Prospective neuropathological validation of Hachinski's Ischaemic Score in dementias

P Fischer, K Jellinger, G Gatterer, W Danielczyk

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.

There is a need for valid and reliable methods to distinguish in life between primary degenerative dementia (PDD) and multi-infarct dementia (MID). 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. 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. 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. 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.

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.

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. Severity of dementia was assessed by the Mini Mental State (MMS) examination. Only patients with scores of less than 24 were included. 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, VDRL, folic acid, and serology for syphilis and AIDS. The clinical

Table 1 Original and revised scorings of the ischaemic scale

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<tr>
<td>Abrupt onset</td>
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<td>Stepwise deterioration</td>
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<td>Fluctuating course</td>
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<td>2</td>
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<td>2</td>
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<td>Nocturnal confusion</td>
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<td>1</td>
<td>1</td>
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<td>Preserved personality</td>
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<tr>
<td>Hypertension</td>
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<td>Assoc atherosclerosis</td>
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<td>Focal neural symptoms</td>
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<td>Focal neural signs</td>
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<tr>
<td>One low density area on CCT</td>
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<td>3</td>
<td></td>
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<tr>
<td>Multiple foci on CCT</td>
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<td>2</td>
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<tr>
<td>White matter change on CCT</td>
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<td>Maximum</td>
<td>18</td>
<td>12</td>
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*From Katzmann (1986).
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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 were excluded 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 dementering 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, 14.5 (9.5; range: 4-23) in MIX, and 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: $z = 3.310; p = 0.009$). 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. 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: $z = 1.028; p = 0.049$).

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.
According to some authors, the IS is able to correctly identify MIX patients, who should score five to six on Hachinski’s IS. 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 0.005. 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-ROSEN 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’ 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 diagnosing the IS-ROSEN 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%.

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

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Our clinico-pathological results depend on the applied neuropathological criteria. While neuropathology is the gold-standard for diagnosing...
nosis in most neurological diseases, this does not hold true for dementia research.22 The
diagnosis of DAT in a patient with 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 any-
thing 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.24 We diagnosed MID in
demented patients, when vascular lesions were extensive enough to make such a diagnosis
probable. One patient (MMS = 10) hadBins-
wanger’s disease with additional cortical in-
farcts, 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 neuro-
psychological deficits, the diagnoses of mixed
dementia depended highly on our histopa-
thological criteria, because the presence of either disor-
der might lower the threshold for clinical
evaluation 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 symp-
toms 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 clinicopathological
validation of the IS showed it to be useful in
the differentiation between PDD and MID. Rosen et al21 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
clínico-pathological study, prospective in
design, “attested the usefulness of Hachinski’s
Ischaemic Score in differentiating between the
major forms of senile dementia”22. The
latter study, however, also reported a notable trend
toward 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 con-
servative series of elderly institutionalised
patients. However, the IS might help 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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