5 asymptomatic members as a group showed significant decreases in 18F-FDG uptake in bilateral lateral and medial premotor areas (x, y, z = −30, −14, 56; z score, 5.31; and x, y, z = −10, −6, 52; z score, 4.24), right dorsal prefrontal cortex (x, y, z = −46, −54, 8; z score, 5.42) and bilateral striatum (x, y, z = −6, −16, 8; z score, 4.7; and x, y, z = 20, −12, 8; z score, 4.15) compared with controls (Figure 2).

Figure 3 shows the genealogical trees for kindred 1 and kindred 2. The members scanned with 18F-FDG and/or 18F-dopa and those asymptomatic subjects with abnormal scans are also indicated.

In our familial PSP patients, striatal 18F-dopa uptake was significantly reduced bilaterally, with putamen and caudate being similarly affected. Such a uniform reduction of dopamine storage throughout the striatum has also been reported for sporadic idiopathic PSP patients<sup>15-18</sup> and suggests that the substantia nigra in PSP patients is globally involved. Glucose metabolism was also reduced in the striatum of our patients, in agreement with findings reported for sporadic PSP patients<sup>15-21</sup> and in contrast to findings for patients with PD in which striatal 18F-FDG uptake is preserved.<sup>19</sup> The reduction in prefrontal, prefrontal, and thalamic glucose metabolism that we have found in our familial PSP members is also typical of patients with sporadic PSP,<sup>19,22</sup> although other areas, such as pa-
rietal cortex and cerebellum, have also been reported to be involved in this condition.23

Four of 15 asymptomatic relatives (27%) showed reductions in striatal 18F-dopa and 18FDG uptake bilaterally. These 4 subjects also had decreased 18FDG uptake in a pattern similar to that of their clinically affected relatives; cortical glucose metabolism was reduced in lateral and medial premotor areas and right dorsal prefrontal cortex, while left dorsal prefrontal cortex and thalamus were spared. In addition to these 4 relatives, we identified a fifth asymptomatic subject with normal striatal 18FDG and 18F-dopa uptake who had reduced glucose metabolism in the premotor cortex bilaterally and the right dorsal prefrontal cortex. If we include this last subject, the percentage of asymptomatic adult relatives with abnormal PET findings increases to 33%.

Since the pattern of cerebral glucose hypometabolism and reduction of 18F-dopa uptake in the clinically asymptomatic relatives is similar to that observed in the cases with established disease, we assume that these 5 among the 15 subjects at risk for PSP indeed have subclinical disease. In support of this assumption, 1 of the relatives with abnormal 18F-dopa and 18FDG scans developed clinical PSP 2 years after scanning at age 59 years (kindred 2, III.26). When we arbitrarily divided the asymptomatic relatives who underwent PET scanning into groups older and younger than age 50 years, we observed that none of the 4 subjects younger than 50 years had subclinical abnormalities, while the percentage of subclinical abnormalities among the 11 subjects who were aged 50 years or older rose to 45%. Since the mean age of onset of the disease in the two families is 61 years, this additional finding implies that the duration of the subclinical phase of PSP, at least in these families, is only a few years.

The reduced 18FDG uptake in the frontal cortex of some asymptomatic relatives suggests that frontal cortex hypometabolism constitutes an early disease marker. In agreement with this hypothesis, a previous 18FDG PET/neuropsychological study conducted in a cohort of 41 PSP patients in different stages of the disease reported that, although frontal glucose uptake decreases with disease duration, frontal hypometabolism is already present in the very early stage of the disease and precedes the onset of overt frontal lobe deficits.22

In 1 of our asymptomatic subjects, 18FDG uptake was found only to be reduced in cortical areas with sparing of subcortical structures. In early reports of PSP, the cortex was thought to be spared,24 and this led to the concept of a “subcortical dementia” supposedly owing to an impairment of afferent stimulating systems, maybe reticular or thalamic in origin.24,25 Subsequent postmortem studies have consistently reported neurofibrillary tangles in frontal cortex,26-29 suggesting that at least some of the intellectual deficits in PSP are owing to lesions in the cortex itself.29 The finding in 1 of our asymptomatic subjects of cortical hypometabolism in a pattern similar to that of his affected relatives but without subcortical involvement supports the idea that some of the dysfunction in PSP is cortical in origin and can occur very early.

The presence of subclinical cases detected with 18F-dopa and 18FDG PET in asymptomatic members of PSP families suggests that the familial aggregation for this disease is greater than that ascertained on the basis of clini-

| Characteristics of the Clinically Affected Members and of the Asymptomatic Members Studied With 18F-Dopa and 18FDG PET* |
|---|---|---|---|---|---|
| Subject | Kindred | Sex | Age, y | Duration, y | PET Studies Performed |
| Clinically affected relatives | | | | | |
| III.1 | 1 | F | 75 | 5 | Yes Yes |
| III.6 | 1 | M | 63 | 4 | Yes Yes |
| III.11 | 2 | F | 58 | 5 | Yes Yes |
| Asymptomatic relatives | | | | | |
| III.2 | 2 | F | 69 | | Yes Yes |
| III.3 | 2 | M | 68 | | Yes Yes |
| III.4 | 2 | F | 67 | | Yes Yes |
| III.5 | 2 | F | 62 | | Yes Yes |
| III.15 | 2 | F | 53 | | Yes No |
| III.16 | 2 | F | 50 | | Yes Yes |
| III.21 | 2 | M | 70 | | Yes Yes |
| III.23 | 2 | F | 69 | | Yes Yes |
| III.26 | 2 | M | 57† | | Yes Yes |
| Total | | | 55.4 ± 13.2‡ | | 15‡ | 10‡ |

*18FDG indicates 18fluorodeoxyglucose; PET, positron emission tomography.
†Mean ± SD for kindred.
‡No. of studies performed or number of subjects studied.
cal surveys alone, indicating that PSP could have a greater hereditary component than previously realized. Factors that may explain the difficulty in recognition of familial cases of PSP on the basis of clinical findings include the late onset of the condition and the presence of occasional atypical cases given the variation in clinical phenotype. The typical syndrome is characterized by a variable combination of supranuclear ophthalmoplegia, axial dystonia, akinesia, pseudobulbar palsy, and mild dementia.30,31 However, PSP can present with atypical clinical pictures, including a pure akinetic syndrome and pure dementia.30,32,33 Recently, an elderly patient with pathologically confirmed PSP has been described who had a pure psychiatric syndrome without neurological signs.34

The prevalence of PSP in the United States is reported to be 77 times lower than the prevalence of PD,36 while, in contrast, the incidence of PSP has been reported to be only 12 times lower than that of PD.36 Although the median survival time from symptom onset is shorter in PSP than in treated PD patients,38 survival differences cannot explain the discordance in incidence and prevalence rates reported for PSP.31 With current clinical diagnostic tools, PSP patients are diagnosed late in their disease course, and many PSP patients die with other diagnoses,39,40 so it is likely that clinical prevalence estimates have been grossly underestimated.31

There have been a few previous reports of familial cases with pathologically confirmed PSP. To date, familial clustering of PSP has been reported in a total of 20 kindreds.4 The pattern of inheritance in these reports was variable but generally suggestive of dominant transmission. Higgins et al41 suggest that PSP can also be inherited as an autosomal recessive disorder linked to the TAU gene, but these data have not been confirmed. Other familial PSP clusters need to be recognized and included in a wider genetic search.

In conclusion, we have used 18F-dopa and 18FDG PET to assess clinically affected and asymptomatic adult members of 2 kindreds with familial PSP. Cortical and subcortical glucose and dopaminergic metabolic abnormalities with a pattern similar to that of their clinically affected relatives were found in 33% of asymptomatic adult members, suggesting that these subjects have subclinical PSP. The possibility of detecting subclinical cases and atypical phenotypes by using 18F-dopa and 18FDG PET could therefore improve the diagnostic recognition of PSP cases and be a valuable aid in finding a gene or genes responsible for this disease.

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