Cerebral Perfusion in Progressive Supranuclear Palsy

Keith A. Johnson, Reisa A. Sperling, B. Leonard Holman, J. Steven Nagel, and John H. Growdon

Departments of Radiology and Medicine, Brigham and Women's Hospital, Boston, Department of Neurology, Massachusetts General Hospital, Boston, and Harvard Medical School, Boston, Massachusetts

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder in which structurally preserved cerebral cortex is thought to be functionally disconnected by subcortical lesions. To assess brain functional activity in patients with PSP, we measured regional cerebral perfusion, as estimated by [^{123}I] iofetamine (IMP) and single-photon emission computed tomography (SPECT), in 11 patients with a clinical diagnosis of PSP and 10 healthy control subjects. IMP uptake was measured in 2 basal ganglia and 24 cortical regions. Neuropsychological tests were administered to assess cognitive function. Compared to age-matched normal control subjects, relative IMP uptake was significantly reduced in PSP patients in basal ganglia (21%), superior frontal (25%), anterior parietal (19%), and inferior frontal (18%) regions. Cognitive performance was most abnormal on tests thought to be subserved predominantly by frontal lobes. Our study demonstrates that IMP-SPECT detects physiological abnormalities in the cortex that parallel behavioral impairments in PSP.

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Progressive supranuclear palsy (PSP) is a bradykinetic parkinsonian syndrome with neck dystonia, axial rigidity, and postural imbalance in association with supranuclear oculomotor palsy; cognitive impairments are common (*1–4*). Typical neuropathological findings include neuronal loss with gliosis and neurofibrillary tangles in diencephalic and brain stem nuclei with sparing of the cerebral cortex (*2–5*). Despite the lack of cortical histopathology, physiological measurements using positron emission tomography (PET) have revealed decreases in cerebral glucose and oxygen metabolism (*6–10*) and in perfusion (*11*). These data supported speculation that behavioral impairments in PSP resulted from disruptions in the reciprocal connections linking frontal lobes and striata (*7*). The present study was undertaken to test this hypothesis by using another imaging technique for assessing brain function. We sought to determine whether regional cortical abnormalities in PSP can be observed with [^{123}I]iofetamine (IMP), a tracer of cerebral perfusion, and single-photon emission computed tomography (SPECT). We also examined the relationship between perfusion abnormalities and specific cognitive impairments in PSP.

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For reprints contact: Keith A. Johnson, MD, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

METHODS

Patients and Control Subjects

Eleven patients with a clinical diagnosis of PSP (8 men and 3 women, mean age 67.5 ± 5.8 yr) and 10 healthy control subjects (6 men, 4 women; mean age 70.8 ± 9.0 yr) were studied with IMP-SPECT (Table 1). All patients presented with a progressive syndrome of rigidity and bradykinesia associated with a characteristic supranuclear gaze palsy and each had progressive cognitive impairment. All patients met clinical criteria for the diagnosis of PSP (*2–4*) and were unresponsive to antiparkinsonian dopaminergic therapy. Patients' Hoehn and Yahr stages (*12*) ranged from 2 to 5 (mean 3.6 ± 0.9) and illness duration ranged from 1.5 to 8 yr (mean 4.6 ± 2.1). The Blessed Dementia Scale (BDS) (*13*) was administered to 8 of the 11 patients and to all of the control subjects. The BDS is a structured mental status interview that assesses memory, fund of information, orientation, and concentration. A normal score is 0 to 2 and the maximum abnormal score is 37. Scores among patients with PSP ranged from 1 to 6 (mean 3.5 ± 2.0); control subjects scored 0 or 1. Roentgen ray and/or magnetic resonance (MR) computed tomographic studies were performed in 8 of 11 patients. Three had normal images, four had enlarged lateral ventricles and hemispheric sulci, and three had patchy white matter abnormality on MR images. Postmortem examination in one case confirmed the clinical diagnosis of PSP.

Control subjects were matched to PSP patients for age; they had no histories of neurologic, psychiatric, or cardiovascular diseases, and had normal neurologic examinations. This study was approved by the hospital Institutional Review Board and informed consent was obtained from all normal control subjects and patients or their legal representatives.

Neuropsychological Testing

To determine the behavioral correlates of perfusion abnormalities in PSP, 8 of the 11 PSP patients took cognitive tests (Table 2) that assessed a range of abilities, including language [Boston Naming Test (*14*), Stroop Color Word Test (*15*), and verbal fluency (*16*)]; abstract reasoning [Raven's Progressive Matrices (*17*)]; visuospatial orientation [Luria Mental Rotation (*18*)] ; temporal ordering, ability to shift set, and working memory [Picture Arrangement Subtest of WAIS-R (*19*), Stroop Selective

TABLE 1
Demographic Data for Progressive Supranuclear Palsy (PSP) Patients and Separate Groups of Normal Control Subjects Studied with SPECT or Neuropsychological Tests

	Age (yr)	Sex, M:F	Duration (yr)	Hoehn and Yahr scores
PSP (n = 11)	67.5 ± 5.8* (61–76)	8:3	4.6 ± 2.1 (1.5–8)	3.6 ± 0.9 (2–5)
SPECT Controls (n = 10)	70.8 ± 9.0† (60–81)	6:4	na	na
Neuropsychology Controls (n = 16)	66.5 ± 7.8‡ (57–86)	5:11	na	na

* Values are mean ± s.d. (range); na indicates not applicable.
† Age-matched with PSP patients (t = 1.03, p = 0.32).
‡ Age-matched with PSP patients (t = 0.71, p = 0.49).

Attention (*15*) and verbal fluency (*16*)] and verbal and nonverbal tests of long-term memory [Story Recall (*20*) and Benton Visual Retention Test (*21*)]. These tests required minimal motor responses, and, with the exception of the language tests, only untimed test scores were used. Motor performance was not quantitatively assessed for comparison to basal ganglia perfusion deficits because the striata are known sites of pathology. We sought to assess cognitive functions, especially those behaviors subserved by the frontal lobes, inasmuch as these brain regions are histopathologically normal. The 10 control subjects who underwent SPECT imaging did not take these neuropsychological tests. The PSP patients' scores on cognitive tests were compared to the scores of a separate group of 16 healthy control subjects who were spouses or siblings of parkinsonian patients attending the Massachusetts General Hospital Movement Disorders Unit.

IMP-SPECT

Iodine-123-IMP (5 mCi, Mediphysics, Paramus, N.J.) was infused into an antecubital vein while the subjects were seated, with eyes open, in a softly lit, quiet room. Approximately 10 min later, patients were placed supine using a soft head restraint to minimize motion. SPECT was performed as previously described

TABLE 2
Cognitive Test Scores of PSP Patients Compared to Age-matched Normal Control Subjects

Cognitive test	Capacity tested	Mean control score	Mean PSP patient score
New York Univ. Stories, initial (15, 8)##	Initial verbal recall	8.33 ± 2.5 #	5.75 ± 3.0
New York Univ. Stories, delayed (16, 6)	Delayed verbal recall	7.47 ± 3.2	6.50 ± 2.8
Benton Visual Retention (15, 6)	Nonverbal immediate recognition	12.73 ± 1.7	9.50 ± 1.5**
Boston Naming (16, 8)	Object naming	38.25 ± 3.9	33.50 ± 2.3**
Verbal Fluency			
"S" words (9, 8)	Semantic fluency	18.78 ± 7.0	4.13 ± 2.2***
Animals (7, 8)	Symbolic fluency	14.87 ± 5.3	7.00 ± 2.3**
Stroop (16, 7)	Selective attention	106.38 ± 9.0	37.86 ± 23.7***
	Color naming	65.38 ± 14.3	24.14 ± 15.0**
	Speed to read word	30.25 ± 9.9	13.43 ± 8.2***
Raven's Matrices (15, 8)	Abstract reasoning	32.47 ± 3.3	23.63 ± 5.2***
Luria Mental Rotation (14, 7)	Mental rotation	88.57 ± 11.7	60.00 ± 33.7*
Picture Arrangement Subtest, WAIS-R (16, 6)	Temporal ordering Ability to shift Set	11.38 ± 4.5	4.00 ± 2.8**

\# Values are mean ± s.d.
Number of control subjects tested, number of PSP patients.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, Mann-Whitney U-test.

(*22*) with a General Electric 400 AC rotating gamma camera equipped with a long-bore collimator (*23*). Data acquisition time was approximately 40 min per subject. Data sets (reconstructed spatial resolution, 1.8 cm full width at half maximum) were reconstructed in axial planes parallel to the orbitomeatal line, as estimated from the projection image. Orthogonal sagittal images of 1.2 cm thickness were reconstructed from the axial images. Average [^{123}I]IMP activity was measured in 3 × 3 pixel (19 × 19 mm^2) regions of interest (ROIs) placed over right and left parasagittal slices that extended from approximately 1.0 cm to 2.2 cm lateral to the midline. To ensure consistent ROI placement, a reference line was drawn on each parasagittal image between the inferior margins of the occipital and frontal lobes, and a midpoint was placed between the occipital and frontal poles (Fig. 1). Using the midpoint, the image above the reference line was divided into 12 sectors of 15° each and ROIs were centered over cortical IMP activity in each sector. To locate and measure IMP uptake in the basal ganglia, a 3 × 3 pixel ROI was placed on each image at 0.35 times the distance from frontal to occipital poles (*7*) and centered at 30° above the reference line. Iodine-123-IMP uptake in the cerebellum was measured with 3 × 3 pixel ROIs placed over the region of maximal activity in right and left cerebellar hemispheres.

Data Analysis

Relative IMP uptake for each of 26 cerebral ROIs (12 homologous cortical pairs and one homologous basal ganglia pair) was calculated as the ratio of each cerebral ROI activity to mean (right and left) cerebellar ROI activity, yielding an average IMP activity/pixel normalized to the cerebellar activity/pixel for each subject. Bilateral symmetry of relative IMP uptake was calculated in two ways: (1) absolute value of right minus homologous left regional relative IMP uptake divided by the mean (right and left) relative IMP uptake (i.e., percent asymmetry), and (2) right minus homologous left ROI (i.e., right-left bias). Regional relative IMP uptake in patients with CT or MR evidence of hemispheric atrophy (n = 4) was compared with uptake in patients with CT or MR images without signs of atrophy (n = 4) using Dunn's multiple comparison t-test (*23*).

Comparisons of relative regional IMP uptake between PSP patients and control subjects were made with Dunn's Multiple Comparison t-test (*24*). Among patients, comparisons of regional relative IMP uptake with age, duration of illness, BDS score, and neuropsychological test scores were made with Spearman Rank correlation coefficients. Comparisons between PSP and control subjects' cognitive test scores employed the Mann-Whitney U-test.

RESULTS

Neuroimaging Studies

SPECT was successfully performed in all 11 PSP patients despite significant nuchal rigidity and dystonia. The rotating gamma camera and three-dimensional data acquisition permitted important flexibility in patient positioning. Visual comparison of SPECT images of 11 PSP patients and 10 normal control subjects revealed widespread reductions in cortical IMP uptake in PSP that were most prominent in superior frontal regions (Fig. 2). Calculated relative IMP uptake was significantly lower in PSP patients compared to control subjects in 16/24 cortical regions and in basal ganglia regions (Fig. 3). The greatest reductions in uptake were in superior frontal regions (decreased by 25%; $p < 0.01$), and in basal ganglia regions (decreased by 21%; $p < 0.01$). Significant decreases were also detected in anterior parietal (19%; $p < 0.05$) and inferior frontal (18%; $p < 0.05$) regions. No significant percent asymmetry or right-left bias difference was found between patients and control subjects in any of the 13 pairs of brain regions. Significant differences in regional relative IMP uptake were not found between patients with CT or MR evidence of hemisphere atrophy (n = 4) and those without evidence of atrophy (n = 4).

One PSP patient's brain at autopsy was compared to his SPECT study in corresponding coronal planes (Fig. 4). Gross pathologic examination showed a normal cortical ribbon, mild ventricular enlargement, and atrophy of deep gray structures. In contrast, this patient's SPECT study demonstrated cortical IMP uptake that was markedly abnormal, especially in the frontal lobes. Histopathologic examination of this brain revealed the characteristic findings of PSP (*2*). Neurofibrillary tangles were found in periaquaductal gray, loci coerulei, and raphe nuclei, but not in multiple samples of cerebral cortex.

Neuropsychological Testing

PSP patients differed significantly from neuropsychological control subjects on all tests except those assessing verbal memory (Table 2). Poorest performance was found in tests of verbal fluency (semantic fluency was 22% of the control value), and on the Picture Arrangement Test (35% of control value). On the Stroop Color Word Test, speed

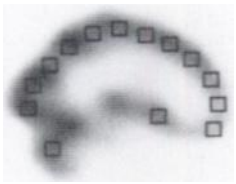

FIGURE 1. Parasagittal [^{123}I]IMP SPECT image depicts placement of one striatal, one cerebellar and 12 cortical ROIs.

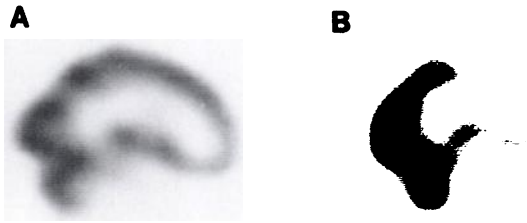

FIGURE 2. Parasagittal [^{123}I]IMP SPECT images in the plane of the caudate and putamen from a normal control subject (A) and a patient with autopsy proven PSP (B). Iofetamine uptake in the superior frontal regions is reduced.

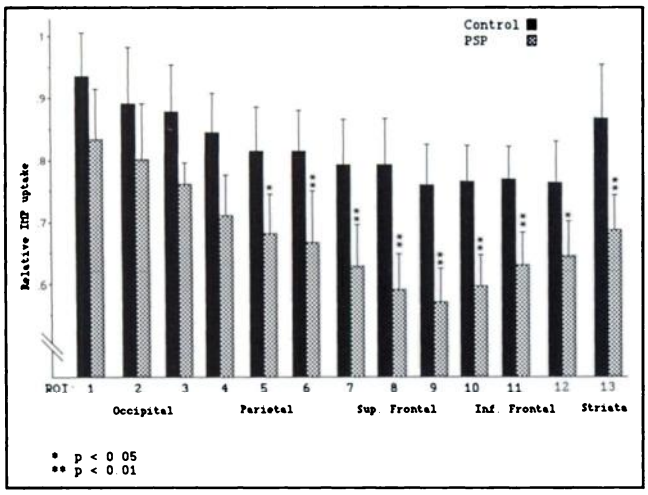

FIGURE 3. Mean relative [^{123}I]IMP uptake in one striatal and 12 cortical homologous right-left pairs of ROIs from 10 normal control subjects and 11 PSP patients.

in reading words and naming colors was greatly reduced, as would be expected in patients with severe bradykinesia and dysarthria, but performance on the portion of the test assessing attention was decreased to 36% of control value. Lesser but still significant deficits were documented on tests of naming, abstract reasoning, visuospatial, and nonverbal memory abilities. The most severe cognitive impairments were found in tests (fluency, Picture Arrangement, and Stroop Color Test of Attention) that are believed to depend upon the functional integrity of the frontal lobes.

To determine whether the degree of cognitive impairment was related to the degree of perfusion impairment, we compared the rank ordering of PSP patients' deficits in both domains. While perfusion was lowest in frontal regions and cognitive performance was most impaired on tests of frontal lobe function, there were no significant rank order correlations of regional relative IMP uptake with individual neuropsychological test scores or with patient age, duration of illness, Hoehn and Yahr score, or BDS score (Spearman Rank correlation coefficients).

DISCUSSION

The results of this study demonstrate that IMP-SPECT can detect a pattern of reduced cerebral perfusion in PSP. In addition to the striata, relative IMP uptake was significantly reduced throughout the anterior parietal and frontal lobes, with greatest reductions in superior frontal regions. These observations are similar to PET findings in PSP of reduced perfusion and metabolism that was most severe in striatum and frontal lobes (*6–11*).

Data from PET studies provided the first convincing evidence that striatal lesions functionally disconnect the frontal lobes from ascending subcortical projections (*6–11*). The pathologically confirmed case in our study demonstrated the characteristic sparing of cerebral cortex in PSP, despite widespread pathology evident in subcortical areas. Nevertheless, this patient showed frontal predominant IMP uptake reductions in cortical areas (Fig. 4), suggesting that damage to subcortical projections may be responsible for cortical hypometabolism.

Due to expense and technical complexity, most PET studies of brain function in PSP have been limited to a small number of patients. Additional and independent confirmation of frontal lobe dysfunction in PSP is desirable in order to undertake larger scale clinical studies. SPECT is a method for assessing brain physiology that is widely available and relatively inexpensive. SPECT methods commonly used at present, however, do not provide quantitative measurements of cerebral perfusion and therefore must rely on internal comparisons of one brain region with another. To compute relative IMP uptake, we used a normalization procedure in which cerebral uptake was divided by mean (right and left) cerebellar uptake, thereby providing an index of cerebral IMP activity/pixel normalized to cerebellar uptake. Our IMP-SPECT studies were performed without arterial blood sampling and quantitative measurements of reduced cerebral perfusion were not possible. Avoiding arterial catheterization simplifies the experimental procedure and makes SPECT readily accepted by patients; our method of data analysis compensated for intersubject variability in absolute IMP uptake by using each subject as his own control. Cerebellar normalization has the disadvantage of assuming that cerebel-

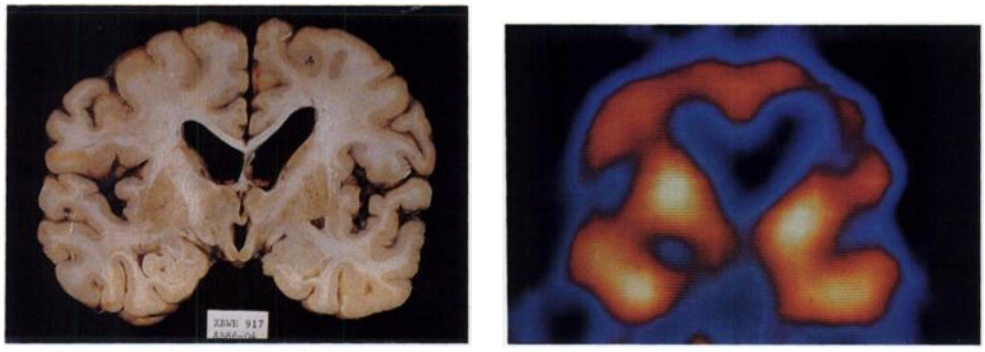

FIGURE 4. Postmortem coronal slice at the level of the mammillary bodies from a patient with PSP (left) reveals a grossly normal cortical ribbon and mildly enlarged lateral and third ventricles. This patient's corresponding coronal SPECT image (right) demonstrates markedly reduced frontal lobe perfusion.

lar perfusion is normal in PSP. PET studies of PSP have found that cerebellar glucose metabolism is reduced (*8*, *10*). If cerebellar perfusion is reduced in PSP, our method of assessing cortical functional activity would be less sensitive to abnormality. Despite this methodologic limitation, we found significant reductions in cortical normalized SPECT perfusion.

Signs of cerebral atrophy by CT or MR were seen in four of our cases and, as in any functional imaging technique, atrophy may have lowered our estimate of perfusion artifactually. Although we found no significant differences in relative IMP uptake between our small number of patients with or without structural evidence of atrophy, cerebral atrophy remains a possible confounding factor in functional imaging. The problem of correcting physiologic data for morphologic alterations such as atrophy has limited interpretation of PET data (*25*) and remains equally challenging for SPECT.

In previous studies, IMP-SPECT was found useful in the assessment of patients with Alzheimer's disease (AD), in which there is a characteristic pattern of bilateral temporoparietal perfusion deficits (*22,26–31*). Moreover, among 58 patients with AD, the severity of dementia estimated with the BDS correlated significantly with reductions in parietal lobe perfusion (*27*). The pattern of cerebral perfusion in PSP differs markedly from that observed in AD. Frontal hypoperfusion is clearly more severe in PSP than in AD, although total cerebral perfusion is reduced in both conditions. Frontal perfusion is normal or mildly abnormal in Parkinson's disease but parietal perfusion reduction has been associated with coexisting dementia (*32,33*).

Our SPECT data closely parallel findings using PET techniques and suggest that SPECT examinations may be as useful in assessing cerebral physiology in PSP as it is in AD. However, the proper role of SPECT and PET perfusion and metabolism studies in the clinical diagnosis of patients with neurodegenerative diseases remains to be fully elucidated. While a functional "signature" characteristic of either AD or PSP has been suggested, the specificity of functional imaging methods among all neurodegenerative diseases is unknown and may be low. For example, among 14 patients with a clinical diagnosis of PSP studied by Foster et al. (*7*), the one patient studied postmortem did not have the histopathologic findings for PSP, even though the PET findings were typical for PSP.

Another goal of this study was to detect a correlation between IMP-SPECT images and patients' cognitive deficits. In three studies of PSP using PET the examination of brain-behavior correlation were inconclusive. D'Antona et al. (*6*), Goffinet et al. (*8*), and Leenders et al. (*11*) each found no significant relation between level of functional image abnormality and scores on tests of cognition function. Blin et al. reported results of PET scans from 41 patients with the clinical diagnosis of PSP. Image data were obtained with single- or multi-slice cameras using either [^{18}F]fludeoxyglucose or [^{15}O]oxygen. Seven cortical regions were assessed in these combined patient groups and a significant negative rank order correlation was found between frontooccipital metabolic ratio and a composite neuropsychological frontal score; caudate and thalamic metabolism was negatively correlated with a parkinsonian motor score (*10*). We sought to overcome some of the limitations of previous studies by assessing a broad set of cognitive behavioral measures and estimating cerebral perfusion in 24 cortical areas. Among our patients with PSP who underwent cognitive testing, there was evidence for widespread cortical dysfunction with cognitive deficits affecting aspects of memory, language, abstract reasoning, and visual perception. The most prominent deficits, however, were in functions believed to be subserved by the frontal lobes, including attention, set-shifting, verbal fluency and temporal ordering. These data suggest that brain activity would be most severely impaired in frontal lobes, but that temporal and parietal lobe functions would be compromised as well. Our SPECT data, showing that cerebral perfusion was significantly reduced throughout all frontal and anterior parietal regions, supported the prediction of widespread cortical dysfunction in PSP. None of the individual cognitive test scores was significantly correlated with reductions in regional cerebral perfusion, however, patients' scores were clustered in the severely impaired range and this may have rendered rank order correlations with perfusion estimates non-significant. The frontal lobes were most severely affected in both behavioral and physiological measures. This finding suggests that the cerebral perfusion deficits detected with IMP-SPECT imaging are relevant to the behavioral manifestations of PSP.

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CORRECTION

In the March 1992 issue of the *Journal*, Fig. 1B in "The Frequency of Asymptomatic and Electrically Silent Exercise-Induced Regional Myocardial Ischemia During First-Pass Radionuclide Angiography with Upright Bicycle Ergometry," by Williams et al., was printed incorrectly. The corrected figure is shown below.

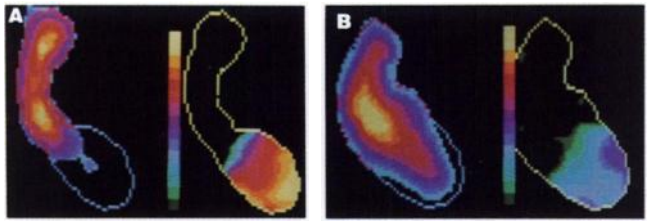

FIGURE 1. First-pass RNA images obtained in a 72-yr-old man with a history of typical angina pectoris are shown. The resting left ventricular end-diastolic perimeter and end-systolic counts (A, left image) demonstrate normal ventricular size and wall excursion. Regional systolic performance is also assessed with a regional ejection fraction image (A, right image), which shows a normal regional ejection fraction pattern (A, right) at rest. The resting ejection fraction was 76%. With exercise to a heart rate of 126 bpm, he developed typical angina pectoris and ST-segment depression on ECG. Stress RNA demonstrated slightly left ventricular dilatation with a marked fall in ejection fraction to 38% (B, left). The regional ejection fraction pattern shows anteroseptal moderate hypokinesis with apical severe hypokinesis and tardokinesis (B, right). Coronary angiography revealed a tight proximal left anterior descending coronary artery stenosis.