A clinical role for ^{99m}Tc -HMPAO SPECT in the investigation of dementia?

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Abstract

Objectives—To provide the clinician with a guide to the clinical utility of ^{99m}Tc -HMPAO single photon emission computed tomography (SPECT) and to the interpretation of specific test results in the differential diagnosis of dementia.

Methods—Three hundred and sixty three patients with dementia were studied prospectively for a median three (range 1–6) years and classified into disease groups on the basis of established clinical criteria. The degree to which different patterns of cerebral blood flow (CBF) abnormality found on ^{99m}Tc -HMPAO SPECT imaging at the time of initial patient presentation modified clinical diagnoses was determined by calculating the likelihood ratios for pairwise disease group comparisons. The optimal clinical usage of ^{99m}Tc -HMPAO SPECT was determined by calculating the percentage of significant test results for each pairwise disease group comparison.

Results—Bilateral posterior CBF abnormality was found to significantly increase the odds of a patient having Alzheimer's disease as opposed to vascular dementia or frontotemporal dementia. Bilateral anterior CBF abnormality significantly increased the odds of a patient having frontotemporal dementia as opposed to Alzheimer's disease, vascular dementia, or Lewy body disease. "Patchy" CBF changes significantly increased the odds of a patient having vascular dementia as opposed to Alzheimer's disease. Unilateral anterior, unilateral anterior plus unilateral posterior, and generalised CBF abnormality failed to contribute to the differentiation of any of these forms of dementia.

Conclusions— ^{99m}Tc -HMPAO SPECT was found to be most useful in distinguishing Alzheimer's disease from vascular dementia and frontotemporal dementia, and least useful in differentiating between Alzheimer's disease and Lewy body disease, and between vascular dementia, frontotemporal dementia, and progressive aphasia. It is suggested that CBF SPECT should be used selectively and as an adjunct to clinical evaluation and CT.

Cerebral blood flow imaging with SPECT discloses changes that reflect patterns of neuropsychological impairment characteristic of particular dementing conditions. For example, posterior CBF abnormality has commonly been reported in Alzheimer's disease^{1–5} in keeping with the presence of "parietal lobe" symptomatology,^{6,7} whereas anterior CBF abnormality has been reported in frontotemporal dementia^{1,5,8,9} reflecting the presence of a "frontal lobe" syndrome.^{10,11} These findings have served to promote CBF SPECT as a diagnostic test in the investigation of dementia.^{12–14} Indeed, confidence inspired by such findings has led some clinicians to view CBF SPECT as a substitute for detailed clinical assessments such as neuropsychological analysis. However, previous CBF SPECT studies have typically considered disease groups rather than individual patients, and have involved relatively few disease group comparisons. It has, therefore, not been possible to determine the clinical value of CBF SPECT imaging in the investigation of dementia. The aim of this study is to determine the extent to which individual patterns of CBF abnormality contribute to clinical diagnoses by calculating likelihood ratios for pairwise disease group comparisons. In this way, it is possible to provide information that is useful to the clinician in the interpretation of individual test results and a guide to the optimal clinical usage of ^{99m}Tc -HMPAO SPECT in the differential diagnosis of dementia.

Patients

Three hundred and sixty three patients referred consecutively to the cerebral function unit at Manchester Royal Infirmary for diagnostic assessment of dementia underwent neuropsychological evaluation, neurological examination, CT, and ^{99m}Tc -HMPAO SPECT at initial presentation. Neuropsychological evaluation was performed using a test instrument developed in this centre, designed to characterise performance in the areas of language, calculation, visual perception, spatial skills, praxis, memory, and "frontal lobe" executive abilities.⁶ Patients were reviewed prospectively for a median three (range 1–6) years with six monthly neuropsychological and neurological evaluation, and classified on the basis of established clinical criteria into the following disease groups: Alzheimer's disease (132), vascular dementia (78), Lewy body disease (24), frontotemporal dementia (58), progressive aphasia (22), corticobasal degeneration (12), progressive supranuclear palsy (nine), multiple system atrophy (four),

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Table 1 Age and sex characteristics of patients in the five largest disease groups

	No	M:F	Age (mean (SD)) at initial presentation
Alzheimer's disease	132	52:80	63.6 (8.1)
Vascular dementia	78	41:37	63.8 (7.0)
Lewy body disease	24	14:10	67.6 (4.8)
Frontotemporal dementia	58	32:26	58.9 (11.1)
Progressive aphasia	22	7:15	64.9 (6.8)

idiopathic Parkinson's disease (four), Huntington's disease (five), autoimmune encephalitis (eight), Creutzfeldt-Jakob disease (five), and normal pressure hydrocephalus (two). In view of the few patients in some disease groups, only the five more commonly encountered forms of dementia were considered for further analysis. Table 1 shows the age and sex of patients in each of these disease groups, and the clinical and CT findings are described below.

ALZHEIMER'S DISEASE GROUP

During prospective evaluation, all patients showed memory problems and deficits in more than two cognitive domains indicative of cortical dysfunction. Patterns of neuropsychological breakdown were characterised by amnesia together with visuospatial dysfunction or linguistic impairment. Personality and social conduct were preserved in all patients, and none manifested features suggestive of "subcortical" dysfunction.¹⁵ Neurological examination was either normal or disclosed mild extrapyramidal features or myoclonus with disease progression. Brain CT was normal or showed periventricular lucency or generalised cerebral atrophy. All patients fulfilled clinical criteria for probable Alzheimer's disease,¹⁶ and pathological confirmation of diagnosis has since been obtained in eight patients.¹⁷ All patients that fulfilled clinical criteria for vascular dementia, Lewy body disease, frontotemporal dementia, or progressive aphasia were excluded from the Alzheimer's disease group regardless of whether or not they fulfilled criteria for this condition.

VASCULAR DISEASE GROUP

All patients exhibited, during the period of prospective evaluation, evidence of memory problems and deficits in more than two cognitive domains indicative of cortical or subcortical dysfunction.¹⁵ Neurological examination disclosed focal signs suggestive of cerebrovascular disease such as hemianopia, lower facial

weakness, dysarthria, hemisensory deficit, hemiparesis, or extensor plantar response. Brain CT showed multiple large vessel infarcts, single strategically placed infarcts, or multiple subcortical infarcts and/or periventricular lucency. All patients fulfilled criteria for probable vascular dementia,¹⁸ and pathological confirmation of diagnosis has since been obtained in one patient.

LEWY BODY DISEASE GROUP

During prospective evaluation, all patients showed fluctuating cognition and a pattern of neuropsychological breakdown indicative of subcortical dysfunction¹⁵: mental slowing, difficulty on tasks involving manipulation of information, difficulty in motor sequencing tasks, perseveration, failure in tests sensitive to frontal lobe dysfunction, and memory impairment suggestive of retrieval and organisational failures. In addition, 17 patients developed visuospatial or language impairment indicative of cortical dysfunction, and neurological examination disclosed evidence of parkinsonism in all. Brain CT was normal or disclosed generalised cerebral atrophy. All patients fulfilled clinical criteria for Lewy body disease,¹⁹ and pathological confirmation of diagnosis has since been obtained in three patients.²⁰

FRONTOTEMPORAL DEMENTIA GROUP

All patients presented with a profound breakdown in personality and social conduct. Spontaneous speech became increasingly economical with disease progression, culminating in mutism in some patients. By contrast, visuospatial and motor functions were preserved in all patients. Neurological examination was normal or disclosed frontal lobe release phenomena. Brain CT was normal or disclosed anterior or generalised cerebral atrophy. All patients fulfilled clinical criteria for frontotemporal dementia,²¹ and pathological confirmation of diagnosis has since been obtained in four patients.²²

PROGRESSIVE APHASIA GROUP

All patients presented with a profound disorder of language. In most, spontaneous speech was non-fluent and effortful, and contained literal paraphasias. Word finding difficulty was considerable and comprehension, although initially preserved, was eventually affected late in the disease progression. Other patients presented with word comprehension and naming

Table 2 Actual frequencies of different patterns of abnormal cerebral blood flow (CBF) for the five largest disease groups

Pattern of CBF abn	Alzheimer's disease	Vascular dementia	Lewy body disease	Frontotemporal dementia	Progressive aphasia
Bilateral posterior	39	5	4	4	0
Bilateral posterior plus unilateral anterior	20	3	9	0	0
Unilateral posterior	9	6	0	1	7
Bilateral anterior	3	13	0	21	5
Bilateral anterior plus unilateral posterior	2	8	0	7	4
Unilateral anterior	2	3	0	3	1
Unilateral anterior plus unilateral posterior	5	7	0	4	2
Generalised	26	10	5	6	1
Patchy	14	20	4	8	2
No abnormality	12	3	2	4	0
Total	132	78	24	58	22

CBF abn = cerebral blood flow abnormality.

Examples of individual patterns of cerebral blood flow abnormality: (a) bilateral posterior CBF abnormality; (b) bilateral anterior CBF abnormality; (c) bilateral anterior plus unilateral posterior CBF abnormality; (d) unilateral anterior plus unilateral posterior CBF abnormality; (e) generalised CBF abnormality; (f) patchy CBF abnormality.

difficulty, occurring in the context of fluent, effortless conversational output and preservation of repetition skills. In all patients, visuospatial and motor functions were preserved, and neurological examination was normal or showed frontal lobe release phenomena. Brain CT was normal or disclosed left sided, anterior, or generalised cerebral atrophy. All patients fulfilled clinical criteria for progressive aphasia,⁷ and pathological confirmation of diagnosis has since been obtained in two patients.²³

Methods

^{99m}Tc -HMPAO SPECT

Cerebral blood flow imaging with ^{99m}Tc -HMPAO SPECT was performed on patients within one month of initial presentation to the cerebral function unit at Manchester Royal Infirmary. Patients were injected with 500 MBq ^{99m}Tc -HMPAO while seated in quiet and relaxed surroundings with eyes open. Patient data were acquired and reconstructed using a Toshiba GCA-901A/SA integrated digital gamma camera and computer system using a single rotating detector fitted with a low energy high resolution collimator. Sixty 20 second views over a 360° elliptical orbit were acquired on a 64×64 matrix with twice linear magnification (zoomed pixel size 4 mm). The raw data were corrected for uniformity variations and then smoothed using an 11×11 preprocessing filter (Parzan, cut off 0.4 cycles/pixel). Transaxial sections were produced using filtered back projection with a Butterworth filter order 4, cut off 0.25 cycles/pixel. These were corrected for γ ray attenuation using the Chang method with an attenuation coefficient of 0.1 cm^{-1} . The data were reformatted to provide transaxial slices 2 pixels (8 mm) thick parallel to the orbitomeatal line. The resolution was 4 pixels (16 mm) within transaxial sections and 2.5 pixels (10 mm) between sections. Transaxial, coronal, and parasagittal sections were reconstructed.

^{99m}Tc -HMPAO SPECT images were reported by a consultant in nuclear medicine experienced in the interpretation of CBF images in patients with dementia and normal control subjects. Images were viewed on a monitor with standardised display settings and reported blind to clinical and CT findings. The display of each set of sections was such that the pixel with the highest counts was displayed at the highest level and the lowest displayed level corresponded to 45% of the highest counts. A coloured display (magenta heat scale) was used ranging from blue (lowest) through purple, red, and yellow to white (highest). Image areas were considered abnormal if they were below the halfway point of this scale (red) on more than two sections. For ease of data analysis, patterns of CBF abnormality were classified into one of the following groups (figure): Bilateral posterior CBF abnormality, bilateral posterior plus unilateral anterior CBF abnormality, unilateral posterior CBF abnormality, bilateral anterior CBF abnormality, bilateral anterior plus unilateral posterior CBF abnormality, unilateral anterior CBF abnormality, unilateral anterior plus unilateral posterior

CBF abnormality, bilateral anterior plus bilateral posterior (generalised) CBF abnormality, "patchy" CBF abnormality, and "normal" CBF pattern. Images that revealed pronounced asymmetric CBF changes were classified as unilateral rather than bilateral CBF abnormality. Images that showed bilateral anterior plus bilateral posterior CBF changes with relative preservation of sensory-motor cortices or visual cortices were classified as generalised CBF abnormality.

STATISTICAL ANALYSIS

The frequencies of individual patterns of CBF abnormality for the five largest disease groups were determined. To evaluate the diagnostic gain of individual test results, likelihood ratios²⁴ were calculated pairwise for disease group (for example, disease A *v* disease B) comparisons. The likelihood ratio (LR) for disease A given a particular test result $\text{LR}(A[|]R_i)$ is the ratio of the probability of obtaining that result in disease A $p(R_i[|]A)$ to the probability of that result in disease B $p(R_i[|]B)$:

$$\text{LR}(A[|]R_i) = p(R_i[|]A)/p(R_i[|]B)$$

Likelihood ratios²⁵ provide an indication of the degree to which a particular result modifies the pretest odds of a patient having a particular disease to provide a new post-test odds ratio:

Post-test odds = Pretest odds $\times$ likelihood ratio

The odds of a patient having disease A rather than B is defined as the ratio of the probability of disease A (p_A) to the probability of disease B (p_B). In the case where only two possible diseases are considered then:

$$\text{Odds}(A) = p_A / (1 - p_A)$$

A likelihood ratio of 1 therefore indicates that a test result has not changed the odds of a patient having a particular disease. A likelihood ratio >1 indicates that a test result has increased the odds of a patient having a particular disease, whereas a ratio <1 indicates the opposite. A test result with a likelihood ratio of 5 provides the same degree of diagnostic gain to a test result with a likelihood ratio of 0.2 (1/5), except that there is an increase, rather than a decrease in post-test compared with pretest odds. The 95% confidence intervals for all likelihood ratios were calculated.²⁶ Only those ratios which were different from 1 with 95% confidence were considered to be significant. To provide a guide to the optimal clinical usage of CBF imaging, the percentage of significant test results for each pairwise disease group comparison was calculated.

A technical difficulty arises if a given test result never occurs in a particular disease (frequency=0). In this case, the likelihood ratio for that disease is zero and the ratio for the alternative disease is infinity. The confidence intervals in these cases are undefined. Therefore, to estimate whether such results are significant, likelihood ratios were recalculated with the frequency of zero replaced by a frequency of one.

Results

Table 2 shows the frequencies of individual patterns of CBF abnormality for the five largest

Table 3 Likelihood ratios (95% CI) of individual patterns of cerebral blood flow abnormality for pairwise disease group comparisons (significant results are underlined and the direction of change in odds indicated)

Pattern of CBF abn				
(a) Alzheimer's disease v				
Bilateral posterior	Vascular dementia	Lewy body disease	Frontotemporal dementia	Progressive aphasia
	<u>4.6 (1.9–11.2)↑</u>	1.8 (0.7–4.5)	<u>4.3 (1.6–11.4)↑</u>	∞
Bilateral posterior plus unilateral anterior	<u>3.9 (1.2–12.8)↑</u>	<u>0.4 (0.2–0.8)↓</u>	∞(↑)	∞
Unilateral posterior	0.9 (0.3–2.4)	∞	4.0 (0.5–30.5)	<u>0.2 (0.1–0.5)↓</u>
Bilateral anterior	<u>0.1 (0.0–0.46)↓</u>	∞	<u>0.1 (0.0–0.2)↓</u>	<u>0.1 (0.0–0.4)↓</u>
Bilateral anterior plus unilateral posterior	<u>0.2 (0.0–0.7)↓</u>	∞	<u>0.1 (0.0–0.6)↓</u>	<u>0.1 (0.0–0.4)↓</u>
Unilateral anterior	0.4 (0.1–2.3)	∞	0.3 (0.1–1.7)	0.3 (0.0–3.5)
Unilateral anterior plus unilateral posterior	0.4 (0.1–1.3)	∞	0.6 (0.1–2.0)	0.4 (0.1–2.0)
Generalised	1.5 (0.8–3.0)	1.0 (0.4–2.2)	1.9 (0.8–4.4)	4.3 (0.6–30.0)
Patchy	<u>0.4 (0.2–0.8)↓</u>	0.6 (0.2–1.8)	0.8 (0.3–1.7)	1.2 (0.3–4.8)
No abnormality	2.4 (0.7–8.1)	1.1 (0.3–4.6)	1.3 (0.4–3.9)	∞(↑)
(b) Vascular dementia v				
Bilateral posterior	Alzheimer's disease	Lewy body disease	Frontotemporal dementia	Progressive aphasia
	<u>0.2 (0.5–0.1)↓</u>	0.4 (0.1–1.3)	0.9 (0.3–3.3)	∞
Bilateral posterior plus unilateral anterior	<u>0.3 (0.8–0.1)↓</u>	<u>0.1 (0.0–0.4)↓</u>	∞	∞
Unilateral posterior	1.1 (3.1–0.4)	∞	4.5 (0.6–36.1)	<u>0.2 (0.1–0.7)↓</u>
Bilateral anterior	<u>7.3 (24.9–2.2)↑</u>	∞	<u>0.5 (0.3–0.8)↓</u>	0.7 (0.3–1.8)
Bilateral anterior plus unilateral posterior	<u>6.8 (31.1–1.5)↑</u>	∞	0.9 (0.3–2.2)	0.6 (0.2–1.7)
Unilateral anterior	2.5 (14.9–0.4)	∞	0.7 (0.2–3.6)	0.9 (0.1–7.7)
Unilateral anterior plus unilateral posterior	2.4 (7.2–0.8)	∞	1.3 (0.4–4.2)	1.0 (0.2–4.4)
Generalised	0.7 (1.3–0.3)	0.6 (0.2–1.6)	1.2 (0.5–3.2)	2.8 (0.4–20.9)
Patchy	<u>2.4 (4.5–1.3)↑</u>	1.5 (0.6–4.1)	1.9 (0.9–3.9)	2.8 (0.7–11.2)
No abnormality	0.4 (1.5–0.1)	0.5 (0.1–2.6)	0.6 (0.1–2.4)	∞
(c) Lewy body disease v				
Bilateral posterior	Alzheimer's disease	Vascular dementia	Frontotemporal dementia	Progressive aphasia
	0.6 (1.4–0.2)	2.6 (8.9–0.8)	2.4 (0.7–8.9)	0
Bilateral posterior plus unilateral anterior	<u>2.5 (4.8–1.3)↑</u>	<u>9.8 (33.2–2.9)↑</u>	∞(↑)	∞(↑)
Unilateral posterior	0	0	0	0
Bilateral anterior	0	0	0	0(↓)
Bilateral anterior plus unilateral posterior	0	0	0	0
Unilateral anterior	0	0	0	0
Unilateral anterior plus unilateral posterior	0	0	0	0
Generalised	1.1 (2.5–0.5)	1.6 (4.3–0.6)	2.0 (0.7–6.0)	4.6 (0.6–36.2)
Patchy	1.6 (4.4–0.6)	0.7 (1.7–0.3)	1.2 (0.4–3.6)	1.8 (0.4–9.0)
No abnormality	0.9 (3.8–0.2)	2.2 (12.2–0.4)	1.2 (0.2–6.2)	∞
(d) Frontotemporal dementia v				
Bilateral posterior	Alzheimer's disease	Vascular dementia	Lewy body disease	Progressive aphasia
	<u>0.2 (0.6–0.1)↓</u>	1.1 (3.8–0.3)	0.4 (1.5–0.1)	∞
Bilateral posterior plus unilateral anterior	0(↓)	0	<u>0(↓)</u>	0
Unilateral posterior	0.3 (2.0–0.0)	0.2 (1.8–0.0)	∞	<u>0.1 (0.0–0.4)↓</u>
Bilateral anterior	<u>15.9 (51.3–5.0)↑</u>	<u>2.2 (4.0–1.2)↑</u>	∞(↑)	1.6 (0.7–3.7)
Bilateral anterior plus unilateral posterior	<u>8.0 (37.2–1.7)↑</u>	1.2 (3.1–0.5)	∞	0.7 (0.2–2.1)
Unilateral anterior	3.4 (19.9–0.6)	1.3 (6.4–0.3)	∞	1.1 (0.1–10.4)
Unilateral anterior plus unilateral posterior	1.8 (6.5–0.5)	0.8 (2.1–0.2)	∞	0.8 (0.2–3.9)
Generalised	0.5 (1.2–0.2)	0.8 (2.1–0.3)	0.5 (1.5–0.2)	2.3 (0.3–17.9)
Patchy	1.3 (2.9–0.6)	0.5 (1.1–0.3)	0.8 (2.5–0.3)	1.5 (0.4–6.6)
No abnormality	0.8 (2.3–0.3)	1.8 (7.7–0.4)	0.8 (4.2–0.2)	∞
(e) Progressive aphasia v				
Bilateral posterior	Alzheimer's disease	Vascular dementia	Lewy body disease	Frontotemporal dementia
	0	0	0	0
Bilateral posterior plus unilateral anterior	0	0	0(↓)	0
Unilateral posterior	<u>4.7 (11.2–1.9)↑</u>	<u>4.1 (11.1–1.6)↑</u>	∞(↑)	<u>18.5 (141.5–2.4)↑</u>
Bilateral anterior	<u>10.0 (38.9–2.6)↑</u>	1.4 (3.4–0.6)	∞	0.6 (1.5–0.3)
Bilateral anterior plus unilateral posterior	<u>12.0 (61.6–2.3)↑</u>	1.8 (5.3–0.6)	∞	1.5 (4.7–0.5)
Unilateral anterior	3.0 (31.7–0.3)	1.2 (10.8–0.1)	∞	0.9 (8.0–0.1)
Unilateral anterior plus unilateral posterior	2.4 (11.6–0.5)	1.0 (4.5–0.2)	∞	1.3 (6.7–0.3)
Generalised	0.2 (1.6–0.0)	0.4 (2.6–0.1)	0.2 (1.7–0.0)	0.4 (3.5–0.1)
Patchy	0.9 (3.5–0.2)	0.4 (1.4–0.1)	0.6 (2.7–0.1)	0.7 (2.9–0.2)
No abnormality	0	0	0	0

↑Significant increase in likelihood ratio for target disease; ↓Significant decrease in likelihood ratio for target disease; (↑)/(↓)significant increase/decrease in likelihood ratio for target disease if frequency is set to one for those disease group comparisons for which the actual frequency of a particular test result is zero (see statistical methods); ∞=infinity (denominator is zero); CBF abn = cerebral blood flow abnormality.

disease groups and table 3 the likelihood ratios for individual test results for pairwise disease group comparisons. Significant results are underlined and the direction of change in odds indicated. The results are effectively shown twice. For example, bilateral posterior CBF abnormality significantly increases the odds of a patient having Alzheimer's disease as opposed to vascular dementia (likelihood ratio 4.6; table 3a), and decreases the odds of a patient having vascular dementia as opposed to Alzheimer's disease (likelihood ratio 0.2 (1/4.6); table 3b).

For the diagnostic gain of individual patterns of CBF abnormality, bilateral posterior CBF abnormality significantly increases the odds of a patient having Alzheimer's disease as opposed to vascular dementia or frontotemporal

dementia, but does not contribute to the differentiation of any other form of dementia. Bilateral posterior plus unilateral CBF abnormality significantly increases the odds of a patient having Alzheimer's disease as opposed to vascular dementia or frontotemporal dementia, and of a patient having Lewy body disease as opposed to all other forms of dementia. Unilateral posterior CBF abnormality significantly increases the odds of a patient having progressive aphasia as opposed to all other forms of dementia. Bilateral anterior CBF abnormality significantly increases the odds of a patient having vascular dementia, frontotemporal dementia, or progressive aphasia as opposed to Alzheimer's disease. In addition, bilateral anterior CBF abnormality significantly increases the odds of a patient having

Table 4 A guide to the optimal clinical use of ^{99m}Tc -HMPAO SPECT (% of significant test results* for pairwise disease group comparisons)

	Alzheimer's disease	Vascular dementia	Lewy body disease	Frontotemporal dementia
Vascular dementia	60			
Lewy body disease	18	12		
Frontotemporal dementia	50	25	36	
Progressive aphasia	27	13	35	10

* Those with likelihood ratios different from 1 with 95% confidence.

frontotemporal dementia as opposed to vascular disease or Lewy body disease. Bilateral anterior plus unilateral posterior CBF abnormality significantly increases the odds of a patient having vascular dementia, frontotemporal dementia, or progressive aphasia as opposed to Alzheimer's disease. "Patchy" CBF changes significantly increase the odds of a patient having vascular dementia as opposed to Alzheimer's disease. Unilateral anterior, unilateral anterior plus unilateral posterior, generalised CBF abnormality, and "normal" CBF patterns fail to contribute to the differentiation of any of these forms of dementia.

To provide a guide to the optimal clinical usage of ^{99m}Tc -HMPAO SPECT, table 4 shows the percentage of significant test results for each pairwise disease group comparison. The CBF imaging is most useful (>50% significant test results) in distinguishing Alzheimer's disease from vascular dementia and frontotemporal dementia, and least useful (<25% significant test results) in differentiating between Alzheimer's disease and Lewy body dementia, and between vascular dementia, frontotemporal dementia, and progressive aphasia.

Discussion

This is the first study to have determined the extent to which ^{99m}Tc -HMPAO SPECT contributes to the clinical differentiation of dementing conditions. Moreover, it has provided information that is useful to the clinician in the interpretation of individual test results and a guide to the optimal clinical usage of CBF imaging in the diagnosis of dementia.

To facilitate the interpretation of individual patterns of CBF abnormality, it is suggested that table 3 is used as follows: if a demented patient is considered to have either Alzheimer's disease or vascular dementia at initial presentation (table 3a) on the basis of neuropsychological evaluation, neurological examination, and CT, then bilateral posterior CBF abnormality or bilateral posterior plus unilateral anterior CBF abnormality provides support for the diagnosis of Alzheimer's disease. By contrast, bilateral anterior CBF abnormality, bilateral anterior plus unilateral posterior CBF abnormality, or "patchy" CBF changes provide support for vascular dementia, and unilateral posterior, unilateral anterior, unilateral anterior plus posterior, generalised CBF abnormality and a "normal" CBF pattern fail to differentiate either disorder. Similarly, table 3 can be helpful in the diagnosis of other dementing conditions. For example, if a demented patient is considered to have either Alzheimer's disease or frontotemporal dementia at initial presentation (table 3a), then bilateral posterior CBF

abnormality or bilateral posterior plus unilateral anterior CBF provides support for the diagnosis of Alzheimer's disease whereas bilateral anterior CBF abnormality or bilateral anterior plus unilateral posterior CBF abnormality provides support for frontotemporal dementia. All other CBF patterns fail to differentiate these two conditions. If a demented patient is considered to have either vascular dementia or frontotemporal dementia (table 3b), then bilateral anterior CBF abnormality provides support for the second diagnosis and all other CBF patterns fail to provide support for either disorder.

The usefulness of a particular test result depends on the particular diagnoses under consideration. For example, bilateral posterior CBF abnormality significantly increases the odds of a patient having Alzheimer's disease as opposed to vascular dementia or frontotemporal dementia, but does not change the odds of a patient having Alzheimer's disease as opposed to Lewy body disease or progressive aphasia. Similarly, bilateral anterior CBF abnormality significantly increases the odds of a patient having frontotemporal dementia as opposed to Alzheimer's disease, vascular dementia, or Lewy body disease, but does not change the odds of a patient having frontotemporal dementia as opposed to progressive aphasia. These findings draw attention to the limitations as well as the strengths of ^{99m}Tc -HMPAO SPECT as a clinical tool in the investigation of dementia, and the importance of interpreting test results in the light of the particular diagnoses under consideration.

The clinical value of ^{99m}Tc -HMPAO SPECT depends not only on how useful a particular test result is, but also on how often useful test results are obtained in the diagnosis of dementia. Table 4 shows the percentage of significant test results for each pairwise disease group comparison. Brain CBF imaging is most useful in distinguishing Alzheimer's disease from vascular dementia and frontotemporal dementia (>50% significant test results), and least useful in differentiating between Alzheimer's disease and Lewy body dementia, and between vascular dementia, frontotemporal dementia, and progressive aphasia (<25% significant test results). These findings provide a rationale for the selective use of ^{99m}Tc -HMPAO SPECT in the clinical diagnosis of dementia. To optimise its clinical use, it is suggested that CBF imaging should be restricted to those circumstances under which ^{99m}Tc -HMPAO SPECT provides most diagnostic gain (table 4), and its use in differentiating between Alzheimer's disease and Lewy body disease, and between vascular dementia, frontotemporal dementia, and progressive aphasia should be avoided to minimise inappropriate or unnecessary testing.

The findings of this study are largely consistent with the results of previous CBF SPECT studies²⁷⁻²⁹ that have shown posterior CBF abnormality in Alzheimer's disease,^{1-5 30} "patchy" CBF changes in vascular dementia,^{4 31} posterior CBF abnormality in Lewy body disease,³² anterior CBF abnormality in frontotemporal dementia,^{1 5 8 9 33} and left

sided CBF abnormality in progressive aphasia.^{5 7 34} However, these earlier studies have typically considered CBF findings in disease groups rather than individual patients, and have involved relatively few disease group comparisons. It has therefore not previously been possible to determine the diagnostic value of individual test results or the optimal role for CBF SPECT imaging in the clinical differentiation of dementia.

A potential limitation of this study is that the diagnostic gain of ^{99m}Tc-HMPAO SPECT has been determined for dementia patients grouped on clinical rather than gold standard neuropathological criteria, raising the possibility of diagnostic misclassification. It is therefore important to note that pathological confirmation of diagnosis has subsequently been obtained in 18 patients with no examples of misdiagnoses. Furthermore, study results are in agreement with those of others that have considered selected disease group comparisons of patients classified on neuropathological criteria.²⁹ It would therefore seem that study findings are robust. Nevertheless, the design of this study has not allowed the direct comparison of ^{99m}Tc-HMPAO SPECT with either neuropsychological evaluation or CT, so that the relative strengths of these methods of evaluation cannot be quantified. Furthermore, it has not been possible to determine whether ^{99m}Tc-HMPAO SPECT *itself* can strengthen a clinical diagnosis when the evolution of a patient's condition (over several years) is already known. A prospective study of an unselected population of patients with dementia with necropsy confirmation of diagnosis would be needed to consider these particular issues. Nevertheless, this study has shown that ^{99m}Tc-HMPAO SPECT can strengthen a tentative clinical diagnosis at the time of initial patient presentation, when the future evolution of the condition is unknown. This is an important finding given that the early and accurate diagnosis of dementia is essential to patient management and a necessary prerequisite for the critical evaluation of putative disease modifying drugs.

This study has relied on the visual interpretation of CBF images obtained using ^{99m}Tc-HMPAO and a multipurpose single headed gamma camera system available in most nuclear medicine departments throughout the United Kingdom. It is possible that the diagnostic gain of ^{99m}Tc-HMPAO SPECT might have been improved had CBF images been analysed in a semiquantitative manner. Furthermore, the use of a high resolution dedicated multiheaded detector system,³⁴ or repeat CBF imaging after an interval might have provided further diagnostic gain.³⁵ Nevertheless, this study has provided information that is useful to the clinician in the differential diagnosis of patients with dementia, and of relevance to many clinicians in other centres with access to similar facilities.

In evaluating the precise contribution of CBF imaging to the investigation of dementia, it is important to provide a measure of "usefulness" which is of value to the clinician in the

interpretation of individual test results. The measures of test accuracy most commonly used are sensitivity (the proportion of those with a particular disease who have a particular test result) and specificity (the proportion of those without that disease who do not have that test result). However, with the exception of wholly sensitive tests, which have no false negatives (when a negative test result excludes the diagnosis) and wholly specific tests, which have no false positives (when a positive test result is diagnostic), knowledge of the sensitivity and specificity of a test is of limited value because these indices do not directly inform the clinician of the post-test probability of a patient having a particular disease. Moreover, sensitivity and specificity values are difficult to apply to multiple disease group comparisons because under these circumstances the indices are affected by disease prevalence and results are not therefore applicable to other patient populations. Predictive values inform the clinician of the post-test probability of a patient having a particular disease and as such provide information that is useful in the interpretation of an individual test result.²⁷ However, predictive values do not provide an indication of diagnostic gain and their values are also dependent on disease prevalence. By contrast, likelihood ratios indicate the change in the pretest to post-test odds of a patient having a particular disease²⁵ and therefore provide a clinically useful measure of diagnostic gain. Furthermore, likelihood ratios can be applied to multiple test results and to multiple disease group comparisons.²⁴ If for a given test result, the post-test to pretest odds ratio is calculated for a particular disease compared with the absence of that disease, then its value is dependent on disease prevalence. However, if likelihood ratios are recalculated for pairwise disease group comparisons, then their values are independent of disease prevalence and results are therefore applicable to other patient populations. In clinical practice, the diagnostic task is often to choose between just two possible diseases¹³ and therefore likelihood ratios can provide a useful indication of the diagnostic gain of a test result and be applied to tests with multiple results and to multiple disease group comparisons.

In conclusion, this study shows that ^{99m}Tc-HMPAO SPECT provides a valuable contribution to the clinical differentiation of dementia. Moreover, it provides information that is useful to the clinician in the interpretation of individual test results, and a guide to the optimal clinical usage of CBF imaging in the differential diagnosis of dementia. This study reveals that patterns of CBF abnormality are not specific to a single disease, yet test results can be used to modify clinical diagnoses. It is therefore suggested that CBF imaging should be used selectively and as an adjunct to clinical evaluation and CT in the investigation of dementia.

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