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Prospective neuropathological validation of Hachinski's Ischaemic Score in dementias

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Abstract

The sensitivity and specificity of Hachinski's Ischaemic Score (IS) in the diagnosis of the vascular aetiology of dementia was studied in a series of 32 demented patients, dementia of the Alzheimer type (16), multi-infarct dementia (7), mixed dementia (6), Pick's disease (3), with neuropathological diagnosis as the point of reference. The IS distinguished between primary degenerative dementia and multi-infarct or mixed dementia. As single features of the IS "a positive history of stroke" and "a fluctuating course" showed differing prevalences in the latter two diagnostic categories. The IS labelled 21% of patients with primary degenerative dementia as having a vascular aetiology. The uncritical application of the IS to large samples in epidemiological studies may cause incorrect labelling of a significant proportion of patients with primary degenerative dementia as vascular dementia. These results are based on observations of long-term inpatients and depend on neuropathological criteria. While the definite diagnosis of DAT by threshold criteria concerning plaque and tangle counts is well established, neither clinical nor pathological evidence of stroke necessarily means that cerebrovascular disease has anything to do with a patient's dementia.

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There is a need for valid and reliable methods to distinguish in life between primary degenerative dementia (PDD) and multi-infarct dementia (MID).[1 2] The PDD of Alzheimer's type (DAT) is the most frequent type of dementia in the elderly, having a two- to fourfold incidence compared with MID.[3 4] The coexistence of DAT and MID, commonly labelled as mixed dementia (MIX), is seen in about 10% of demented patients and further complicates this discrimination.

In 1975, Hachinski *et al*[5] described the "ischaemic score" (IS) as an empirical scale for the clinical differentiation between PDD and MID. Thirteen items were scored one or two points according to a handbook of clinical psychiatry.[6] Hachinski *et al* found a sum score of four or less indicative of patients with PDD and a sum score of seven or more for MID patients. This scale has been used in numerous clinical dementia studies. The validity of the IS, however, has been questioned and modified versions have been proposed (table 1), most of them having differing maximal scores and/or include additional items.[7–14]

In view of the clinical importance of distinguishing between DAT and MID, further prospective clinico-pathological studies on the accuracy of the IS are necessary. We tried to validate the IS in a prospective clinico-pathological study of a consecutive series of 32 demented elderly patients.

Table 1 Original and revised scorings of the ischaemic scale

		Hachinski 1975	*Rosen 1980*	*Loeb 1983*	*Kawas* 1986*	*Fischer 1989*
1	Abrupt onset	2	2	2	2	2
2	Stepwise deterioration	1	2		1	1
3	Fluctuating course	2				2
4	Nocturnal confusion	1				1
5	Preserved personality	1				1
6	Depression	1				1
7	Somatic complaints	1	1			1
8	Emotional incontinence	1	1			1
9	Hypertension	1				1
10	History: strokes	2	2	1	2	2
11	Assoc atherosclerosis	1	0			1
12	Focal neurol symptoms	2	2	2	2	2
13	Focal neurol signs	2	2	2	2	
One low density area on CCT				2		
Multiple foci on CCT				3		
Definite infarct on CCT					2	2
White matter change on CCT					1	
Maximum		18	12	12	12	18

*From Katzmann (1986).

Material and methods

The series includes necropsies on 32 consecutive, demented chronic inpatients from the neurology department of a geriatric hospital. Females were over-represented because of a ratio of five female:one male wards. Dementia was diagnosed according to the DSM-III-R criteria.[15] Severity of dementia was assessed by the Mini Mental State (MMS) examination.[16] Only patients with scores of less than 24 were included.[17] The patients were part of a prospective-longitudinal study on dementia in the elderly and previously had given their consent to participate in our investigations. No patient was accepted into the study who had a history of major psychiatric illness (especially depressive and schizophrenic illness), alcoholism, or cancer, or who had not finished secondary school. Clinical diagnosis was based on a complete medical and neuropsychiatric examination including history, physical examination, electrocardiography, electroencephalography, cranial CT, blood count, biochemistry (electrolytes, liver and kidney function tests), thyroid function, Vit B_{12}, folic acid, and serology for syphilis and AIDS. The clinical

diagnosis of MID and PDD relied on the criteria of the DSM-III-R,[15] that of DAT on the criteria for "probable DAT" of the Working Group on the Diagnosis of Alzheimer's Disease of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).[18] The clinical diagnosis was carried out independently from the IS. Cause of dementia other than MID or DAT were excluded according to the DSM-III-R.

The IS was rated one month after admission between six months and 4·1 years before death. A history of the course of the disease was available in each patient from an interview with the patient and a close informant. The IS used was a German translation of the original scale of Hachinski[5] and had a maximum score of eighteen (IS-HACH). To increase the reliability of the scale we gave descriptions for each clinical feature of the IS according to the literature.[5 6] Scores according to Rosen (IS-ROSEN) were also calculated.[7] In German speaking neurology there is no distinction between "objective neurological signs" and "subjective neurological symptoms". On the other hand cranial CT should be available for every demented patient. We therefore put together two items of the IS into the new item "neurological signs and/or symptoms (two points)" and introduced a new item "definite cerebral infarct on cranial CT (two points)", which had been proposed previously.[8 11 14]

Details of the neuropathological procedure have been described elsewhere.[4] Due to the design of the study the neuropathological criteria were only applied in clinically demented patients. Morphological criteria for "pure" DAT followed the inclusion criteria (A1, A2 or A3) and the exclusion criterion V1 by Tierney *et al.*[19] The morphological criteria for the diagnosis of dementia due to vascular causes were the absence of Tierney's inclusion criteria (A1, A2 and A3) and the presence of 1) one or more large cerebral infarcts or extensive cortical granular atrophy; 2) diffuse or multiple focal white matter damage with small disseminated infarcts or lacunes but relatively preserved cerebral cortex—Binswanger's subcortical vascular encephalopathy;[20] 3) multiple small lesions or lacunes in basal ganglia and hippocampus or mixed cortical and subcortical vascular lesions.[1] The importance of these three neuropathological features for dementia in MID has been shown recently.[21] Mixed type dementia was defined by the presence of histopathological criteria of DAT (inclusion criteria A1, A2 or A3) together with multiple vascular lesions involving neocortex, basal ganglia, and hippocampus or at least 50 ml of tissue loss from infarction.[1 4] We believe that most patients with one cerebral infarct of 50 ml without Alzheimer's disease are not demented, but chose this infarcted-volume criterion for the diagnosis of mixed dementia. According to our criteria a case with clear Alzheimer's pathology and one or two small subcortical infarcts is not labelled mixed dementia.

Statistical analysis was performed at the Computer Centre of the University of Vienna using Statistical Package for the Social Sciences, procedures Mann-Whitney U-test and Crosstabs. Level of significance was $p = 0.05$ (two-tailed). In the case of multiple (k) significance tests the Bonferroni correction for the level of significance (0,05/k) was used.

Results

Seven patients had PDD and five patients had MID according to clinical criteria and these diagnoses were confirmed by neuropathology. Twenty patients, however, were not unequivocally classified in life by the strict application of diagnostic criteria. These patients were classified as "possible DAT", "mixed dementia" or "possible MID", because clinical data differed. At necropsy these patients were diagnosed as PDD (nine cases), MID (two cases) and MIX (six patients). At necropsy 16 (50%) cases fulfilled the neuropathological criteria for Alzheimer's disease, seven presented as MID, six as MIX and three had Pick's disease. All Pick's cases presented with Pick bodies, massive atrophy, nerve cell loss and gliosis in the temporal lobe (one case) or frontotemporal lobe (2 cases).

Mean (SD) age in years of MID patients at death was 81·6 (6·4), ranging from 75 to 94 years; mean (SD) age of MIX patients was 83·3 (3·9), ranging from 81 to 91 years; mean (SD) age of PDD patients was 75·4 (9·4), ranging from 58 to 88 years; two PDD patients had an onset of the dementing disorder before the age of 65 years. Mean (SD) MMS at the time of IS scoring was 11·1 (7·0; range: 1–20) in MID, was 14·5 (9·5; range: 4–23) in MIX, and was 8·8 (9·5; range 0–23) in PDD.

DISCRIMINATIVE POWER OF THE ISCHAEMIC SCORE

The mean (SD) IS, scored according to Hachinski's original device, was 9·4 (3·9) in MID, 11·3 (2·1) in MIX and 5·0 (3·5) in PDD. While the IS-HACH showed no difference between MIX and MID patients (Mann-Whitney: $z = 0.506$; $p = 0.613$), the difference between MID-MIX and PDD was highly significant (Mann-Whitney: $z = 3.310$; $p = 0.0009$). The IS-HACH was smaller in Pick's disease than in DAT and this difference reached significance (Mann-Whitney: $z = 1.969$; $p = 0.049$).

The mean (SD) IS, scored according to Rosen *et al*,[15] was 7·3 (2·9) in MID, 8·0 (2·0) in MIX and 3·1 (2·5) in PDD. While the IS-ROSEN showed no difference between MIX and MID patients (Mann-Whitney: $z = 0.218$; $p = 0.827$), the difference between MID-MIX and PDD was highly significant (Mann-Whitney: $z = 3.482$; $p = 0.0005$). The IS-ROSEN did not differ between DAT and Pick's disease (Mann-Whitney: $z = 1.028$; $p = 0.304$).

The IS-HACH (cut-off 6/7) correctly classified 84·4% of patients into the categories MID-MIX versus PDD. Using the cut-off 4/5 the IS correctly classified 68·8% of patients into the latter two categories. The IS-ROSEN (cut-off 3/4) correctly classified 81·3% of patients.

Table 2 Prevalence of features of the IS in PDD and MID-MIX

		Percent of patients with positive feature			
		MID-MIX n = 13	PDD n = 19	Chi square	p
1	Abrupt onset	30·8	15·8	1·013	0·314
2	Stepwise deterioration	53·8	21·1	3·680	0·055
3	Fluctuating course	76·9	21·1	9·791	0·002*
4	Nocturnal confusion	23·1	31·6	0·276	0·599
5	Preserved personality	46·2	21·1	2·264	0·132
6	Depression	46·2	68·4	1·587	0·208
7	Somatic complaints	46·2	26·3	1·347	0·246
8	Emotional incontinence	30·8	31·6	0·002	0·961
9	Hypertension	53·8	31·6	1·587	0·208
10	History: strokes	84·6	10·5	17·565	0·0000†
11	Signs and symptoms	61·5	21·1	5·398	0·020
12	Definite infarct on CT	84·6	42·1	5·783	0·016
13	Assoc atherosclerosis	53·8	47·4	0·130	0·719

*Significant at level 0·05.
†Significant at level 0·001.

According to some authors, the IS is able to correctly identify MIX patients, who should score five to six on Hachinski's IS.[8 13] Using these cut-off points, only 50% of patients of our series were classified correctly: all MIX patients were labelled as MID; five DAT patients were labelled as MIX and further four DAT patients were labelled as MID; one MID patient was labelled as PDD.

DISCRIMINATIVE POWER OF SINGLE FEATURES OF THE ISCHAEMIC SCORE

Table 2 shows the percentages of "Yes" answers regarding each item of the IS in MID-MIX versus PDD patients. The adjusted alpha-error for 13 comparisons was 0·05/13 = 0·004. Two items of the IS significantly differentiated between PDD and MID-MIX. One was "history of stroke" which was found positive in 84·6% of MID-MIX patients against 10·5% of PDD patients; the other was "fluctuating course", which was found in 76·9% of MID-MIX against 21·1% of PDD patients. Before adjustment of alpha-error two more items of the IS would have been found significant. Of the MID-MIX patients, 61·5% showed "neurological signs or symptoms" and 84·6% had at least one definite infarct on CT. Nevertheless, 21·1% of PDD patients showed "neurological signs or symptoms" and 42·1% showed "a definite infarct" on CT.

There were no significant differences between MID patients and MIX patients or between DAT patients and patients with Pick's disease regarding any item of the IS.

SENSITIVITY AND SPECIFICITY OF THE ISCHAEMIC SCORE IN THE DIAGNOSIS OF A VASCULAR PATHOGENESIS OF DEMENTIA

Table 3 shows that the IS was able to diagnose MID-MIX correctly in 92·3% and this accuracy was independent of the cut-off and scoring system used. On the other hand there was a high rate of false positive cases, who were labelled MID-MIX by the IS but were found to have DAT at necropsy. Using the IS-HACH, with a cut-off between four and five, 47·4% of PDD patients were incorrectly labelled as having a vascular dementia; applying the IS-HACH with a cut-off between six and seven, 21·1% of PDD patients and applying the IS-ROSEN 26·3% of PDD patients were incorrectly classified as having vascular dementia. This implies that the sensitivity of the diagnosis of PDD by the IS ranged from 52·6 to 78·9%.

SENSITIVITY AND SPECIFICITY OF SINGLE FEATURES OF THE ISCHAEMIC SCORE IN THE DIAGNOSIS OF VASCULAR PATHOGENESIS OF DEMENTIA

Table 3 shows that item 10 "history of stroke" had a higher accuracy in the diagnosis of MID-MIX and PDD than any other item scoring of the IS. The percentage of correctly diagnosed cases after application of this item was 87·5. This item had a sensitivity to diagnose PDD of 89·5 per cent. Nevertheless the sensitivity to detect clinically a vascular pathogenesis of dementia was slightly higher by total IS score (92·3%) than by single IS features (84·6%).

Discussion

In our small series, we found the IS was a sensitive test for vascular dementia. The modified scoring of the IS[7] did not improve the diagnostic accuracy of the scale. On the other hand the IS was insufficiently sensitive to diagnose PDD. The IS could be used to exclude (additional or pure) vascular dementia and thus may help to define a group of pure PDD in experimental designs. The IS is not accurate enough to define a group of patients suffering from dementia of pure vascular origin. This is not only due to cases with mixed dementia but also due to 21·2% pure PDD patients labelled as vascular dementia. The accuracy to differentiate between PDD and MID-MIX of the best item of the IS ("history of stroke") was rather undermined by other items. Thus we conclude that the IS is not useful in the differentiation between MID-MIX and PDD.

Our clinico-pathological results depend on the applied neuropathological criteria. While neuropathology is the gold-standard for diag-

Table 3 Percentage of patients with PDD or MID-MIX (in)correctly classified by the IS and by single features of the IS

	% of MID-MIX correctly classified intra vitam	% of PDD correctly classified intra vitam	% of PDD misdiagnosed during life as MID-MIX	% of MID-MIX misdiagnosed during life as PDD
IS-HACH Cut-off 4/5	92·3	52·6	47·4	7·7
IS-HACH Cut-off 6/7	92·3	78·9	21·1	7·7
IS-ROSEN Cut-off 3/4	92·3	73·7	26·3	7·7
SINGLE FEATURES OF THE IS				
History of stroke	84·6	89·5	10·5	15·4
Fluctuating course	76·9	78·9	21·1	23·1
Neurological signs/symptoms	61·5	78·9	21·1	38·5
Definite infarct on CT	84·6	57·9	42·1	15·4

nosis in most neurological diseases, this does not hold true for dementia research.[22] The diagnosis of DAT in a patient without cerebrovascular disease is usually made by counting Alzheimer's lesions. Nevertheless, small vascular lesions frequently coexist and are of questionable importance for the clinical syndrome of dementia. Neither clinical nor pathological evidence of stroke necessarily means that cerebrovascular disease has anything to do with a patient's dementia.[23] The diagnosis of MID in cases lacking Alzheimer's pathology is usually made by quantitating lesion volume, which on the one hand is impossible in the subset of cases with multiple small lesions and on the other hand neglects the location of strokes.[22] We diagnosed MID in demented patients, when vascular lesions were extensive enough to make such a diagnosis probable. One patient (MMS = 10) had Binswanger's disease with additional cortical infarcts, the other four MID patients had mixed cortical and sub-cortical lesions of frontal, parieto-occipital and temporal lobe and in each case at least one large infarct. While all five MID cases of our series had large and multiple infarcts corresponding to their neuropsychological deficits, the diagnoses of mixed dementia depended highly on our histopathological criteria, because the presence of either disorder might lower the threshold for clinical expression of the other.[23] Only two of our eight MIX cases had massive cerebrovascular changes comparable to that of the MID cases. The other six cases either had one large cerebral infarct of more than 50 ml (one case) or small multiple lesions, which alone (that is, without Alzheimer's pathology) would not be expected to lead to dementia. The contribution of these vascular lesions to the clinical symptoms of dementia was uncertain in every case, which by stricter criteria could also had been labelled as DAT. Nevertheless the diagnosis of DAT in the latter six patients would have further decreased the usefulness of the IS.

Our findings are derived from a sample of elderly, female, institutionalised subjects. It is the former subset of patients in which the IS is frequently applied. Nevertheless, our results may not apply to mildly affected or younger or male patients. Because severely demented cases may be over-represented in our series we found a relatively high prevalence of Pick's disease.

Three comparative clinico-pathological validations of the IS showed it to be useful in the differentiation between PDD and MID. Rosen *et al*[7] studied 14 patients (five DAT, four MID, five MIX) at necropsy. They devised a modification of the IS, because they found five items not to be characteristic of MID. Another clinico-pathological study, prospective in design, "attested the usefulness of Hachinski's Ischaemic Score in differentiating between the major forms of senile dementia".[13] The latter study, however, also reported a notable trend to overdiagnose MID by the IS and described 58% false positives. Our results are similar as we also found a significant percentage (21%) of false positive MID patients. A third clinico-pathological validation of the IS found 35 of 38 cases of pure DAT with a score of four or less on the original IS, but neuropathological criteria for the definite diagnosis of DAT, MID or MIX were not given.[24]

The usefulness of the IS depends on the purpose of it's application. We found it to be of no advantage in the differential diagnosis of MID, MIX and PDD nor in the selection of patients with MID or MID-MIX in a consecutive series of elderly institutionalised patients. However, the IS may be used to exclude patients with vascular pathogenesis of dementia from studies of PDD, for example, pharmacological drug trials in DAT. The application of the IS in epidemiological studies on dementia may lead to overdiagnosis of MID, because a considerable percentage of PDD patients will be labelled as vascular dementia.

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