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Reversible dementia in elderly patients referred to a memory clinic

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Abstract Dementia has a reversible cause in some cases, and these should be diagnosed without over-investigating the many patients with irreversible disease. We prospectively studied the prevalence of reversible dementia in a memory clinic, determined the added value of investigations compared with clinical examination and assessed the outcome of treatment of potentially reversible causes by measuring (1) cognition, (2) disability in daily functioning, (3) behavioural changes and (4) caregiver burden. Two hundred patients aged 65 years and over were examined, using the CAMDEX-N. If they were demented, the probable cause was diagnosed clinically and confirmed or excluded by a standard set of investigations, which were done in all patients. Of the patients, 170 (mean age 79.2 years) were demented; 31 were treated for potentially reversible causes. At follow-up after 6 months, no patients showed complete reversal of dementia. Five patients improved on clinical impression, but only one on clinical measurement. Thirty patients were cog-

nitively impaired, but not demented; seven were treated. Judged clinically, three patients improved, but on assessment only one did so; she recovered completely. Blood tests often produced diagnostic results that were not expected clinically, but electroencephalography and computed tomography of the brain did not. None of the investigations had an effect on outcome of dementia after treatment. We conclude that in elderly patients referred to a memory clinic, the prevalence of reversible dementia is of the order of 1%, if outcome after treatment is assessed by a standardized measurement. We recommend blood tests in all patients, to detect not only metabolic causes of dementia but also co-morbidity possibly worsening the dementia. Other investigations can be performed on clinical indication. Clinical evaluation remains the mainstay of diagnosis in dementia.

Key words Dementia · Computed tomography · Electroencephalography · Blood tests

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-in-

vestigating 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 missed 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 dilemma. 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 difference between potential reversal (improvement that might occur on treatment) and actual reversal (that did occur after treatment), concluding that in actual reversal, partial improvement is seen in 8% and full recovery in 3% of patients [4]. Second, the clinical procedure and diagnosis should be well defined, so that the added value of investigations 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 relevant outcomes [13]. We think assessment in dementia should include not only cognitive tests, but also measurement of disability in daily functioning, changes in behaviour, and burden experienced by the caregiver. To our knowledge, these have not previously been applied to assess reversibility of dementia.

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

Patients and methods

Patients

Inclusion criteria were: (1) referral for suspected dementia by general practitioners, who were systematically informed and encouraged to refer all such patients; (2) age 65 years and over; (3) presence of a caregiver to provide information. Exclusion criteria were: (1) previous investigation for dementia; (2) co-morbidity substantially 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 diagnosis 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-morbidity possibly worsening the severity of dementia) and non-cognitive disturbances were systematically looked for.

The severity of dementia was assessed with regard to (1) cognition, using the CAMCOG subscale of the CAMDEX-N [10]; (2) disability in daily functioning, using the Interview for Deterioration in Daily living activities in Dementia (IDDD) [26]; (3) behavioural 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 evaluation by the neurologists. The other measures were completed by the informant in the presence of the neuropsychologist or her assistants. 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 indicated, 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 discussed with a panel of two other neurologists with an interest in dementia.

Investigations

All demented patients, regardless of clinical diagnosis and indications, were subjected to the complete following set of investigations. Laboratory tests according to the Dutch Consensus on diagnostics in dementia syndrome were: sedimentation rate, total blood count, serum electrolytes, calcium, urea, creatinine, glucose, bilirubin, liver enzymes, cholesterol, triglycerides, vitamin B₁, B₆ and B₁₂, folate, thyroid stimulating hormone (TSH), Venereal Disease Research Laboratory (VDRL) test and treponemal haemagglutination assay (TPHA), and urinalysis. In addition, a chest radiograph, electrocardiogram (ECG), 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 according to DSM-III-R criteria [2]. The added value of investigations for diagnosis was established by comparing the clinical with the final 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) dementia, 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

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 B₁₂ 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 hypothyroidism 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 Diagnoses in demented patients ($n = 170$) before and after ancillary investigations (AI). All numbers refer to number of patients. Potentially reversible causes of dementia ($n = 33$) are underlined

Diagnosis or differential diagnosis before AI		Diagnosis after AI according to DSM-III-R	
		Primary degenerative dementia of the Alzheimer type	Dementia not otherwise specified, MIX and multi-infarct dementia
PDD certain	59 ^a	53 (3 also <u>depressed</u>)	Vitamin <u>B₁₂ deficiency</u> (5)
PDD almost certain	31	19	Vitamin <u>B₁₂ deficiency</u> (12)
PDD/other	51	36	Vitamin <u>B₁₂ deficiency</u> (5), <u>hypothyroidism</u> (1), <u>hyperthyroidism</u> (1), vascular factor (3), vascular factor/vitamin <u>B₁₂ deficiency</u> /alcohol (1), Parkinson's disease (1), diffuse Lewy body disease (1), dementia pugilistica (1), <u>depression</u> /epilepsy (1)
PDD/MIX	8	1	MIX (7)
PDD/MIX/other	12	6	MIX (2), MIX/ <u>hypothyroidism</u> (1), MIX/vitamin <u>B₁₂ deficiency</u> (1), intracerebral haematoma (1), vitamin <u>B₁₂ deficiency</u> (1)
MID/MIX	3	0	MIX (2), MID (1)
MID/MIX/other	6	2	MIX (2), intracerebral haematoma (1), vitamin <u>B₁₂ deficiency</u> (1)

^a Ancillary investigations were performed in 58 patients

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-Self* 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)

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

Scale ^a	Scale characteristics			Change-scores	
	Number of items	Range	Criterion for real change in individual case	Mean	95% CI
CAMCOG	59	106–0	> 7	–1.5	–5.6/ 2.6
IDDD-Init	9	0–36	> 7	–3.9	–7.3/–0.5
IDDD-Perf	11	0–44	> 8	–6.3	–10.4/–2.2
RMBPC-Mem	7	0–28	> 8	–0.1	–2.5/ 2.3
RMBPC-Dis	8	0–32	> 4	–1.9	–3.5/–0.3
RMBPC-Dep	9	0–36	> 7	0.6	–1.4/ 2.6
Burden-Self	12	12–48	> 8	–1.0	–3.4/ 1.4
Burden-Pat	7	7–28	> 5	–0.6	–1.6/ 0.4
Burden-Con	8	8–32	> 6	0.9	–1.9/ 3.7

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 B₁₂ 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, 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 reversibility (Table 2); functioning of patients and caregivers at follow-up was comparable with or worse than at baseline on all subscales. When change-scores of patients treated with cobalamin were compared with those of (untreated) patients with Alzheimer's disease, no clear indications were found of slowing of progression in treated patients [27]. Treatment of secondary pathology (e.g. cardiac failure) and non-cognitive disturbances (e.g. hallucinations) was often effective in itself, but had no effect on the severity of dementia; this will be reported in detail elsewhere.

A survey among the participating general practitioners revealed that during the study period they had also referred patients to other specialists for pragmatic reasons such as travel distance, but no reversible dementia had been detected. Others had not been referred because of poor condition or refusal by patients or caregivers.

Added value of investigations

Clinical prediction of results of blood tests proved unreliable, both for potential causes of dementia (vitamin B₁₂, 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 B₁₂, 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 demen-

tia 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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