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Brain perfusion defect size in SPECT predicts outcome in cerebral infarction

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Summary

The results of previous reports on the usefulness of brain perfusion single photon emission computed tomography (SPECT) in predicting the outcome of patients with acute cerebral infarction are conflicting. We therefore studied brain perfusion in 64 patients with a single supratentorial infarction. Contradictory to previous results the perfusion defect volume estimated from transversal and coronal slices correlated significantly with both presenting clinical findings and outcome. Although the clinical status at admission also correlated well with outcome, there was a subgroup of patients in which the favourable outcome was predicted only by SPECT and not by physical or any other examination at admission.

Introduction

The outcome of patients with brain infarction is influenced by the size and location of the infarction and by age and previous diseases. A large infarcted area, space occupying oedema, lowered state of consciousness, parietal lobe involvement [1] and the dense middle cerebral artery sign in CT scanning [2] are associated with an unfavourable outcome.

Brain perfusion scanning utilizing single photon emission computed tomography (SPECT) and lipophilic blood flow tracers, especially ^{123}I-N-isopropyl-iodoamphetamine (IMP) and ^{99m}Tc^{m}-hexamethylpropyleneamine oxime (HM-PAO) [3, 4], is now in clinical use, epilepsy [5], dementia [6], encephalitis [7], and stroke [8] being the most common indications. Surprisingly little is known about the usefulness of this method in predicting the outcome of patients with brain infarction. Lee *et al.* [9] reported that IMP-SPECT could not predict the long-term outcome in 16 patients imaged within a

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Table 1. Status and outcome of patients included in the study.

Sex	*Age*	*DV-index*	*Laterity of SPECT finding*	*Location of SPECT finding*	*Status at admission*	*Status at time of SPECT*	*Outcome*	*Days between onset and SPECT*	*Follow-up in days*
M	31	0.00	—	—	2	1	1	14	14
F	52	0.00	—	—	3	2	1	18	90
M	60	0.00	—	—	3	2	1	5	74
M	45	0.00	—	—	2	2	1	1	403
F	54	0.00	—	—	1	1	1	6	44
F	32	0.00	—	—	3	2	1	9	90
F	49	0.00	—	—	3	3	1	13	94
M	68	0.00	—	—	3	3	1	5	20
M	21	0.00	—	—	3	2	1	2	7
F	21	0.00	—	—	1	1	1	17	19
F	21	0.00	—	—	2	2	1	8	65
F	50	0.00	—	—	3	3	1	2	6
M	65	0.32	L	MCA	3	2	1	20	42
F	24	0.36	R	MCA	2	2	1	3	17
F	69	0.40	L	MCA	3	3	1	1	84
F	42	0.42	L	MCA	4	4	2	7	22
F	42	0.42	R	MCA	2	2	1	16	97
M	56	0.45	R	MCA	3	3	1	8	258
M	57	0.47	L	MCA	2	2	1	10	17
M	43	0.49	R	PCA	2	2	1	46	73
F	71	0.49	R	MCA	2	2	1	2	67
F	54	0.51	L	ACA	1	1	1	6	77
M	60	0.52	L	MCA	1	1	1	29	89
M	61	0.53	R	ACA	4	2	1	2	16
F	47	0.55	L	ACA	3	3	2	6	125
M	57	0.55	L	MCA	2	1	1	5	143
M	53	0.56	L	MCA	2	1	1	2	57
M	53	0.56	L	PCA	2	2	1	1	10
M	65	0.56	R	MCA	2	2	1	1	88
M	76	0.57	R	MCA	2	2	1	1	99
M	74	0.57	L	MCA	3	3	2	0	88

F	53	0.57	L	MCA	2	1	1	31	32
F	58	0.59	R	MCA	2	2	1	14	281
M	44	0.63	R	PCA	5	5	4	2	92
M	56	0.69	L	MCA	3	3	1	3	204
F	37	0.71	R	MCA	3	3	1	24	91
F	37	0.71	R	MCA	3	3	1	3	91
M	56	0.73	L	MCA	4	3	2	6	342
M	30	0.76	L	MCA	2	2	1	12	78
F	53	0.76	R	MCA	3	3	1	6	21
M	16	0.77	R	PCA	2	2	1	9	117
M	57	0.81	R	PCA	3	3	1	3	102
M	56	0.82	R	MCA	3	3	2	71	398
M	51	0.82	R	MCA	3	3	3	14	66
F	41	0.82	L	MCA	3	3	2	120	412
F	61	0.90	L	MCA	2	2	2	2	55
M	72	0.96	L	ACA	4	4	4	10	156
M	64	1.00	R	MCA	4	4	3	3	92
M	57	1.02	R	MCA	5	5	4	2	50
M	66	1.02	L	MCA	4	4	5	3	12
M	65	1.08	L	MCA	3	3	2	41	40
F	54	1.08	R	MCA	3	3	3	21	36
F	41	1.08	R	MCA	4	4	4	9	49
F	14	1.09	R	MCA	4	3	2	5	83
M	38	1.09	R	MCA	4	4	2	60	71
M	56	1.11	L	PCA	2	2	1	7	337
F	36	1.13	L	MCA	4	4	3	6	87
M	65	1.15	R	MCA	4	4	4	9	196
F	52	1.23	R	MCA	3	3	3	1	82
M	58	1.24	L	MCA	3	3	3	9	24
M	59	1.27	R	MCA	5	5	4	2	106
M	55	1.39	L	MCA	4	3	4	3	50
M	57	1.44	R	ACA	4	4	3	1	168
F	56	2.89	R	MCA	3	3	3	1	92

F = female; M = male; L = left; R = right.
ACA, MCA, PCA = anterior, middle, posterior cerebral artery area, respectively.

week of brain infarction, although the lesion size and magnitude of perfusion decrease in the lesion correlated well with the early symptoms. Defer *et al.* [10] reported that filling-up of the perfusion defect in the delayed IMP-SPECT scan 4 h after injection predicts the outcome, wheras local hypoactivity in scintigraphy performed 20 min after the injection does not. Also, the increased retention of tracer followed by reduced washout after an ischaemic stroke has been suggested to indicate a good prognosis [11] although this view has been challenged also [12].

Both groups estimated the degree of hypoperfusion in the affected area relative to an unaffected brain region, and the defect size in tomographic slices. The importance of the volume of the infarction for the outcome [13], and the frequent discordance between brain perfusion scan and CT results in stroke [14], are well known. It has also been shown that the size of the periinfarct area visualized in regional blood flow scans may be an important predictor of the clinical outcome [14].

Keeping the importance of the periinfarct area in mind, we measured the volume of the perfusion defect relative to the brain volume. This method was used to examine if the SPECT result could predict clinical outcome in cerebral infarction. We report here that both IMP and HM-PAO SPECT imaging results correlate with the clinical outcome. SPECT is also capable of predicting favourable outcome in patients with unfavourable clinical status at the time of SPECT.

Patients and methods

Patients

We studied 89 patients with supratentorial brain infarction referred to the Department of Neurology, Helsinki University Central Hospital. All patients were hospitalized due to ischaemic cerebral signs and symptoms lasting for over 24 h. Noncontrast CT scanning was performed to verify the brain infarction or to exclude intracranial haemorrhage. Patients with incomplete medical records were excluded from analysis, as were patients with current multiple infarctions or a history of previous cerebral damage. Sixty-four patients fulfilled all the criteria and were included in the study (Table 1). Information on clinical status at the time of admission, SPECT imaging and discharge was obtained from the patients' charts. The patients were grouped into five categories in terms of physical examination findings (Table 2) and also in terms of activities of daily living (ADL) (Table 3). Both status and outcome were regarded as unfavourable in groups 3–5.

Table 2. Grouping of patients with cerebral infarction according to clinical status

1. Minimal hemiparesis; or dysphasia; or disturbance of coordinative function; or dysfunction of cranial nerves without hemiparesis
2. Moderate hemiparesis; or dysphasia; or a distinct visual defect without hemiparesis; or a moderate isolated cognitive defect
3. Hemiparesis with only some movement left in the upper or lower extremity; or cortical blindness; or a severe cognitive defect with or without hemiparesis
4. Hemiparalysis
5. Hemiparesis and lowered state of consciousness

Table 3. Grouping of patients with cerebral infarction as based on activities of daily living (ADL) at outcome.

1. Completely independent in ADL
2. Requires some, but not daily, assistance in ADL
3. Requires daily assistance in ADL
4. Requires hospital care
5. Dead

Subjects in groups 3 to 5 were considered to have unfavourable outcome.

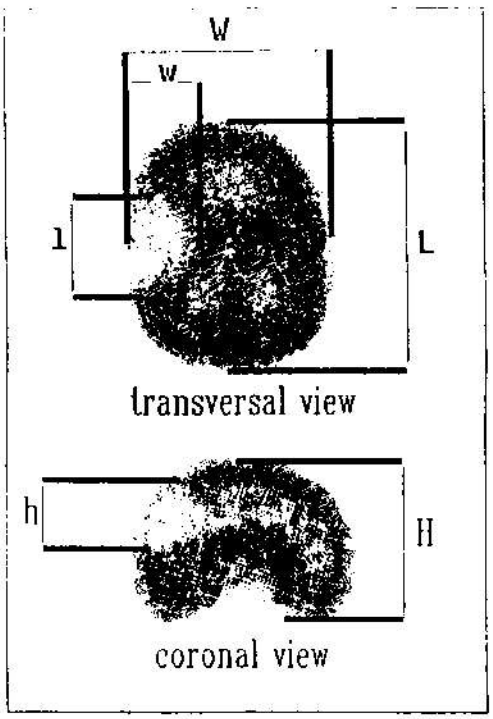

Fig. 1. A schematic illustration of how the defect size was measured. W = width of the brain, w = width of the defect, L = length of the brain in the anteroposterior projection, l = length of the defect, H = height of the brain, and h = height of the defect. See text on how the defect volume (DV) index was calculated.

The hospitalization time varied from 6 to 412 days (Table 1). Patients with only modest neurological symptoms were usually rapidly discharged from the hospital while those with more severe neurological symptoms were rehabilitated in the Department of Neurology. In spite of the differences in hospitalization time three distinct outcome categories could be defined and used for decision making: (1) discharge from hospital, (2) transfer to another institution in a disabled but stable condition, and (3) dead.

CT imaging

CTs were obtained using the General Electric 8080 or Siemens Somatom scanners. Intravenous contrast medium was not routinely used.

SPECT imaging

SPECT scanning was performed with a General Electric 400T rotating large field-of-view gamma camera equipped with a high resolution low energy parallel hole collimator. The camera was connected to a Digital PDP-11 computer equipped with Gamma-11 software. Filtered back projection algorithm was used for producing the tomograms.

Imaging was performed either by using 4.6–7.0 mCi of ^{123}I-labelled IMP and one frame per 40 s (36 patients), or 10.0–16.0 mCi of ^{99m}Tc-labelled HM-PAO and one frame per 30 s (28 patients). The tracer was injected into the antecubital vein with the patient in recumbent position in a dimly lit room. Data acquisition was started after 20 min (IMP) or 2 min (HM-PAO) according to the manufacturers' instructions.

Transversal, coronal and sagittal tomographic slices were printed on X-ray film using the Illinois Imaging Electronics Inc. (IL, USA) Model 5000C microdot multiformatter. The lower threshold value was set at 15%.

Analysis of SPECT images

The perfusion defect was identified and its size was measured from the transversal and sagittal slices in which the defect appeared largest. The perfusion defect volume (DV) index was calculated according to the formula:

$$DV = l \cdot L \cdot h \cdot H + w \cdot W \tag{1}$$

where:

L = maximal length of the transversal slice in the fronto-occipital projection
l = maximal length of the defect in the above slice
W = maximal width of the transversal slice
w = maximal width of the defect in the above slice
H = maximal height of the supratentorial part of the brain in the coronal slice
h = maximal height of the defect in the above slice

In cases where a clear defect contralateral to the patient's symptoms existed, but measurements were inaccurate because of the small size of the defect, the value of the size of the system's resolution element in the microdot pictures (2 mm) was given to l, w and h. In cases with no visible defects a *DV*-index value of 0 was used. Fig. 1 gives a schematic representation of how the measurements were made.

Statistical analysis

Spearman's rank correlation test was used for calculating the correlations. The Mantel-Haenszel chi-square test was used to test significance of the difference in outcome and the Wilcoxon's rank sum test to test the differences in outcome of patients imaged with IMP or HM-PAO.

Results

Data on status at admission, SPECT imaging, outcome, interval between onset of stroke and SPECT imaging, and *DV* index is given in Table 1. A significant correlation was found between the clinical outcome and the *DV*-index ($r = 0.75$, $p < 0.001$). Also,

both the status at admission and at the time of SPECT correlated significantly with the outcome ($r = 0.72$, $p < 0.001$ and $r = 0.77$, $p < 0.001$, respectively). Thirty-five out of 64 patients had unfavourable status at the time of SPECT, while 16 out of 64 had unfavourable outcome (Fig. 2).

Age did not correlate significantly with the outcome ($r = 0.16$, $p = 0.20$). The patients with unfavourable status at the time of SPECT were imaged somewhat earlier (median 6.0 days, range 0–120) than those with favourable status (median 7.0 days, range 1–46). The median follow-up period of all patients was 82.5 days (range 6–412); 80.5 days (range 6–412) in patients with favourable outcome and 84.5 days (range 12–196) in patients with unfavourable outcome. There was a significant correlation between the *DV*-index and status on admission ($r = 0.49$, $p < 0.001$) and also at the time of SPECT imaging ($r = 0.59$, $p < 0.001$). No significant difference between the outcome in patients imaged with IMP or HM-PAO was found ($z = 1.28$, $p = 0.20$).

The correlation between the *DV*-index and outcome was most significant in cases of

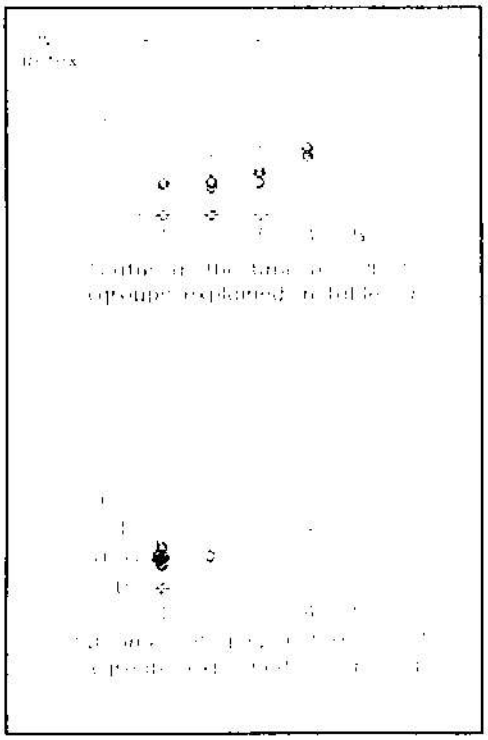

Fig. 2. The distribution of defect volume (*DV*) index values relative to status at the time of SPECT and outcome. Both outcome and the status at the time of SPECT correlate significantly with the *DV*-index representing the volume of the ischaemic defect seen on SPECT. Note the very small overlap of *DV*-index values in patients with favourable and unfavourable outcomes when 1.00 is used as an arbitrary cut off value

middle cerebral artery (MCA) area infarctions. In cases of anterior cerebral artery (ACA) infarctions there was a tendency in the same direction, although not statistically significant. In posterior cerebral artery (PCA) infarctions the *DV*-index did not predict the outcome (Table 4).

In the subgroup with favourable status at the time of SPECT, the *DV*-index did not significantly correlate with outcome ($r = 0.30$, $p = 0.11$). However, in the subgroup with unfavourable status at the time of SPECT, the patients with favourable outcome tended to have smaller *DV*-indices (median 0.71, range 0–1.11) than patients with unfavourable outcome (median 1.11, range 0.63–2.89) (Table 1, Fig. 2).

Discussion

The defect visualized by SPECT often consists of two areas, a central area corresponding to the region of irreversible ischaemic damage, and a periinfarct area which probably represents a region of deafferentated neurons with reduced metabolism [14]. Histologically only a very narrow transitional zone between the infarcted area and viable tissue exists [13]. The discordance between SPECT and CT scans [16] is caused, at least in part, by this periinfarct area. Therefore it is probable that the whole area of diminished radiotracer uptake – regardless of whether caused by infarction or deafferentation – correlates best with the initial neurological symptoms as reported earlier [9, 10, 15].

Contradictory to these earlier reports [9, 10, 15], a significant correlation between the SPECT finding and clinical outcome was found by us. The status at the moment of SPECT and at the time of admission also correlated well with the SPECT results. Lee *et al.* [9] studied 16 patients in whom CT predicted the ultimate recovery better than IMP SPECT. Defer *et al.* [10] studied 24 patients, 21 of whom had a completed stroke. They found a subgroup in whom the defect seen in the first scan, recorded immediately after injection of the tracer, was not visualized in a delayed scan several hours later. The tracer may thus redistribute into areas of preserved, although reduced, perfusion. This phenomenon may be explained either by a small brain infarction in combination with a large periinfarct area, or by a noncompleted stroke with viable neurons capable of regaining function in a low-perfused area. Thus, the small number of permanently damaged neurons seems to account for the favourable outcome in these cases.

We did not try to differentiate between central and periinfarct areas, but measured the actual size of the defect visualized in SPECT. Nor did we semiquantitate the decrease of blood flow in the defect area relative to any brain area assumed normal as such a method seems to be of limited value in stroke [9, 10]. The validity of such a method has recently been questioned, as the semiquantitative SPECT results and quantitative positron emission tomography regional cerebral blood flow values correlate poorly [17]. In the report by Raynaud *et al.* [15] the size of the periinfarct area correlated with outcome. In our material, there is, however, some overlap in the *DV*-indices of patients with favourable and unfavourable outcomes. The method of

assessing defect size not based on defect volume, and the significantly smaller number of patients than in our study probably explains why Lee *et al.* [9] and Defer *et al.* [10] did not find a significant correlation between outcome and defect size.

In our material the most significant correlation between *DV*-index and outcome was seen in the MCA vascular area infarctions. In infarctions involving the ACA vascular territory there was a similar tendency, but probably due to the small number of patients this was not statistically significant. Both MCA and ACA vascular territory infarctions can cause a disabling hemiparesis, as the motor functions are largely associated with these areas. PCA area infarctions usually cause either visual or cognitive defects and it is therefore not surprising that the *DV*-index did not correlate with the outcome measured in terms of ADL in this group.

We conclude that measuring defect volume index is helpful in determining the outcome of patients with recent brain infarction, especially in the ACA and MCA areas. The role of the newly proposed dual imaging [11] needs further clarification, but using the information gained from both *DV*-index and dual scanning might improve the accuracy. A *DV*-index value of 1.00 seems to differentiate reasonably well between the two outcome groups and is therefore suggested as an arbitrary cut off limit. SPECT is now generally available, relatively uncostly, simple and, most importantly, reveals data that cannot be obtained by clinical findings, CT or MRI. Especially patients with grave neurological symptoms but only a small defect in SPECT seem to have a more favourable outcome than can be predicted from clinical findings. Identifying such a subgroup may be of value, and it should be further studied if this method could be employed in identifying patients most likely to benefit from rehabilitation or other treatment.

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