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$^{99}Tc^{m}$-HMPAO SPECT in suspected dementia

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Summary

To evaluate the usefulness of $^{99}Tc^{m}$-hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) in suspected dementia we studied 160 consecutively imaged elderly patients from our hospital's memory disorder clinic. The diagnosis was based on clinical data, laboratory tests, neuropsychological examination, computed tomography (CT) and EEG. The patients were divided into six diagnostic categories: Alzheimer's disease (AD), multi-infarct dementia (MID), frontal lobe-type dementia (FTD), vascular encephalopathy not fulfilling the criteria of dementia, specific organic conditions, and psychiatric disorders. SPECT images were assessed without knowing the clinical diagnosis, and divided into AD pattern, FTD pattern, MID pattern, abnormal but unclassifiable, and normal. Twenty-three of 36 patients with clinical AD, 25/33 patients with clinical MID, and 2/5 patients with clinical TFD had compatible SPECT patterns. SPECT distinguished AD from MID in the majority (80%) of cases. In patients with depression or anxiety SPECT was abnormal in 16/21 cases, suggesting that SPECT may give early clues to the presence of an underlying organic disease in such elderly patients. Thus, SPECT with $^{99}Tc^{m}$-HMPAO seems to be useful in the diagnosis of suspected dementia.

Introduction

The differential diagnosis of suspected dementia is still problematic. Although the *ante mortem* accuracy of the diagnosis of Alzheimer's disease (AD) and multi-infarct dementia (MID), as verified *post mortem*, may be around 80% [1, 2], less favourable results have also been reported [3, 4]. Differential diagnosis may be especially difficult in the early stage of a dementing disease and therefore treatment may be delayed in patients with potentially treatable diseases. Thus, new diagnostic tools are still needed.

With $^{99}Tc^{m}$-hexamethylpropyleneamine oxime (HMPAO) regional cerebral blood flow (rCBF) can be studied with a tomographic gamma camera [5]. This now standard technique has already given promising results in selected demented patients showing

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bilateral parieto-temporal hypoperfusion in AD and multiple often asymmetric areas of hypoperfusion in MID [6–13].

The aim of this study was to test the diagnostic value of $^{99}Tc^{m}$-HMPAO SPECT, assuming that typical rCBF patterns exist for certain types of dementia in a large series of consecutively imaged patients with suspected dementia.

Patients and methods

Patients

We studied 160 patients with suspected dementia (98 females, 62 males, mean age 64 ± 8 years) admitted to the out-patient memory disorder clinic of the Helsinki University Central Hospital (Table 1).

Table 1. Clinical characteristics of 160 patients with suspected dementia.

	Clinical diagnosis					
	AD	*MID*	*FTD*	*SPEC*	*VASC*	*PSYCH*
n	36	33	5	32	33	21
Age ± S.D.	64.9 ± 8.1	68.0 ± 7.9	66.0 ± 5.1	58.4 ± 12.0	67.6 ± 7.8	60.0 ± 7.7
Duration of disease ± S.D.	2.8 ± 2.0	3.2 ± 2.0	3.2 ± 1.5	2.0 ± 3.1	2.6 ± 1.2	2.6 ± 2.0
Females	25	24	2	16	19	12
Males	11	9	3	16	14	9

AD = Alzheimer's disease, MID = multi-infarct dementia, FTD = frontal lobe-type dementia, SPEC = specific causes for dementia, VASC = vascular encephalopathy without dementia, PSYCH = psychiatric disorder (depression or anxiety).

Clinical assessment

The patients were examined by a neurologist (RS or TE). Each patient was assessed by means of history taking including an interview of a close informant, physical and mental examination, a neuropsychological examination, blood tests, EEG, and computed tomography (CT) [14, 15]. The SPECT results were unknown to the clinicians.

The neuropsychological assessment was based on the D-test battery [15]. The severity of cognitive involvement was divided into no cognitive impairment, cognitive impairment not fulfilling the criteria of dementia, and mild, moderate, or severe dementia [16].

The underlying conditions were divided into AD, MID, frontal lobe-type dementia (FTD), vascular encephalopathy without dementia, specific organic conditions and psychiatric disorders.

The clinical criteria for AD were those of McKhann *et al.* [17]. The DSM-III-R clinical criteria were used for the diagnosis of MID [18]. The MID group was also expected to include patients with combined vascular and degenerative dementia. Patients with FTD fulfilled the AD criteria, but had frontal behavioural symptoms and normal background EEG [19]. The patients with psychiatric disorders (depression and anxiety) had no evident organic disorders explaining their symptoms and fulfilled the clinical criteria of DSM-III-R for these disorders.

Assessment of regional cerebral blood flow

The rCBF patterns on the SPECT scans were interpreted visually and without knowledge of the clinical data into five different rCBF patterns according to the criteria in Table 2. Illustrative examples are presented in Fig. 1.

Table 2. Criteria for classifying SPECT imaging findings.

Alzheimer's disease (AD) pattern
A bilateral posterior parieto-temporal or parieto-temporo-occipital hypoperfusion
Asymmetries as well as focal bilateral or unilateral perfusion abnormalities elsewhere were allowed if the first criterion is fulfilled
Multi-infarct dementia (MID) pattern
A single large defect or multiple perfusion defects but no bilateral posterior parieto-temporal hypoperfusion
Crossed cerebellar diaschisis often present
Frontal lobe-type dementia (FTD) pattern
A bilateral frontal or frontotemporal area of hypoperfusion
Unclassifiable
Scans that could not be regarded as normal (e.g. a single small area of hypoperfusion unilaterally, abnormally poor tracer uptake in the basal structures) but not classifiable as AD, MID or FTD
Normal
Scans with no perfusion abnormalities

As the perfusion defects are not known to be preferentially located in any particular brain areas in MID and a number of other dementing conditions, in contrast to AD and FTD, we did not semiquantify the rCBF (e.g. by calculating cortical/cerebellar count density ratios).

Imaging

SPECT imaging was performed with a General Electric 400T rotating large field of view gamma camera equipped with a general purpose parallel hole collimator. The camera was connected to a Digital PDP-11 computer equipped with Gamma-11 software. A 370–600 MBq dose of $^{99}Tc^{m}$-HMPAO was injected intravenously. The patients were not instructed to close their eyes. Data acquisition was started 2–5 min after the injection. Using the Gamma-11 system's filtered back projection algorithm with a modified Shepp-Logan filter transversal, coronal and sagittal tomograms were reconstructed and printed on Polaroid colour film. The lower threshold value was set at 25%.

Statistics

Risk ratios and Miettinen's test based confidence limits were calculated for 2 × 2 tables [20], and statistical differences between groups were tested by the Mantel–Haenzel test. Differences between groups were tested using the χ^2 test.

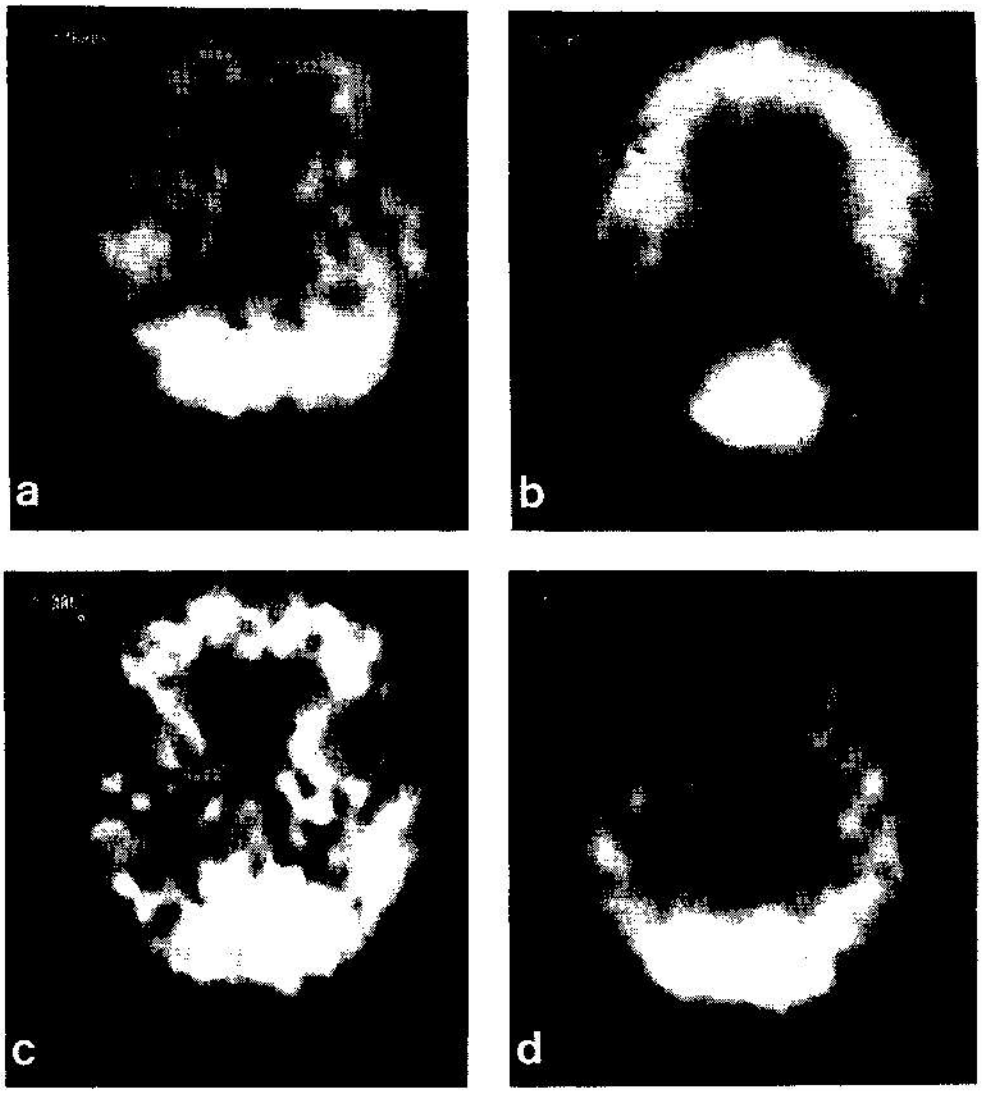

Fig. 1. (a) Normal regional cerebral blood flow in a 70-year-old female. (b) Alzheimer's disease pattern: bilateral posterior temporo-parietal hypoperfused areas. (c) Multi-infarct dementia pattern: multiple small perfusion defects in the cerebral cortex. (d) Frontal lobe-type dementia pattern: severe hypoperfusion in both frontal and anterior parts of temporal lobes.

Results

The number of abnormal SPECT scans was 140/160 (87.5%). SPECT scans were abnormal in 50/62 (80.6%) patients without dementia, in 41/47 (87.2%) patients with mild dementia, in 36/38 (94.7%) patients with moderate dementia, and in 13/13

(100%) patients with severe dementia. Altogether 139/160 (86.9%) patients had an organic brain disorder explaining their symptoms.

Non-demented patients

The distribution of the SPECT findings in the 62 non-demented patients is presented in Table 3. Among the 21 psychiatric patients 16 had an abnormal SPECT scan. Of the abnormal scans three were of AD type and 10 were of MID type. Two-thirds of the patients with a non-dementing vascular disorder were classified into the MID group. In the non-demented group SPECT could not differentiate between patients with psychiatric (χ^2 0.09, n.s.) or vascular disease (χ^2 0.88, n.s.), and the rest of the group.

Table 3. $^{99}Tc^{m}$-HMPAO regional cerebral blood flow pattern in the 62 non-demented patients studied due to suspected dementia

Clinical diagnosis	*AD pattern*	*MID pattern*	*FTD pattern*	*Unclassifiable*	*Normal*	*Total*
Patients without dementia						
Psychiatric disorder	3	10	–	3	5	21
Vascular disorder	7	22	–	–	4	33
Specific causes*	–	5	–	–	3	8
Total	10	37	–	3	12	62

* Epilepsy, global amnesia, head injury (one patient each) and alcohol abuse (five patients).
AD = Alzheimer's disease, MID = multi-infarct dementia, FTD = frontal lobe-type dementia.

Demented patients with Alzheimer's disease

The SPECT findings in the 98 demented patients are presented in Table 4. Of the 36 patients with the clinical diagnosis of AD 23 (63.9%) had an AD SPECT pattern. Compared with all the demented patients studied this corresponds to a risk ratio (RR) of 13.9 [95% confidence limits (95% CL 5.2–37.4)].

Demented patients with multi-infarct dementia

Of the 33 patients with clinical MID 25 (75.8%) had a MID SPECT pattern [RR 5.7 (95% CL 2.2–14.9) compared with all demented patients].

Differentiation between Alzheimer's disease and multi-infarct dementia

The AD and MID groups differed significantly [χ^2 15.8, $P < 0.001$; RR 11.50 (95% CL 3.5–10.5)] with regard to their SPECT patterns. Divided according to the severity of dementia, SPECT did not significantly differentiate between AD and MID in the mildly demented group [χ^2 2.19, n.s.; RR 5.0 (95% CL 0.6–42.1)] where 21 (72.4%) cases were correspondingly classified, or in the moderately demented group where 18 (64.3%) cases correspondingly classified (χ^2 1.20, n.s.; RR 4.1 (95% CL 0.3–50.1)], or

Table 4. $^{99}Tc^{m}$-HMPAO regional cerebral blood flow pattern in the 98 demented patients studied.

Clinical diagnosis	*AD pattern*	*MID pattern*	*FTD pattern*	*Unclassifiable*	*Normal*	*Total*
All patients with dementia						
AD	23	10	1	–	2	36
MID	5	25	2	1	–	33
FTD	1	2	2	–	–	5
Specific causes*	1	11	5	1	6	24
Total	30	48	10	2	8	98
Patients with mild dementia						
AD	5	1	1	–	2	9
MID	1	16	2	1	–	20
FTD	1	1	2	–	–	4
Specific causes	–	8	2	–	4	14
Subtotal	7	26	7	1	6	47
Patients with moderate dementia						
AD	13	8	–	–	–	21
MID	2	5	–	–	–	7
FTD	–	1	–	–	–	1
Specific causes	–	3	3	1	2	9
Subtotal	15	17	3	1	2	38
Patients with severe dementia						
AD	5	1	–	–	–	6
MID	2	4	–	–	–	6
FTD	–	–	–	–	–	–
Specific causes	1	–	–	–	–	1
Subtotal	8	5	–	–	–	13

* Hereditary spinocerebellar ataxia, sleep apnoea syndrome, Huntington's chorea, sequelae of encephalitis, brain tumour, Wernicke–Korsakoff syndrome, head injury, hydrocephalus (three patients), metabolic abnormality (five patients) and alcohol abuse (nine patients).
AD = Alzheimer's disease, MID = multi-infarct dementia, FTD = frontal lobe-type dementia.

in the severely demented group where nine (75%) patients correspondingly classified [χ^2 1.37, n.s.; RR 10 (95% CL 0.2–471.7)]. However, when the groups of mildly and moderately demented patients were combined SPECT differentiated significantly between AD and MID [χ^2 6.84, $P < 0.01$; RR 5.3 (95% CL 1.5–18.2)].

Demented patients with frontal lobe-type dementia

Two of the five patients with clinical FTD were classified correspondingly by SPECT [χ^2 2.25, n.s.; RR 7.1 (95% CL 0.5–91.1)].

Table 4. $^{99}Tc^{m}$-HMPAO regional cerebral blood flow pattern in the 98 demented patients studied.

Clinical diagnosis	*AD pattern*	*MID pattern*	*FTD pattern*	*Unclassifiable*	*Normal*	*Total*
All patients with dementia						
AD	23	10	1	–	2	36
MID	5	25	2	1	–	33
FTD	1	2	2	–	–	5
Specific causes*	1	11	5	1	6	24
Total	30	48	10	2	8	98
Patients with mild dementia						
AD	5	1	1	–	2	9
MID	1	16	2	1	–	20
FTD	1	1	2	–	–	4
Specific causes	–	8	2	–	4	14
Subtotal	7	26	7	1	6	47
Patients with moderate dementia						
AD	13	8	–	–	–	21
MID	2	5	–	–	–	7
FTD	–	1	–	–	–	1
Specific causes	–	3	3	1	2	9
Subtotal	15	17	3	1	2	38
Patients with severe dementia						
AD	5	1	–	–	–	6
MID	2	4	–	–	–	6
FTD	–	–	–	–	–	–
Specific causes	1	–	–	–	–	1
Subtotal	8	5	–	–	–	13

* Hereditary spinocerebellar ataxia, sleep apnoea syndrome, Huntington's chorea, sequelae of encephalitis, brain tumour, Wernicke–Korsakoff syndrome, head injury, hydrocephalus (three patients), metabolic abnormality (five patients) and alcohol abuse (nine patients).
AD = Alzheimer's disease, MID = multi-infarct dementia, FTD = frontal lobe-type dementia.

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Demented patients with frontal lobe-type dementia

Two of the five patients with clinical FTD were classified correspondingly by SPECT [χ^2 2.25, n.s.; RR 7.1 (95% CL 0.5–91.1)].

Specific organic causes for dementia
Most of the patients with specific organic causes of dementia had normal, MID or FTD SPECT patterns (10, 16 and five patients, respectively), but only one patient showed the AD pattern.

Discussion

To the best of our knowledge, this is the first study where the rCBF of consecutively imaged patients with suspected dementia has been assessed blindly. The number of SPECT abnormalities in our material was high, and the number of abnormal scans increased with the severity of the disorder.

For classifying the scans into diagnostic groups, we used criteria reported by others [6–13, 21, 22]. By these criteria, SPECT classified the various patient groups reasonably well (Table 3), although the sensitivity and specificity were not particularly high for any patient category studied. The sensitivity would probably have improved had the scans been assessed as being against or in favour of two alternative diagnoses (e.g. AD versus MID) rather than blindly. No weight was given to the severity of the rCBF abnormalities, which might have prevented the misclassification of some of the midly abnormal scans.

Non-demented patients
The number of abnormal SPECT findings in patients with depression and anxiety was surprisingly high. Most of the patients had one large or several smaller areas of hypoperfusion and were thus classified into the MID group. These abnormal findings may be secondary to depression, or may reflect organic brain changes that trigger the psychiatric disorder, as e.g. in early MID or AD [23, 24].

Demented patients with Alzheimer's disease
In AD hypoperfusion is often seen bilaterally in the posterior parieto-temporal areas and the severity of the hypoperfusion may reflect the severity of the disease [25]. In our study, the number of abnormal findings in AD patients increased with the severity of the dementia. Also, when cognitive deterioration is not stepwise, a SPECT scan with multiple perfusion defects may suggest rather a vascular than a degenerative aetiology. Thus, SPECT scanning may be the only routinely used imaging method suggesting the diagnosis of AD.

Demented patients with multi-infarct dementia
In MID, in contrast to AD and FTD [24], so far no particular brain areas where the perfusion abnormalities are preferentially located have been identified. The pattern of MID in SPECT does not appear to depend on the mental ability of the patient, as two-thirds of the non-demented patients with vascular encephalopathy had this type of SPECT pattern and were misclassified into the MID group.

Differential diagnosis of Alzheimer's disease and multi-infarct dementia

The ability of rCBF SPECT to differentiate between AD and MID was fairly good, especially considering that our material contains a variety of other diagnoses and the scans were assessed blindly. SPECT separated AD from MID especially in the mildly and moderately demented groups.

Demented patients with frontal lobe-type dementia

Frontal lobe-type dementia could not reliably be separated from other forms of dementia by SPECT in our study. The number of patients in this subgroup is so small that far reaching conclusions cannot be made, but our findings may reflect the heterogeneity of FTD [26].

We conclude that brain perfusion SPECT is helpful in the diagnosis of patients with suspected dementia, especially in cases of early dementia or less severe cognitive impairment, but the results of the scans should always be interpreted together with those of other investigations [26, 27].

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