Reversible dementia in elderly patients referred to a memory clinic
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Introduction

Dementia represents an increasing burden on society [23]. It is usually progressive [23], but some of its causes, such as hypothyroidism and hydrocephalus, are potentially reversible [8]. These should be diagnosed, without over-investigating the many patients with irreversible disease. That creates a dilemma: should (ancillary) investigations, such as blood tests and computed tomography (CT) of the brain, be performed routinely or selectively in dementing patients? Routine investigations will detect most reversible causes, but are burdensome for patients and costly for society; they may also lead to false-positive results, some-
times with harmful consequences. Selective investigation may lead to under-diagnosis of reversible causes and mis-
ised therapeutic opportunities; but it causes less discomfort and less risk to patients and it may be more cost-effective
[5, 6, 12, 14, 17, 22, 29].

Several factors are important in resolving this dilem-
ma. First, the prevalence of reversible dementia must be
known. Estimations of this vary widely, from 0% to over
20% [3, 16, 21]. A critical review emphasized the differ-
ence between potential reversal (improvement that might
occur on treatment) and actual reversal (that did occur af-
after treatment), concluding that in actual reversal, partial
improvement is seen in 8% and full recovery in 3% of pa-
tients [4]. Second, the clinical procedure and diagnosis
should be well defined, so that the added value of investi-
gations can be established, which has not been done so
far. Finally, treatment effects should be assessed not only
by clinical judgement, but also by measurement of rele-
vant outcomes [13]. We think assessment in dementia
should include not only cognitive tests, but also measure-
ment of disability in daily functioning, changes in be-
aviour, and burden experienced by the caregiver. To our
knowledge, these have not previously been applied to as-
sess reversibility of dementia.

We prospectively studied the prevalence of reversible
dementia in a memory clinic to which general practition-
ers refer their patients suspected of dementia. Using stan-
ardized methods of clinical examination and diagnosis,
and assessment of treatment effects, we also determined
the added value of investigations for the diagnosis, treat-
ment and outcome of reversible dementia.

Patients and methods

Patients

Inclusion criteria were: (1) referral for suspected dementia by gen-
eral practitioners, who were systematically informed and encour-
aged to refer all such patients; (2) age 65 years and over; (3) pres-
ence of a caregiver to provide information. Exclusion criteria were:
(1) previous investigation for dementia; (2) co-morbidity substan-
tially shortening life expectancy.

Clinical examination

Two neurologists used a standardized examination based on the
Dutch version of the Cambridge Examination for Mental Disorders
of the Elderly (CAMDEX-N), aimed not only at dementia, but also
at delirium, depression and other psychiatric conditions [10]. They
diagnosed dementia according to DSM-III-R [2] and on clinical
grounds only, diagnosed its probable cause: “primary degenerative
dementia” (PDD), “multi-infarct dementia” (MID) [15], “mixed
dementia” (MIX) if co-existence of PDD and a vascular factor was
suspected, and “other”, including any reversible cause. They had
to specify whether this initial diagnosis was clinically certain or a
differential diagnosis was necessary. The diagnosis of PDD was
based mainly on positive clinical features. It was considered as
“certain” if all of the following criteria were met: cortical type of
dementia [9], gradual onset and steadily progressive course, mem-
ory disturbance as initial symptom, duration of more than 6 months,
Hachinski score 4 or less [15], standard neurological examination
normal for age, and no clinical indications for other disease(s) that
may cause dementia. Patients with isolated neurological signs
without consequences for the differential diagnosis were classified
as “PDD almost certain”. MIX was included in the differential di-
agnosis for Hachinski scores of 5 and 6, and MID for scores of 7
and more [15]. If a specific cause other than PDD, MIX or MID
was suspected, “other” was chosen. Secondary pathology (co-mor-
bidity possibly worsening the severity of dementia) and non-cog-
nitive disturbances were systematically looked for.

The severity of dementia was assessed with regard to (1) cog-
nition, using the CAMCOG subscale of the CAMDEX-N [10]; (2)
disability in daily functioning, using the Interview for Deteriora-
tion in Daily living activities in Dementia (IDDDD) [26]; (3) behav-
ioural changes, using a Dutch translation of the Revised Memory
and Behavioral Problems Checklist (RMBPC) [24]; and (4) burden
experienced by the caregiver, using the Competency Questionnaire
[28]. Completion of the CAMCOG was part of the clinical evalua-
tion by the neurologists. The other measures were completed by
the informant in the presence of the neuropsychologist or her as-
sistants. All these instruments have good reliability and validity
[25, 27].

After the initial clinical diagnosis, the neurologists documented
which investigations were indicated in each patient, for causes of
dementia and for secondary pathology. For causes of dementia, the
following rules were applied. If PDD was certain, investigations
were not indicated. If MID or MIX were considered, CT was indi-
cated, and the cause of any vascular lesions was sought. If “other”
was suspected, investigations were directed at that specific cause.
All clinical diagnoses and indications for investigations were dis-
cussed with a panel of two other neurologists with an interest in
dementia.

Investigations

All demented patients, regardless of clinical diagnosis and indica-
tions, were subjected to the complete following set of investiga-
tions. Laboratory tests according to the Dutch Consensus on diag-
nostics in dementia syndrome were: sedimentation rate, total blood
count, serum electrolytes, calcium, urea, creatinine, glucose, bili-
rubin, liver enzymes, cholesterol, triglycerides, vitamin B12, B6 and
B12, folate, thyroid stimulating hormone (TSH), Venerable Disease
Research Laboratory (VDRL) test and treponemal haemagglutina-
tion assay (TPHA), and urinalysis. In addition, a chest radiograph,
electrocardiogram (ECC), electroencephalogram (EEG) and CT of
the brain (without contrast enhancement) were performed. Further
investigations could be ordered if appropriate. After the results of
all investigations were known, a final diagnosis was made accord-
ing to DSM-III-R criteria [2]. The added value of investigations
for diagnosis was established by comparing the clinical with the fi-
nal diagnosis. Non-demented patients were investigated as seemed
proper on an individual basis.

Treatment and outcome assessment

Potentially reversible causes of dementia (including depression,
following the Dutch Consensus) were treated, asking specialist
consultation if required, and advising general practitioners in the
other cases. Assuming that secondary prevention of brain infarcts
may slow down progression of vascular (components of) demen-
tia, aspirin and anti-hypertensives were given when indicated.
Secondary pathology and non-cognitive disturbances were also
treated. Thus, more than one treatment modality in one patient was
possible, as it is in practice. After a follow-up period of 6 months,
the patients were re-examined (checking the diagnosis) and the
severity of dementia was re-assessed as described above, by the

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neuropsychologist or her assistants, who did not know the diagnosis and treatment. Partial or total reversal of dementia was then ascertained per patient. In this way, the added value of investigations for treatment and outcome after 6 months was established.

The study protocol, including informed consent from patients and caregivers, was approved by the institutional medical ethics committee.

Analysis

To analyse reversibility of dementia, several variables were examined, for all nine (sub)scales:

1. Size of change-scores in individual patients: based on the literature [19] and a test-retest study at our memory clinic, we computed the standard measurement error and its 68% and 95% confidence intervals (CI) of each subscale [20]; positive change-scores exceeding the 68% CI were considered as a trend to improvement, and those exceeding the 95% CI as real improvement in functioning (see Table 2: criterion for real change in individual case).

2. Pattern of individual change-scores: real improvement on at least two subscales in the absence of (a trend toward) deterioration on other subscales was considered as (partial or total) reversibility.

3. Mean change-scores on all subscales in the group of patients treated for a potentially reversible cause of dementia.

Results

Patients

Two hundred consecutively referred patients entered the study. Of these, 170 met DSM-III-R criteria for dementia. Their mean age was 79.2 years (SD 6.3); 68 were men and 102 women. The severity of dementia according to CAMDEX-N was: 7 minimal, 140 mild, 23 moderate, 0 severe. Mean duration of symptoms was 24 months (2–190).

Clinical diagnosis

PDD was the most frequent diagnosis (Table 1). Vascular (component of) dementia was also diagnosed frequently (Table 1). The panel discussions did not result in major changes of diagnosis or indications for investigations.

Diagnosis after investigations

Complete investigations were performed in 169 demented patients (one patient with PDD refused). PDD of the Alzheimer type, now according to DSM-III-R criteria, remained the most frequent diagnosis (Table 1). There was no significant difference between the two neurologists regarding the percentage of patients with this diagnosis in whom CT was considered to be indicated. The same comparison was made between the first and last 50 patients of the neurologist who examined most patients; again, no significant difference was found.

Treatment and outcome

Twenty-six patients had serum vitamin B<sub>12</sub> levels below 200 pg/l. Two could not be treated; 24 were given cobalamin replacement; two of these died before follow-up. Two patients were treated for hyperthyroidism, one for hypothryoidism and four for depression. Two patients had small tumours with CT characteristics of meningiomas (one parasellar, one parasagittal) but these were regarded as incidental and no surgery was performed. For vascular (components of) dementia, in 16 patients treatment with aspirin and (or) anti-hypertensives was advised; in two others, a small intracerebral haematoma was found and aspirin (given before referral) was stopped. Potentially re-

Table 1

<table>
<thead>
<tr>
<th>Diagnosis or differential diagnosis before AI</th>
<th>Diagnosis after AI according to DSM-III-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDD certain</td>
<td>Dementia not otherwise specified, MIX and multi-infarct dementia</td>
</tr>
<tr>
<td>PDD almost certain</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency (5)</td>
</tr>
<tr>
<td>PDD/other</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency (12)</td>
</tr>
<tr>
<td>PDD/MIX</td>
<td>MIX (7)</td>
</tr>
<tr>
<td>PDD/MIX/other</td>
<td>MIX (2), MIX/hypothyroidism (1), MIX/vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency (1), intracerebral haematoma (1), vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency (1)</td>
</tr>
<tr>
<td>MID/MIX</td>
<td>MIX (2), MID (1)</td>
</tr>
<tr>
<td>MID/MIX/other</td>
<td>MIX (2), intracerebral haematoma (1), vitamin B&lt;sub&gt;12&lt;/sub&gt; deficiency (1)</td>
</tr>
</tbody>
</table>

*Ancillary investigations were performed in 58 patients
versible non-vascular causes of dementia were therefore found in 33 patients (19%, 95% CI 14–25%); 31 of these patients were treated (Table 1, italic). Apart from potential causes of dementia, secondary pathology and non-cognitive disturbances were treated (sometimes several factors in one patient). All patients with treatable causes were seen at follow-up except the two with low vitamin B$_{12}$ levels who died (see above). In the group without treatable causes, eight patients died and three were lost to follow-up.

Complete reversal of dementia was seen in none of the 169 demented patients subjected to investigations. On clinical impression, partly based on patient’s functioning during the follow-up visit, five patients improved after treatment of a potentially reversible cause. Measured assessment did not confirm this. When size and pattern of individual change-scores were taken into account, consistent improvement (on 5 and 6 subscales, respectively) was seen in only two patients. As improvement in one of these might reflect recovery from a respiratory infection, it could be attributed to treatment in only one patient (woman, aged 66 years, treated for dementia complicated by depression and epilepsy; consistent improvement on five subscales, related to disability, behavioural changes, and burden to the caregiver). At group level, assessment showed no reversible disturbances were treated (sometimes several factors in one patient). All patients with treatable causes were seen at follow-up except the two with low vitamin B$_{12}$ levels who died (see above). In the group without treatable causes, eight patients died and three were lost to follow-up.

### Table 2 Outcome in patients treated for potentially reversible cause of dementia. (IDDD-Init initiative to perform daily living activities, IDDD-perf actual performance of daily living activities, RMBPC-Mem memory-related problems, RMBPC-Dis disruptive behaviour, RMBPC-Dep depressive behaviour, Burden-Dep dissatisfaction with oneself as caregiver, Burden-Pat dissatisfaction with the demented person as a patient, Burden-Con consequences of care-giving for the life of the caregiver)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Number of items</th>
<th>Range</th>
<th>Criterion for real change in individual case</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMCOG</td>
<td>59</td>
<td>106–0</td>
<td>&gt; 7</td>
</tr>
<tr>
<td>IDDD-Init</td>
<td>9</td>
<td>0–36</td>
<td>&gt; 7</td>
</tr>
<tr>
<td>IDDD-Perf</td>
<td>11</td>
<td>0–44</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>RMBPC-Mem</td>
<td>7</td>
<td>0–28</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>RMBPC-Dis</td>
<td>8</td>
<td>0–32</td>
<td>&gt; 4</td>
</tr>
<tr>
<td>RMBPC-Dep</td>
<td>9</td>
<td>0–36</td>
<td>&gt; 7</td>
</tr>
<tr>
<td>Burden-Self</td>
<td>12</td>
<td>12–48</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Burden-Pat</td>
<td>7</td>
<td>7–28</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Burden-Con</td>
<td>8</td>
<td>8–32</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

*Assessment was complete in 27 cases, including the 5 patients who improved clinically

Additional value of investigations

Clinical prediction of results of blood tests proved unreliable, both for potential causes of dementia (vitamin B$_{12}$, TSH, VDRL/TPHA) and for secondary pathology. Chest radiography and ECG, useful for secondary pathology, never contributed to diagnosis or treatment when not indicated clinically. EEG was thought to be indicated in only 12 cases, for example in the patient mentioned above. Four categories of indications for CT could be distinguished: (1) suspicion of a neurosurgical cause of dementia in 33 patients (normal pressure hydrocephalus, cerebral tumour, subdural haematoma); (2) clinical diagnosis of vascular dementia in 29 patients; (3) suspicion of other anatomical lesions and Hachinski score of 4 or less in seven patients; (4) isolated neurological signs that could not be explained in 17 patients. In the last group CT never influenced diagnosis or management. If considered not indicated, neither EEG nor CT ever had an effect on diagnosis or treatment. Overall, none of the investigations had an effect on outcome of dementia.

Non-demented patients

Thirty patients were cognitively impaired without meeting all DSM-III-R criteria for dementia. Seven were treated: one completely recovered (woman, aged 94, with severe depression) and two improved as judged clinically (one on vitamin B$_{12}$, who also stopped drinking alcohol; another after antidepressive treatment), but not on assessment.

Discussion

We found a very low prevalence of reversible dementia – 0.6% (95% CI 0–3%) – in this series of patients referred to a memory clinic. A recent quantitative review demonstrated that, although the prevalence of reversible men-
nia in 16 patient series reported between 1972 and 1994 was about 11% on average, it has fallen to about 1% in the four most recent series [30]. This decrease was associated with the change from inpatient to outpatient setting and with the use of stricter diagnostic methods [30]. Both conditions apply to our study.

Measured assessment of treatment effects has not previously been employed in studies of reversible dementia [30]. Such formal measurement, rather than subjective clinical judgement, is usual nowadays in drug trials for Alzheimer’s disease. In our study, five patients improved as judged clinically, but only one (partially) on assessment. This more rigorous evaluation has contributed to the low prevalence of reversible dementia that we found; however, we think it is more valid, because it also includes disability in daily functioning, changes in behaviour, and burden experienced by the caregiver [26].

Our findings may also reflect some “true” decline in prevalence of reversible dementia. We did not find a single case of drug intoxication, which used to be the commonest cause of reversible dementia [4]. Possibly, increasing awareness of this problem among general practitioners (at least in some areas) has borne fruit. The same might hold to some extent for the early detection and treatment of depression as a (usually partial) cause of dementia.

We investigated the added value of investigations by comparing the clinical diagnoses with the diagnoses after investigations. Clinical diagnoses were based on standardized examination methods and strict diagnostic criteria. Before investigations were performed, the clinicians documented which investigations they considered indicated. In this way it could be established whether investigations thought to be not indicated produced diagnostic surprises. This was often the case for blood tests, but not for chest radiographs, ECGs, EEGs and CT. In the same way, the effect of investigations on treatment and on outcome could be determined, with no effect on outcome. Of course, the decisions “(not) indicated” in our study were influenced by the experience gained in a memory clinic and may be different for doctors who rarely see patients with dementia.

Apart from drug intoxication and depression, metabolic conditions are relatively frequent causes of reversible dementia [4, 30]. These can all be detected by clinical examination and blood tests. Normal pressure hydrocephalus has a characteristic presentation. Patients with cerebral tumours or subdural haematomas meeting our clinical criteria for primary degenerative dementia (see Patients and methods) must be very rare if they occur at all [1].

We think our findings have implications for diagnostic management of elderly outpatients with dementia. First, the very low prevalence of reversible dementia – see also [30] – means that the pretest probability of finding actually reversible conditions by routine investigations is very low. False positive results are more likely. Second, routine blood tests seem warranted, as possible metabolic causes of dementia are often not diagnosed clinically. Though treatment of these was disappointing in our study, it may be effective in some cases. Moreover, routine blood tests can detect secondary pathology, which can often be alleviated [18]. However, the question whether blood tests should be performed routinely – and if so, which tests – merits further study. Third, major investigations, such as CT of the brain, can be performed selectively, based on the clinical picture. If vascular dementia is clinically possible and secondary prevention is deemed worthwhile, CT is also appropriate. However, if investigations are targeted at reversible causes of dementia, routine CT does not seem warranted by our findings. Emphatically, our message is not that patients with dementia need not be investigated.

Potentially reversible causes should be looked for with the same diligence in patients with cognitive impairment not meeting DSM-III-R criteria for dementia as in demented patients. Cognitively impaired, but not demented patients tend to have the best prognosis [11]. This is supported by our findings: in 30 non-demented patients one completely recovered after treatment versus none in 170 demented patients. This group of patients may explain part of the higher prevalence of completely reversible “dementia” in older studies.

Painstaking clinical evaluation [7], including a history from a reliable informant, mental status testing and routine application of diagnostic criteria, is the mainstay of diagnosis in dementia. It is time-consuming, but investigations cannot replace it. Together with personal and social evaluation, it is the basis for symptomatic treatment, practical management and counselling, which should be offered to all patients with dementia, including the vast majority with irreversible conditions [23].

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