PAPERS

Reductions in parietal and temporal cerebral metabolic rates for glucose are not specific for Alzheimer's disease

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Abstract

Reduction in the regional cerebral metabolic rate for glucose (rCMRglc) in the parietal and temporal regions has been shown in Alzheimer's disease (AD). The specificity of these findings for this disease state is uncertain. We repeatedly measured rCMRglc with positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose in the resting state in a 68 year old man with slowly progressive dementia who, during life, was initially diagnosed as having dementia of the Alzheimer type, then Parkinson disease with dementia, but was found to have only Parkinson's disease at necropsy. Metabolic ratios (rCMRglc/mean grey CMRglc) were significantly ($p < 0.05$) reduced in parietal and temporal regions, as well as in the prefrontal and premotor areas. This pattern was similar in regional distribution and magnitude of the defect to that seen in patients with probable AD. These results suggest that reductions of glucose metabolism in association neocortex in AD are not specific to the disease process, but may be related to the dementia state.

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Reductions in the regional cerebral metabolic rate for glucose (rCMRglc) in the parietal and temporal regions have been shown in Alzheimer's disease (AD), using positron emission tomography (PET). Such reductions occur early in the disease and persist throughout its course.^{1,2} However, the specificity of these findings for AD has not been determined. To address this issue of specificity, we report a necropsy proved case of Parkinson's disease (PD) in which reductions of parietal and temporal metabolism were found before death, similar to those seen in AD.

An abstract of this work has been published.³

Case report

The subject was a man who first presented on 31 October 1983 at age 65 years with a six year history of mild memory loss, difficulty finding places, nightmares, and occasional visual hallucinations. He was forced to retire as a medical equipment salesman owing to difficulty with paperwork. History was not remarkable for neurological or medical dis-

ease. He received no medications. There was no family history of AD or PD. Review of systems was notable for impotence. On examination, blood pressure was 140/90 (supine) and 104/76 (standing), and heart rate was 54 (supine) and 64 (standing). There was a mild tremor of outstretched hands.

Laboratory investigations revealed normal serum chemistries, cholesterol, thyroid function test, VDRL, folate, vitamin B12, blood counts, and sedimentation rate. Chest x ray showed borderline cardiomegaly and ECG was normal. EEG showed 7-8 Hz, low amplitude background. CT scan showed mild cortical atrophy. CSF was clear with normal opening pressure.

An extensive battery of neuropsychological tests to assess memory, attention to simple and complex sets, planning, language, visuo-spatial functions, and overall dementia severity^{4,5} was administered to the patient five times at roughly annual intervals (table 1). To test whether scores differed significantly from that which would be expected in an age, education, and gender-matched control, predicted scores were calculated based on a multiple regression equation derived from 108 healthy controls. These controls ranged in age from 45 to 90 years (mean 63) with 12 to 20 years of education (mean 16.7). Test scores were predicted based on age, gender, and years of education. The difference between actual and predicted score was converted to a z-score by dividing by the standard deviation of control residuals, calculated with a jackknife procedure whereby the predicted score for each control subject was based on a multiple regression equation derived from all controls but that one. To test for significant impairments in AD patients, the difference between the mean normalised discrepancy and zero was tested with a *t* test. For the single patient with PD, a score with normalised discrepancy less than -1.96 ($p < 0.05$) indicated significant impairment.

On initial evaluation, dementia was mild with significant impairments on two tests of memory, a test of the ability to shift attention between two sequential sets (trials B), planning (Porteus mazes), and visual abstract reasoning (Raven's matrices). Performance on a test of memory for a prose passage (WMS story recall), however, was within normal limits. Whereas all tests of visuospatial construction and immediate visuospatial memory span showed significant impairment at the initial evaluation, all language tests were within normal limits on the first evaluation, and all

Table 1 Results of longitudinal neuropsychological tests in the healthy controls, Alzheimer's disease patients, and the Parkinson's disease subject. Examinations on January 1987 and January 1988 coincided with the patient's first and second PET scans, respectively.

Test	Controls (n = 11)	AD patients (n = 12)	Nov '83	Parkinson disease subject			
				Jan '85	Jan '86	Jan '87	Jan '88
Overall Ability:							
MMSE (max = 30)	29.8 (0.4)	23.8 (2.0)*	24†	22†	25†	23†	21†
WAIS IQ	133 (5)	107 (12)*	105†	97†	87†	95†	86†
Mattis dementia RS	141 (3)	121 (10)*	133†	130†	116†	120†	106†
Memory:							
WMS stories							
Immediate recall	20 (7)	9 (5)*	12	5†	7†	14	4†
Delayed recall	17 (7)	4 (5)*	7	4†	2†	1†	3†
WMS Figures							
Immediate recall	10 (3)	3 (2)*	1†	1†	5	6	1†
Delayed recall	9 (4)	1 (2)*	1†	0†	0†	1	1
Buschke Test							
Total recall	64 (5)	40 (9)*	41†	41†	35†	39†	28†
Delayed recall	8 (1)	2 (3)*	1†	3†	3†	2†	2†
Complex attention, planning, abstraction:							
Trails B (secs)	67 (27)	274 (119)*	(Unable)				
Stroop interference	36 (8)	14 (10)*	22	9†	3†	1†	6†
Porteus mazes (Test, years)	15.8 (1.1)	12.8 (4)*	7.5†	8.0†	6.0†	6.0†	6.5†
Raven's coloured matrices	33 (3)	25 (6)*	21†	15†	19†	16†	13†
Language:							
WAIS VDO	134 (9)	117 (15)*	123	109†	108†	114†	108†
WAIS MDQ	124 (11)	97 (15)*	109	106	91†	97†	100
Syntax comprehension	25 (1)	19.3 (3.9)*	23	21	19†	16†	17†
Boston naming	38 (4)	31 (8)*	37	35	35	34	n.a.
FAS serial naming	44 (10)	28 (14)*	34	11†	11†	14†	16†
WRAT oral reading	16.3 (2.4)	14.3 (2.5)	16.5	14.4	16.8	15.0	15.3
Visuospatial:							
WAIS PDQ	122 (14)	104 (17)*	87†	73†	60†	70†	57†
Extended range drawing	20 (2)	17 (5)*	10†	12†	12†	8†	7†
Hiskey-Nebraska blocks	16 (5)	9 (4)*	6†	4†	4†	3†	3†
Benton facial recognition	46 (3)	43 (6)	43	36†	37†	36†	32†
Block tapping span	4.7 (0.6)	3.8 (0.5)	2.8†	3.0†	2.2†	2.5†	1.5†

Values are mean (SD).

AD = Alzheimer's disease; MMSE = mini-mental status examination; WAIS = Wechsler adult intelligence scale; IQ = intelligence quotient; WMS = Wechsler memory scale; VDO = verbal comprehension deviation quotient; MDQ = memory and freedom from distractibility deviation quotient; WRAT = wide range achievement test; PDQ = perceptual organisation deviation quotient.

*Mean in AD patients less than mean in controls by unpaired *t* test ($p < 0.05$).

†Parkinson subjects's value less than mean in controls by *Z*-score analysis ($p < 0.05$).

but two were normal on the second evaluation. Confrontation naming (Boston naming) and oral reading of irregularly spelled words (WRAT) remained normal on all evaluations. Performance on a test of face discrimination (Benton face recognition) demonstrated significant impairments on the second evaluation and on all evaluations thereafter. Mini-mental state examination (MMSE) score was 24/30.⁶ His Hachinski ischaemic score was 1.⁷ The clinical diagnosis at this time was dementia of the Alzheimer type.⁸

At examination on 7 August 1985 there were mild orthostatic blood pressure changes; increased tone in the upper extremities (with mild cogwheeling) which increased with activation (L > R); tremor of outstretched arms; an intermittent, small amplitude fast tongue tremor; diminished rapid finger movements; and mild bradykinesia. His gait was characterised by decreased arm swing, slow pace, moderate flexion posture, and decreased stride length. He was unable to tandem walk. Vibratory sense and two point discrimination were decreased in the toes. Extraocular movements were full. His MMSE score was 22. At this point the diagnosis was thought to be probable Alzheimer's disease with extrapyramidal signs.^{9,10} A trial of a levodopa/cardidopa combination (Sinemet) was initiated in September 1986 with improvement of his spontaneous movements. However, this drug was discontinued because of hallucinations, not because of any negative effect on his cognitive performance. Other dopamine agonists were not tried.

At the time of his first PET scan (11

January 1987) his MMSE score was 23. A resting tremor and masked facies were also now present. The clinical diagnosis was changed to Parkinson's disease with dementia, due to the slow progression of cognitive changes (table 1). Very slow deterioration of mental status continued to be noticed at subsequent evaluations, with MMSE scores of 18 on 22 July 1987 and 21 on 11 January 1988 (date of his second PET scan). At his last evaluation on 14 June 1988, his MMSE score decreased to 12 and it was noted that he now was dependent in daily living skills. Annual rates of decline (points/year) on both the WAIS IQ and Mattis dementia rating scale were approximately half the mean rate for patients with AD and were significant ($p < 0.05$) in comparison with the mean in the healthy controls (WAIS: +0.4 (SD 1.8) for controls, -8.3 (SD 4.4) for AD patients, -3.8 for the PD patient, respectively. Mattis dementia rating scale: +1.5 (SD 2.1) for controls, -12.4 (SD 6.9) for AD patients, -6.1 for the PD patients).

Progression of motor abnormalities continued through the course of his illness. Extraocular movements remained full, but saccades were hypometric.

At necropsy by one of us (MJB), the fresh brain weighed 1430 grams. On gross inspection, there was no evidence of cortical atrophy, minimal ventricular dilatation, no atherosclerosis, and no cerebral infarctions. Transverse sections through the brainstem showed striking pallor of the substantia nigra and locus ceruleus. Microscopic examination showed severe depletion of pigmented neu-

Table 2 Absolute rCMRglc values measured in the healthy volunteers, Alzheimer's disease subjects, and Parkinson's disease subject (first and second PET scans)

Brain Region Absolute Values (mg/100 g/min)	Controls (n = 19) Mean (SD)	AD (n = 12) Mean (SD)	Patient	
			PET scan 1 (01–15–87)	PET scan 2 (01–21–88)
Orbito frontal				
right	7.42 (1.22)	5.84 (1.55)*	5.65	5.35
left	7.59 (1.16)	6.10 (1.30)*	6.39	5.70
Prefrontal				
right	8.76 (1.45)	7.40 (0.98)*	5.36†§	5.40†§
left	8.78 (1.50)	7.17 (0.92)*	4.95*‡	5.23*‡
Premotor				
right	9.38 (1.70)	7.48 (1.18)*	5.21*	5.56†
left	9.53 (1.56)	7.58 (1.08)*	5.50*	4.80*‡
Inferior parietal				
right	8.67 (1.61)	6.53 (1.22)*	4.33*	3.80*‡
left	8.89 (1.74)	6.06 (1.38)*	4.58*	3.81*
Medial parietal				
right	9.53 (1.75)	6.68 (0.97)*	3.69*‡	4.65*§
left	9.04 (2.02)	6.64 (0.82)*	4.34*‡	3.63*‡
Superior parietal				
right	8.48 (1.52)	6.16 (1.06)*	4.13*	4.06*
left	8.47 (1.56)	6.22 (1.04)*	4.19*	4.37*
Sensorimotor				
right	8.48 (1.48)	7.38 (1.03)†	5.44†	5.19†‡
left	8.89 (1.62)	7.42 (0.97)*	5.89	5.25†§
Calcarine				
right	8.36 (1.32)	7.05 (1.29)*	6.10	5.38†
left	8.47 (1.31)	7.20 (1.24)*	5.25*	4.87*
Occipital association				
right	8.05 (1.42)	6.95 (1.00)†	4.40*‡	4.54*‡
left	8.07 (1.51)	6.73 (1.13)*	4.60†	3.81*‡
Inferior temporal				
right	6.35 (1.31)	4.98 (0.72)*	—	3.80
left	6.08 (1.26)	4.75 (0.67)*	—	3.49†
Middle temporal				
right	7.99 (1.35)	6.00 (0.97)*	4.31*	4.22*
left	8.08 (1.28)	6.14 (0.86)*	4.92*	4.29*§
Superior temporal				
right	8.42 (1.52)	6.74 (0.88)*	4.42*‡	4.24*‡
left	8.59 (1.46)	6.70 (1.07)*	5.08*	4.25*§
Anterior cingulate				
right	8.66 (1.72)	7.05 (0.84)*	6.88	6.27
left	8.58 (1.44)	7.05 (1.10)*	6.82	6.97
Posterior cingulate				
right	9.33 (1.59)	7.01 (1.00)*	3.95*‡	4.62†§
Amygdala				
right	5.57 (0.96)	4.23 (1.35)*	6.65	5.89
left	5.66 (1.11)	3.76 (0.98)*	5.77§	3.97
Insula				
right	8.10 (1.56)	6.53 (1.71)*	5.35	5.24
left	8.17 (1.34)	6.62 (1.40)*	5.35†	4.90*
Paracentral				
right	8.26 (1.77)	6.62 (1.01)*	5.92	6.65
left	8.36 (1.67)	6.72 (0.84)*	6.30	5.89
Hippocampus				
right	6.75 (1.15)	5.47 (0.81)*	5.10	4.62
left	6.78 (1.28)	5.20 (0.54)*	4.41	4.12†
Midbrain				
right	5.37 (0.60)	4.74 (0.76)†	4.87	5.41
Caudate nucleus				
right	8.82 (1.93)	8.11 (1.49)	7.85	5.54
left	9.27 (1.77)	8.19 (1.67)	7.08	6.61
Lenticular nucleus				
right	9.54 (1.66)	8.43 (1.75)	8.11	8.43
left	9.65 (1.34)	8.53 (1.55)†	8.08	8.24
Thalamus				
right	9.17 (1.55)	8.05 (1.40)	7.10	7.53
left	9.22 (1.66)	7.74 (1.58)†	8.69	6.64
Cerebellum				
right	6.84 (1.30)	6.35 (0.57)	5.69	4.86†
left	6.88 (1.58)	6.27 (0.49)	5.38	4.37†
Global grey matter				
right	8.41 (1.37)	6.84 (0.82)*	5.47†	5.10*

Values of rCMRglc are mean (SD) and are expressed in mg/100 g tissue/min. Differences between mean values in the Alzheimer's disease and healthy volunteer groups were compared with an unpaired *t* test.

PD patient was compared to both controls and AD patients by using a Z-score analysis.

*Value differs from mean in controls at *p* < 0.01 level.

†Value differs from mean in controls at *p* < 0.05 level.

‡Value differs from mean in AD patients at *p* < 0.01 level.

§Value differs from mean in AD patients at *p* < 0.05 level.

rons in the substantia nigra, especially in the pars compacta, accompanied by extensive astrocytic gliosis and free neuromelanin pigment. Frequent Lewy bodies were seen in the residual substantia nigra neurons. The remainder of the midbrain showed no significant abnormality. Neurofibrillary tangles were not found. Even more depletion of pigmented nerve cells was shown in the locus ceruleus. The pontine raphe nuclei were normal. In the nucleus basalis of Meynert the average number of nucleolated neurons per 10 μ M paraffin-embedded section was 38.5 in the anterior

division and 13.1 in the intermediate division (the posterior division was not available), a reduction of 90% and 93%, respectively, in comparison with four non-demented subjects aged 67–72 years. Neither Lewy bodies nor neurofibrillary tangles were found in this sample of nucleus basalis of Meynert. There were no lesions seen in samples of the thalamus with subthalamic nucleus, caudate, and putamen, but there was suggestion of a mild, patchy neuronal loss in the globus pallidus. Within the hippocampal formation, there was a relatively well preserved population of pyramidal neurons, with only a very occasional focus of minimal neuronal dropout. The adjacent amygdala nuclei were also generally within normal limits. The neocortical population of nerve cells, including samples from the middle frontal, inferior temporal, and superior parietal gyri, and calcarine cortex, was well preserved. There were no neurofibrillary tangles or senile plaques in either the neocortex or hippocampal formation.

A monoclonal mouse antibody to ubiquitin (Chemicon International, Inc) showed typical ubiquitin-positive staining in the substantia nigra in this case, while simultaneous staining with normal rabbit serum did not show the positive staining. Lewy bodies or ubiquitin-positive inclusions were not seen in numerous neocortical regions, including left middle frontal gyrus, left inferior temporal gyrus, and left superior parietal gyrus, hippocampus, corpus striatum, or basal forebrain. Pathology of the spinal cord and sympathetic ganglia was not obtained.

For the PET scan studies, the PD subject was compared with two groups of subjects who were participants in the National Institute on Aging-Laboratory of Neurosciences Studies of Aging and Dementia.¹¹ One comparison group included 19 healthy male volunteers (mean age (SD) 64 (6) years, range 57–78), whose MMSE score was 29.8 (0.4). The second group consisted of 12 men with probable Alzheimer's disease (AD)⁷ (mean age (SD): 65 (10) years, range 52–80), whose MMSE score was 23.8 (2.0), range 21 to 27 (table 1). MMSE mean scores differed significantly in the two groups (*p* < 0.0001). These subjects were screened with medical, neurological, and laboratory tests. Subjects had no history of neurological (other than AD in the patient group), psychiatric, or systemic medical disorder. None was taking medication for at least two weeks before the study. All the AD patients were still alive at the time of present report; therefore, no necropsy data were available to confirm diagnosis of probable AD.

Healthy volunteers and AD subjects (or their legal guardians) signed an informed consent describing the purpose of the study, the tests performed, and the risks involved. The research was conducted under NIH protocols 81-AG-10 (Parkinson's disease and AD subjects) and 80-AG-26 (controls).

PET scans were performed using procedures previously described in subjects at rest with reduced auditory and visual

Table 3 The ratio values of rCMRglc to mean calcarine CMRglc measured in the healthy volunteers, Alzheimer's disease subjects, and Parkinson's disease subject (first and second PET scans).

Brain region	Controls (n = 19) Mean (SD)	AD (n = 12) Mean (SD)	Patient	
			PET Scan 1 (01-15-87)	PET Scan 2 (01-21-88)
Orbitofrontal				
right	0.88 (0.08)	0.80 (0.18)	1.00	1.04
left	0.90 (0.05)	0.84 (0.15)	1.12*	1.11*
Prefrontal				
right	1.04 (0.08)	1.05 (0.17)	0.94	1.05
left	1.04 (0.08)	1.02 (0.14)	0.87†	1.02
Premotor				
right	1.11 (0.10)	1.07 (0.19)	0.92	1.08
left	1.13 (0.09)	1.09 (0.21)	0.97	0.94†
Inferior parietal				
right	1.03 (0.13)	0.92 (0.14)†	0.76†	0.74†
left	1.05 (0.10)	0.86 (0.22)†	0.81†	0.74*
Medial parietal				
right	1.13 (0.14)	0.95 (0.14)*	0.65*	0.91
left	1.07 (0.13)	0.95 (0.15)†	0.76†	0.71*
Superior parietal				
right	1.01 (0.11)	0.88 (0.16)*	0.73†	0.79†
left	1.01 (0.11)	0.90 (0.21)	0.74†	0.85
Sensorimotor				
right	1.01 (0.09)	1.05 (0.18)	0.96	1.01
left	1.06 (0.10)	1.06 (0.21)	1.04	1.02
Occipital association				
right	0.96 (0.08)	0.98 (0.11)	0.78†	0.88
left	0.96 (0.08)	0.96 (0.21)	0.81	0.74*
Inferior temporal				
right	0.76 (0.09)	0.72 (0.13)	—	0.74
left	0.72 (0.07)	0.69 (0.12)	—	0.68
Middle temporal				
right	0.95 (0.08)	0.83 (0.09)*	0.76†	0.82
left	0.96 (0.07)	0.86 (0.14)†	0.87	0.84
Superior temporal				
right	1.00 (0.09)	0.97 (0.19)	0.78†	0.83
left	1.02 (0.05)	0.97 (0.24)	0.89*	0.83*
Anterior cingulate				
right	1.03 (0.09)	1.01 (0.19)	1.21†	1.22†
left	1.02 (0.07)	1.01 (0.22)	1.20*	1.36*
Posterior cingulate				
right	1.11 (0.11)	1.00 (0.14)†	0.70†§	0.90
Amygdala				
right	0.66 (0.08)	0.59 (0.15)	1.17*‡	1.15*‡
left	0.67 (0.08)	0.53 (0.13)*	1.02*‡	0.77
Insula				
right	0.96 (0.10)	0.92 (0.24)	0.94	1.02
left	0.97 (0.09)	0.94 (0.22)	0.94	0.96
Paracentral				
right	0.99 (0.11)	0.96 (0.19)	1.05	1.30*
left	0.99 (0.09)	0.98 (0.15)	1.11	1.15
Hippocampus				
right	0.80 (0.08)	0.77 (0.09)	0.90	0.90
left	0.80 (0.07)	0.74 (0.12)	0.78	0.80
Midbrain				
right	0.64 (0.07)	0.70 (0.18)	0.86*	1.05*
Caudate nucleus				
right	1.04 (0.13)	1.15 (0.23)	1.38*	1.08
left	1.11 (0.17)	1.16 (0.25)	1.25	1.29
Lenticular nucleus				
right	1.14 (0.14)	1.19 (0.17)	1.43†	1.64*‡
left	1.15 (0.10)	1.21 (0.20)	1.42*	1.61*‡
Thalamus				
right	1.10 (0.17)	1.14 (0.16)	1.25	1.47†§
left	1.10 (0.17)	1.10 (0.19)	1.53†	1.26
Cerebellum				
right	0.82 (0.10)	0.93 (0.15)	1.00	0.95
left	0.83 (0.11)	0.92 (0.15)	0.95	0.85

Values are mean (SD).

To compare controls with AD patients an unpaired *t* test was employed. PD patient was compared with both controls and AD patients by using a Z-score analysis.

*Value differs from mean in controls at *p* < 0.01 level.

†Value differs from mean in controls at *p* < 0.05 level.

‡Value differs from mean in AD patients at *p* < 0.01 level.

§Value differs from mean in AD patients at *p* < 0.05 level.

inputs¹² using a Scanditronix PC-1024-7B scanner and [18]2-fluoro-2-deoxy-D-glucose (18FDG). This is a seven slice machine with a transverse resolution (full width at half maximum) of 6 mm and an axial resolution of 10 mm. Two interleaved transmission scans were performed for correction of attenuation of radiation by the skull. Forty five minutes after intravenous injection of 5 mCi of 18FDG, two interleaved emission scans were obtained parallel to and from 10–100 mm above the IOM line. Arterial blood samples were drawn during the uptake period and scan itself to obtain plasma for measurement of radioactivity and glucose. Regional metabolic rates for glucose (rCMRglc) were calculated in units of

mg/100 g/min using Brooks' modification¹³ of the operational equation of Sokoloff *et al.*¹⁴ Regional brain radioactivities were determined using a template of circular regions of interest 8 mm in diameter.

At time of the first PET scan (15 January 1987) global CMRglc equalled 5.47 mg/100 g/min in the Parkinson's disease subject compared with 8.41 (SD 1.37) in the healthy volunteer group (*p* < 0.05) and 6.84 (SD 0.82) in the AD group (*p* > 0.05). Using a Z score analysis,¹⁵ the PD subject showed significant reductions in absolute rCMRglc values compared with healthy volunteers in all cortical regions, except the bilateral orbitofrontal, anterior cingulate, and paracentral regions, right calcarine, and left sensorimotor (table 2). The later scan on 21 January 1988 showed additional deficits in the right calcarine and left sensorimotor regions. There were no significant reductions of glucose metabolism in the thalamus and basal ganglia. A similar pattern of metabolic reduction was seen in the AD group compared with controls using an unpaired *t* test, with significant reductions in rCMRglc in all cortical regions. In comparison with the AD group, the PD patient showed significant reductions of absolute rCMRglc values in bilateral prefrontal and medial parietal regions as well as in the right occipital association and right superior temporal areas at the time of the first PET scan. The second scan revealed additional deficits in the left premotor, right inferior parietal, bilateral sensorimotor, left occipital association, left superior temporal regions.

To reduce the intersubject variance associated with absolute values of rCMRglc in healthy controls and to examine patterns of metabolism,¹ we calculated ratios of rCMRglc to the mean calcarineCMRglc value (table 3), a region relatively spared in AD.¹⁶ In the PD subject, relative reductions were shown in the parietal and temporal regions on both scans compared with healthy volunteers. On second PET scan, the left premotor became significantly reduced, whereas the left prefrontal region, which was decreased at the time of the first PET scan, was normal. These changes are illustrated in figure 1, which shows PET images at two levels in the PD subject and a healthy volunteer. Relative reductions in rCMRglc also were shown in parietal and middle temporal regions in AD subjects compared with healthy volunteers. Both the PD and AD subjects showed a similar pattern of reduced rCMRglc in the parietal, temporal, and frontal association cortices, whereas there was relative sparing of brain metabolism in primary motor and sensory, and subcortical regions.

Discussion

This is a case of a slowly progressive dementia in a patient who, during life, was initially diagnosed as having AD,⁸ then PD with dementia, but was found to have only PD at necropsy. Visual hallucinations, uncommon in early AD, may have suggested the diagnosis of

Figure 1 PET images at 45 mm (top) and 70 mm (bottom) above the inferior orbital meatal line in a healthy volunteer (right) and the Parkinson's disease subject (left). The colour scale provides values for rCMRglc in mg/100 g/min.

senile dementia of Lewy body type; necropsy examination, however, ruled out this possibility. In some cases of PD, cognitive impairment may be due to bradyphrenia rather than to a true dementing process. However, neuropsychological testing in our patient showed impairment in multiple cognitive areas, including attention, memory, visuospatial ability, while longitudinal studies showed a progressive cognitive decline, similar to that seen in AD patients. In comparison with previous reports of PET scanning with ^{18}F FDG in early AD, and to a mild AD group with comparable MMSE scores in this study, this subject showed similar regional distribution and magnitude of defect in glucose metabolism in the parietal and temporal cortical association areas, with relative sparing of primary neocortex and subcortical regions. Further, these results were replicated on PET scans one year apart. Additional relative reductions in glucose metabolism in prefrontal and premotor regions were found in this subject. Although not among the metabolic findings usually seen in the early AD, such reductions have been described in later stages of AD.⁴ These findings suggest that reductions of glucose metabolism in parieto/temporal and frontal association neocortex in AD are not specific to the disease process, but maybe related to the dementia state.

Such a metabolic pattern has also been described in diseases other than AD, but neuropathology was not always available. In one patient with PD with moderate dementia, who was scanned while on medication, relative reductions of parietal/temporal metabolism were noted; specific reductions of parietal/temporal metabolism were not found in three other cases of PD and dementia in the same report.¹⁷ In addition, whole brain and bilateral parietal/temporal reductions in

metabolism have been described in a patient with normal pressure hydrocephalus whose dementia improved after CSF shunt surgery.¹⁸ Unlike these two previous examples of reductions of parietal/temporal metabolism in diseases other than AD, our case was confirmed not to have AD by autopsy. In addition, asymmetric reductions of temporal metabolism have been reported in a necropsy confirmed case of Creutzfeldt-Jakob disease. However, parietal metabolism was not examined.¹⁹ Patients with vascular dementia (VD) also showed patterns of reduced parietal/temporal and frontal metabolism similar to those seen in AD patients.²⁰ Unlike AD patients, however, patients with VD had significantly reduced metabolic values also in subcortical structures, such as the basal ganglia, thalami, and cerebellum. Moreover, none of the VD patients had necropsy to confirm diagnosis and exclude a coexistent AD process.

Unlike the AD patients, the PD patient showed normal glucose metabolism and absence of neuropathology in the amygdala nuclei. This may explain, in part, the finding that two short memory tests were normal at the time of the first PET exam.

The cause of the dementia in PD remains uncertain. The numbers of senile plaques and neurofibrillary tangles (NFTs) usually do not differ between PD patients with and without dementia and appropriate controls.²¹⁻²³ An occasional case of PD and dementia has been described with concomitance of both AD and PD at necropsy, but these are thought to be the exception. In our case no such pathological changes of AD were present. Further, no cortical Lewy bodies were noted, as described by Clark²⁴ in patients with progressive dementia clinically thought to be AD. Rather, our case showed neuropathological changes characteristic of idiopathic PD.

Previous work has shown that resting regional hypometabolism with ^{18}F FDG PET in life correlates with regional NFT density postmortem in five of six necropsy proved cases of AD,²⁵ suggesting that the hypometabolism in AD results from dysfunction of neurons in regions of high NFT density. Our case suggests that regional cerebral hypometabolism also may result from neuronal dysfunction which is not related to the formation or accumulation of NFTs. Primary damage to several subcortical systems with cortical projections may contribute to cortical hypometabolism. Cortical cholinergic abnormalities usually occur in Parkinson's disease with dementia in the absence of AD pathology.²³ This has been attributed to primary loss of neurons in the subcortical Meynert nucleus,²² also seen in our case, which give rise to cortical cholinergic fibres. However, experimental unilateral and bilateral lesions in the nucleus basalis in rats²⁶ and in non-human primates²⁷ only have caused temporary disturbances in brain metabolism.

As outlined by Rapoport,²⁸ PD is a phylogenetic disease of system II, one of several groups of functionally and anatomically related brain regions that underwent dispro-

portionate expansion during recent evolution of primates, particularly humans. The regions associated in system II, including substantia nigra, basal ganglia, thalamus, and frontal association and motor neocortical areas, participate in several functionally segregated circuits which subserve cognition as well as movement.²⁹ The basal ganglia are linked with association cortex, by several of these segregated circuits. A major subcortical component of system II that is disrupted in PD is the nigrostriatal system. Dementia is inversely related to the neuronal cell count in the medial part of the substantia nigra.³⁰ The cells in this portion generally project to the caudate, and along with cells in the ventral tegmental area which also are lost in PD, project to cortical and limbic regions. Therefore, significant involvement of parts of the segregated circuitry of system II may result in dementia and cortical hypometabolism. The interaction between altered dopamine and cholinergic function may also have together resulted in the dementia and metabolic abnormalities in our subject.

Dementia and an extrapyramidal syndrome may be seen in, among other diseases, AD,⁹ PD with AD, and, as in this case, PD without AD. PET with 18FDG has shown similar reductions in parietal/temporal metabolism in cases from each of these disease categories and therefore has not allowed differentiation of one entity from another. Preliminary work has suggested that PET with [18F]6-fluoro-L-dopa (6-FD) differentiates clinically diagnosed Alzheimer's disease with extrapyramidal features from Parkinson's disease with dementia.³¹ However, it is not known if 6-FD will allow differentiation of demented Parkinson's disease with and without the neuropathological changes of Alzheimer's disease.

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