Observations on dementias with possibly reversible symptoms

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ABSTRACT. While the evaluation of patients with dementia must also address the possibility of treatable illnesses, recent studies found that reversible diseases are detected in only about 1% of dementia cases. Data on the frequency and evolution of potentially reversible dementias (PRD) in defined clinical settings can be useful in order to optimize diagnostic protocols, thus reducing over-investigation and waste of resources. We reviewed a series of 513 patients (mean age 69.3±4.2 years, mean education level 7.4±4.5 years, sex ratio M/F 217/296) referred to a memory clinic by their general practitioner, in order to identify PRD. All the subjects had undergone neurological and neuropsychological examination, and laboratory tests. Patients considered to be demented also underwent CT brain scan. 362 patients (70.6%) met the criteria for dementia. We identified 26 PRD cases (7.2% of dementia cases, 5.1% of the entire sample). In 13 patients (3.6% of dementia cases), a complete clinical and neuropsychological reversal of dementia was seen after treatment. In 5 of them (1.4%), a partial regression was obtained, while 8 showed no improvement. We conclude that potential and actual reversibility do not coincide, and that "true" reversibility is rare (even if not negligible) in clinical practice. Careful clinical history and examination appeared the most useful part of the evaluation to identify PRD. Standard blood tests and vitamin B_{12} assay were also useful, while CT scan detected PRD causes only in patients with evidence of neurological signs.

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INTRODUCTION

Dementia is becoming an increasing burden on society and families, as well as a major public health concern in western countries, where the population is getting older and older.

There are more than 55 causes of dementia, most of which, such as Alzheimer's disease (AD), are irreversible and progressive (1). However, reversible causes of dementia also exist. As a result, the evaluation of patients with dementia must also address the possibility of treatable illnesses (2-4). Highly variable percentages of demented patients with reversible disease have been reported in the literature, ranging from 20% (5, 6) to a more recent 1% (7, 8). This important drop in frequency of reported potentially reversible dementia (PRD) could be due mostly to improvements in diagnostic criteria, and strict application of standardized clinical assessment. Nevertheless, differences in methodology and populations recruited, as well as variability in follow-up assessment may also explain this striking variation.

By "potentially reversible dementia" we mean a condition that fulfills accepted clinical criteria of dementia [DSM IIIR (9), NINCDS-ADRDA (10)], and is diagnosed as due to a curable illness. Potentially reversible conditions include drug- and alcohol-induced dementia, nutritional and metabolic conditions (such as vitamin B_{12} deficiency and hypothyroidism), subdural hematoma, normal pressure hydrocephalus and brain tumors, and "pseudodementia" due to depression (11). In any case, potential reversibility does not imply actual reversibility. By actual reversibility, we mean the demonstration of regression of cognitive impairments by clinical and neuropsychological follow-up examination; however, regression may be partial or complete.

A recent review calculated that when 16 different studies were considered, the frequency for PRD averaged 15.2%, while the mean percentages for partially and fully reversed dementias were 9.3% and 1.5%, respectively (8). Another study (11) identified 45 pa-

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tients with PRD out of 196 dementia cases. Only in 3 patients the dementia fully reversed, 4 patients improved, while most (38) remained unchanged or became worse.

As an extensive diagnostic search of PRD can lead to over-investigation and waste of resources, knowing data about its frequency and evolution in clinical settings can be useful in order to optimize diagnostic protocols.

The purposes of this paper are to show the frequency of PRD among patients referred to a memory clinic, and determine whether the cognitive dysfunction improved or resolved after treatment, taking into account the cost-effectiveness of the diagnostic procedures.

MATERIALS AND METHODS

We reviewed the charts of 513 patients seen between May 1989 and December 1997 in the memory clinic of a public city hospital affiliated with the University of Milan. Patients were referred by their general practitioners for memory complaints and/or other cognitive disturbances. From the start, data were collected (by patients themselves and/or by their relatives) on a computerized standardized chart, which included demographic and historical data, findings of neurological examination, laboratory results, neuropsychological assessment and neuroimaging data.

Laboratory investigations performed in all patients included sedimentation rate, total blood count, serum electrolytes, urea, creatinine, glucose, bilirubin, liver enzymes, cholesterol, triglycerides, protein electrophoresis, thyroid hormones, treponemal hemagglutination assay, and urinalysis.

Neuropsychological assessment explored orientation, memory, language, visuospatial abilities, frontal functions and logical intelligence, and consisted of the following tests: Mini-Mental State examination (12); Digit span forward (13); Corsi's block tapping test (13); Logical memory test (14); Paired associated learning test (14); Verbal fluency (15); Token test (16); Rey-Osterrieth complex figure copy and recall (17); Raven's Coloured progressive matrices (18), and Attentional matrices (19). In 48 cases, however, it was not possible to perform all the tests due to patients' distraction, severe impairment or refusal. Depression was rated according to Hamilton Depression Rating Scale (20).

When there was a suspect of dementia, according to DSM IIIR (9), patients were submitted to Computed Tomographic (CT) scan of the brain, and to assay of vitamin B_{12} and folates.

Other investigations (Magnetic Resonance Imaging, Single Photon Emission Tomography, electroencephalogram, CSF examination, HIV test) were performed if patients presented early onset, recent onset and rapid course, clinical history suggestive of degenerative dementias other than AD or vascular dementia, or other features that make the diagnosis of AD uncertain or unlikely, as suggested by the NINCDS - ADRDA Work Group (10).

The diagnosis of normal pressure hydrocephalus (NPH) was confirmed by continuous CSF pressure registration.

A preliminary diagnosis had been established by a neurologist and a neuropsychologist at the time of the initial visit. The diagnosis had then been updated during follow-up visits on the basis of laboratory data and clinical evolution.

Severity of dementia was rated according to the Clinical Dementia Rating (CDR) scale (21).

We reviewed all clinical diagnoses according to the following criteria: Alzheimer's disease (AD), NINCDS-ADRDA (10); vascular dementia (VaD), ADDTC (22); Lewy Body Dementia (LBD), McKeith et al.'s criteria (23); frontotemporal dementia (FTD), The Lund and Manchester Group criteria (24); other dementias, DSMIII-R (9); age associated memory impairment (AAMI), Crook et al.'s criteria (25). Depression and other psychiatric disturbances were diagnosed according to DSMIII-R criteria (9). Patients with severe depression and evident cognitive impairment, with a CDR at least of 0.5 were considered affected by pseudodementia if the follow-up allowed exclusion of a degenerative dementia. Patients with vitamin deficiency but no improvement after replacement therapy, and whose clinical onset and course were typical for AD, were diagnosed as having "possible" AD.

Diagnostic review was performed by two of us (E.F. and S.P.). Inter rater reliability was 0.89; when conclusions were discordant, C.M. established the final diagnosis.

RESULTS

The mean age of the 513 patients in the sample was 69.3±4.2 years; the mean education level 7.4±4.5 years, and sex ratio (M/F) 217/296.

Nine cases could not be defined properly, due to lack or unsuitability of recorded clinical information.

151 (29.4%) subjects (mean age 64.1±13.7 years, mean education level 9.0±4.5 years, sex ratio 55/96) received a diagnosis other than dementia.

362 patients (70.6%) were diagnosed as demented. The mean age of subjects in this sample was 71.6±8.9 years; the mean education level 6.7±4.3

Table 1 - *Frequencies of diagnoses and demographical data for 513 patients evaluated in a memory clinic.*

Diagnosis	No. of patients	Age (SD)	Years of Education (SD)	M/F ratio
AD	260	72.5 (8.9)	6.7 (4.3)	102/158
VaD	29	73.6 (7.5)	6.3 (4.3)	22/7
LBD	5	64.5 (12.5)	6.0 (2.5)	2/3
FLD	13	62.1 (5.9)	10.8 (4.9)	6/7
Other dementias	29	70.2 (6.7)	7.5 (3.9)	17/12
PRD	26	68.1 (10.4)	5.8 (3.9)	13/13
AAMI	44	72.4 (7.9)	7.7 (4.5)	20/24
Depression	54	62.9 (12.1)	10.0 (5.1)	11/43
Other diagnoses	40	55.9 (16.8)	8.9 (3.4)	21/19
Normal	13	67.2 (9.0)	10.9 (3.8)	3/10
Total	513	69.3 (4.2)	7.4 (4.5)	217/296

AD: Alzheimer's Disease; VaD: Vascular Dementia; LBD: Lewy Body Dementia; FLD: Frontal Lobe Dementia; PRD: Potentially Reversible Dementia; AAMI: Age Associated Memory Impairment.

years, and sex ratio 162/200. AD was the most common cause of dementia (260 cases, that is 71.8% of dementia cases, including both probable - 190 - and possible - 70 - AD). We observed 29 cases of VaD, 5 cases with LBD, and 13 cases with FTD. Table 1 shows frequencies of diagnoses and demographical data for our patients. We found 26 PRD cases (7.2% of dementia cases, 5.1% of the whole sample): 6 patients with hydrocephalic dementia (5 with normal pressure, NPH, and 1 with hypertensive hydrocephalus due to an arteriovenous malformation (AVM) of choroid tela of the third ventricle); 1 patient with cerebral tumor (lymphoma); 2 patients with vitamin B_{12} deficiency and alcohol abuse; 1 patient with hepatic failure, diabetes, and benzodiazepine abuse; 1 patient with pulmonary failure; 1 patient with neurosyphilis (general paresis of the insane), and 14 patients with depressive pseudodementia. The mean age of these subjects was 68.1±10.4 years (range 46-84); the mean education level was 5.8±3.8 years, and the sex ratio was 13/13. CDR ranged from 0.5 to 2 (14 patients had CDR=0.5; 7 patients had CDR=1; 5 patients had CDR=2). Table 2 shows the details.

We did not find any case of PRD due to chronic hypothyroidism or to effects of medications (with the ecception of the patient with hepatic failure, who also showed benzodiazepine abuse).

The mean follow-up was one year (range: six months to six years). In 13 PRD patients (3.6% of dementia cases), a complete regression of dementia (demonstrated both by normal neuropsychological assessment and recovery of full independence in everyday life) was seen after treatment. In 5 (1.4%), a partial regression was obtained (improvement in neuropsychological measures, and activities of daily living as reported by caregivers, without recovery of independence); in 8, no improvement was observed.

DISCUSSION

Dementia is a chronic progressive disease that leads to the affected person's complete dependence on caregivers. This diagnosis is so destructive for the patient and his/her family, and costly for the family and society that the identification of reversible causes

Table 2 - *Diagnoses, demographical data and outcomes of patients with Potentially Reversible Dementia.*

Potentially reversible condition	No. (%) of patients	Mean age (SD)	M/F ratio	Outcome (No. of patients) Dementia reversed	Dementia improved	Dementia unchanged
Vitamin B_{12} deficiency and alcohol abuse	2 (8)	80.5 (4.9)	1/1	1		1
Hepatic failure, diabetes and medication	1 (4)	65	0/1	1		
Pulmonary failure	1 (4)	74	1/0			1
Infectious diseases	1 (4)	46	1/0	1		
Hydrocephalic dementia	6 (23)	66.8 (3.7)	4/2	1	5	
Brain tumors	1 (4)	54	1/0			1
Depression	14 (53)	66.9 (3.1)	5/9	9		5
Total	26 (100)	68.1 (10.4)	13/13	13	5	8

is an ethical and economic duty; a recent study calculated that the cost for the formal and informal care of each AD patient in Italy was 86,265,000 lire per year (44,552.15 Euro; 48,962.8 US dollars) (26). On the other hand, routine investigations are burdensome for patients, and expensive for society. As previously noted by others (7, 27), data on the prevalence and clinical history of PRD cases in defined clinical settings are of value to identify a more cost-effective strategy in dementia screening, determine the added value of investigations, and judge the degree of "reversibility".

Our experience in a memory clinic indicates that PRD exists, but "true" reversibility is not frequent, in agreement with some previous observations (4, 7, 8, 28). While potentially reversible cases represented 7.2% of our dementia sample, complete recovery was observed in only 13 of 26 cases, bringing the percentage to 3.6%. In another 1.4% of the cases, only a partial regression was recorded.

It must be noted that we reduced the number of false positive cases of PRD by excluding patients with vitamin deficiency, but presenting an onset and clinical course typical of AD. This decision was based on several factors: there is a high incidence of folate or cobalamine deficiency in the elderly population (29); AD is often associated with feeding disturbances (30), and a recent study (31) showed that folate and cobalamine levels are lower in AD patients than in normal controls. Several studies have also demonstrated that patients with vitamin B_{12} deficiency, but who fit AD diagnostic criteria, do not reverse after replacement therapy (32, 33); we made the same observation in our sample. Only 2 patients could be diagnosed as affected by true vitamin deficiency dementia, showing, as previously stated (28, 33), that this condition is very rare.

NPH appeared to be slightly more common but, as shown by other series (34, 35), in no patient was a complete reversal of cognitive impairment observed.

Even if PRD was not common in our sample, the possibility of diagnostic error and its consequences must not be overlooked. In our series, 3 of the 13 patients with complete recovery had been erroneously diagnosed before admission to our memory clinic. In one of these cases, symptoms had been present for one year, and in the other two 6 months, before correct diagnosis was made; in the interim, the patients had received inappropriate treatment, and they and their family had been suffering psychologically both for the consequence of the disease, and the expected negative prognosis. The family of our patient with hepatic failure and diabetes, who had been diagnosed as having AD, did not believe the new favorable diagnosis for several years; the diagnosis of AD is a label "glued" to the patient which is difficult to detach.

Neither age at onset, nor sex ratio were useful in the differential diagnosis of PRD, even if women tended to be overrepresented in the AD sample. Severity appeared to be variable in our PRD sample, ranging from mild to moderate; no case of severe dementia was diagnosed as having a reversible cause. Unlike other investigators (11), however, in our series, two patients with moderate impairment also showed recovery after therapy.

Careful clinical history and examination appeared the most useful part of the evaluation to detect PRD, as observed in the literature (7, 8, 36). However, unlike other workers (1, 11), we did not find that impairment of instrumental functions would suggest AD as opposed to PRD: in our series, the patient with AVM showed mild nonfluent aphasia, prosopagnosia and constructional apraxia; the patient with hepatic failure and diabetes showed fluent aphasia, constructional and ideational apraxia, agnosia and acalculia, and two patients with NPH exhibited mild aphasia and constructional apraxia.

Laboratory and blood tests proved to be somewhat useful in our series, at least to detect the case of hepatic failure and diabetes, and that of neurosyphilis. Our patient with hepatic failure and diabetes was particularly puzzling because her clinical presentation mimicked AD. She had an old clinical history of hepatitis which was underestimated by her family. The patient with general paresis of the insane had a suggestive clinical history; however, neurosyphilitic dementia has became so rare nowadays that most neurologists and psychiatrists have never seen a case of general paresis, and can miss the correct diagnosis simply because they no longer consider it.

CT scan was useful to detect PRD causes (NPH, lymphoma, AVM) only in patients with evidence of neurological signs (even if mild in one case) at examination.

In Italy, the Public Health System spends per person about 110,000 lire (56.8 Euro, 62.4 USD) for neurological and neuropsychological assessment, 150,000 lire (77.5 Euro, 85.2 USD) for standard laboratory investigations and vitamin assays, and 100,000 lire (51.6 Euro, 56.7 USD) for CT scan; this means a total expenditure of 174,630,000 lire (90,189 Euro; 99,117 USD) in our group of 513 patients. Such an expense does not appear so high considering that 3.6% (13/362) of our demented patients showed a complete recovery. On the other hand, it is also true that the growing limitations of

economic resources available for health care require a careful evaluation of the cost-effectiveness of diagnostic procedures.

Our experience supports the utility of standard blood tests and vitamin assays in dementia screening; we found that thyroid functions tests were not informative in our series. Syphilis tests should be considered in patients with a suggestive clinical history, as the existence of this disease should always be kept in mind. CT (or MRI) scan should be considered on the basis of the clinical history and physical examination, rather than scheduled routinely for every patient. However, even mild neurological signs should not be disregarded.

Further studies dealing with diagnostic work up in different clinical settings may be helpful in establishing more effective cognitive screening protocols.

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