

# Reversible Dementias

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*Practical Neurology*, 2002, **3**, 138–43

### Introduction

In recent years, more attention has been given to the early diagnostic evaluation of patients with dementia. The availability of symptomatic treatment with cholinesterase inhibitors for Alzheimer's disease has contributed to this changed attitude towards dementia, not only among physicians but also in the general population. Although Alzheimer's disease cannot be cured, some diseases that were previously regarded as hopelessly progressive dementing disorders, with little attention given to them by specialists, have now turned into a group of brain disorders that may be modulated by pharmaceutical treatment and professional support. What we are experiencing is probably only the beginning of a new era, which may bring more efficient and complex treatment possibilities to the field of dementia.

Early diagnostic evaluation of dementia is essential for planning treatment and support. As for any other neurological disorder, the aetiological diagnosis is the key to specific treatment, if available, and to specific advice and support. For patients with Alzheimer's disease, treatment with cholinesterase inhibitors should be initiated early. Many patients and family

caregivers want an early diagnosis so they can plan properly for the future. Decision making on some legal issues, including the assessment of driving ability, also requires early diagnostic evaluation.

However, early diagnostic evaluation is also essential to identify patients with cognitive symptoms who may have *treatable* conditions. For obvious reasons, patients with a reversible disorder should be referred for proper treatment and not be falsely diagnosed with an untreatable progressive dementia disorder. Guidelines suggest that all patients presenting with dementia or cognitive symptoms should be evaluated with a range of laboratory tests, and with structural brain imaging with CT or MRI (Waldemar *et al.* 2000). This diagnostic work-up aims, in part, to identify reversible conditions. However, do reversible dementias really exist? Some clinicians claim that identification of reversible conditions is a very important part of the management of dementia, while in the opinion of other clinicians reversible dementias are so extremely rare that searching for them on a routine basis in every patient is not worthwhile. What is true? Do reversible dementias exist? What are the causes of reversible dementias? and how should the neurologist look for reversible conditions?

### Reversible dementias: are they dementias? are they reversible?

For a clinical diagnosis of dementia, deficits in memory and in at least one other cognitive do-

— do they exist?

main must be documented, the deficits should interfere with occupational or social functioning, and there must be evidence of a systemic or brain disorder that may be the primary cause of the cognitive deficits (American Psychiatric Association 1993). While many of the disorders reported as 'reversible dementias' are conditions that may well be associated with cognitive or behavioural symptoms, these symptoms are not always sufficiently severe to fulfil the clinical criteria for dementia. For example, a patient with depression may experience subjective difficulties with concentration and learning, which may lead to referral for possible dementia. A treatable and reversible condition is diagnosed, but the patient does not meet the criteria for dementia.

The concept of reversible dementia refers to treatable conditions implicitly, if not explicitly. However, while the treatment of the primary cause is often effective, there is seldom any evidence from controlled trials for any impact on cognitive impairment and dementia. For instance, there is still no evidence that treating patients with vitamin B12 deficiency is beneficial, at least with regard to their cognitive function. Yet, reversible conditions are still worth identifying, for example although the cognitive symptoms in a patient with a frontal meningioma may not be fully reversible after surgery, space-occupying lesions should still be identified and treated, if possible. In some conditions, treatment may improve the cognitive symptoms in part, but full reversal of symptoms is rare.

Thus, while the aetiology of a condition may be treatable it should not be assumed that the associated dementia is fully reversible. Potentially reversible dementias should be identified and treatment considered, even if the symptoms are not sufficiently severe to meet the clinical criteria for dementia, and even if partial or full reversal of the cognitive symptoms cannot be guaranteed.

## Reversible dementias: very frequent or extremely rare?

In the literature on reversible dementias, the concepts of cognitive impairment and dementia are often used interchangeably, contributing to the controversy concerning their frequency. Also, some studies report patients with potentially reversible conditions, while in other studies only patients in whom the actual treatment led to partial or full reversal of the cognitive symptoms on follow-up are reported as having reversible dementia. Finally, discrepancies in the frequency may be explained by the fact that studies on the 'epidemiology' of reversible dementias have been performed in a range of different settings: specialized memory clinics, old age psychiatry wards, geriatric wards, out patient neurology clinics.

Table 1 shows the results of two large systematic reviews of data pooled from many different settings and with different definitions of dementia and reversibility. The frequency of potentially reversible dementias was 13% in one and 15% in the other, although in individual reports the frequency varied from 77% to 0. One of the reviews included only studies reporting the results of treatment after a follow-up period, where the mean prevalence of fully reversible dementias was only 1.5%, thus confirming the view that treatment rarely results in full reversal of cognitive symptoms (Weyting *et al.* 1995). For comparison, prospective data from a neurology-based outpatient memory clinic is also shown in Table 1. Here, the frequency of potentially reversible conditions in all referred patients was 20%. However, in the subgroup of patients fulfilling strict clinical criteria for dementia, the frequency was only 6%. This confirms that reversible conditions are seen more often in patients with mild cognitive and behavioural symptoms; more rarely in patients meeting clinical criteria for dementia.

**Table 1** Prevalence of potentially reversible conditions in patients with cognitive impairment or dementia

Type of study	Reference	Setting	Number of patients	Potentially-reversible conditions	Partly reversed	Fully reversed	Not reversible
Systematic review (33 studies)	Clarfield 1988	Various	2889	15.2%	NA	NA	NA
Systematic review (16 studies)	Weyting <i>et al.</i> 1995	Various	1551	13.2%	9.3%	1.5%	2.4%
Prospective study	Hejl <i>et al.</i> 2001	Outpatient neurology-based memory clinic	785	20%	NA	NA	NA

NA, not available.

## Definition of reversible dementias

Reversible dementia has not been defined in any of the official criteria for dementia disorders in ICD 10 (WHO 1992) and DSMIV (American Psychiatric Association 1993). From the arguments above, it seems sensible to include not only conditions with cognitive impairment sufficiently severe to meet clinical criteria for dementia, but also conditions with mild cognitive or behavioural symptoms. Any definition of 'Reversible Dementia' should include conditions with potential reversibility and not just conditions with full reversibility, because the treatment response may vary from one patient to another, and may or may not improve the cognitive symptoms. A practical definition of reversible dementias is presented in Table 2.

## What are the causes of reversible dementias?

Based on the broad definition in Table 2, a wide range of potentially-reversible conditions may present with or be associated with cognitive or behavioural symptoms. A less than exhaustive list is given in Table 3. In the literature, the most frequently observed potentially reversible conditions identified in patients with cognitive impairment or dementia are depression, adverse effects of drugs, drug or alcohol abuse, space-occupying lesions, normal pressure hydrocephalus, and metabolic conditions (Walhund *et al.* 2002; Sachdev *et al.* 2002). Depression is by far the most common

**Table 2** Potentially-reversible dementias – a practical definition

Potentially reversible dementias may be defined as conditions:

- which may be associated with cognitive and/or behavioural symptoms
- in which specific treatment may lead to partial or full reversal of the cognitive and/or behavioural symptoms

of the potentially reversible conditions (Clarfield 1988; Weytingh *et al.* 1995; Hejl *et al.* 2001).

## How are reversible dementias identified?

The diagnostic work-up of a patient referred for cognitive impairment should usually include (Waldemar *et al.* 2000):

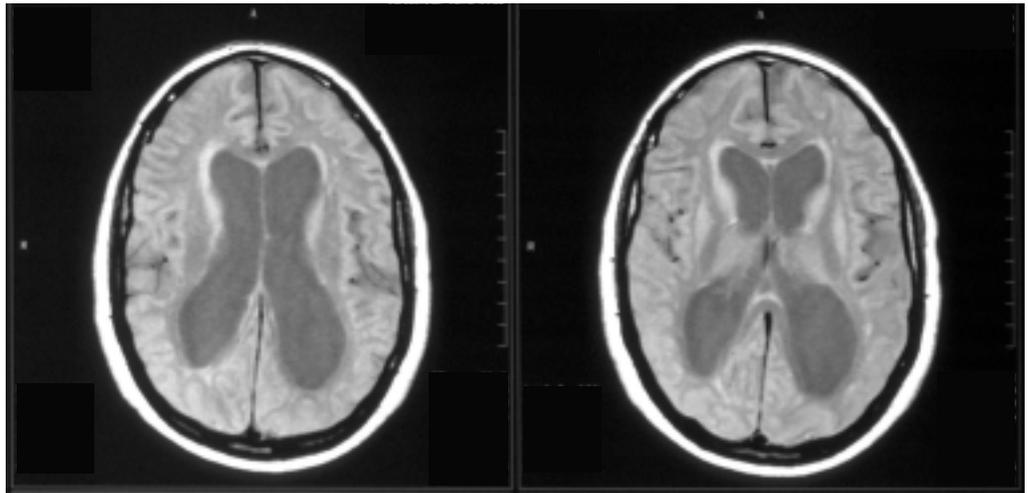
- thorough interview with the patient and a caregiver;
- physical examination including a full neurological examination and assessment of cognitive function;
- assessment of behavioural symptoms and activities of daily living;
- laboratory tests (full blood count, electrolytes, glucose, thyroid function, liver and renal function, blood sedimentation rate, vitamin B12 level);
- brain CT or MRI.

**Table 3** Causes of potentially reversible cognitive impairment or dementia\*

Space-occupying lesions and other neurosurgical conditions	Neuroinfections and inflammatory conditions	Metabolic conditions	Miscellaneous
Subdural haematoma Normal pressure hydrocephalus Intracranial tumours Intracranial empyema or abscess	Neurosyphilis Encephalitis Meningitis Cerebral vasculitis	Hypo- and hyperthyroidism Hypo- and hyperparathyroidism Pituitary insufficiency Hypercalcemia Cushing's disease Addison's disease Hypoglycemia Vitamin deficiencies (B12 and folate) Chronic liver failure Chronic respiratory failure Chronic renal failure Wilson's disease	Depression Epilepsy Drugs and toxins Alcohol abuse Sleep apnoea
*In this table some examples of reversible conditions are given. The list is not complete.			

the neurologist should pay special attention to the possibility of rare causes of cognitive impairment, which may require specific laboratory screening tests of blood or urine, CSF analysis, EEG, or even brain biopsy

Normal pressure hydrocephalus. Brain MRI in a 72-year-old-male patient with mild gait ataxia, mental slowing, learning and concentration difficulties. The clinical symptoms and the enlarged ventricles with periventricular hyperintensity, and lack of severe cortical atrophy, raised the suspicion of normal pressure hydrocephalus. In the lumboventricular perfusion study the intracranial pressure was normal and the resistance to outflow of CSF was significantly increased. The patient improved after a shunt, he had a 'reversible dementia'.



With this programme, most potentially-reversible conditions will be identified. Referral to a neuropsychologist and a psychiatrist, for the evaluation of cognitive and psychiatric symptoms, respectively, may be helpful. Furthermore, the neurologist should pay special attention to the possibility of rare causes of cognitive impairment, which may require specific laboratory screening tests of blood or urine, CSF analysis, EEG, or even brain biopsy (for example, epilepsy presenting as Alzheimer's disease, cerebral vasculitis or other inflammatory conditions, neurosyphilis or other neuroinfections, Wilson's disease or other systemic disorders).

### Reversible comorbidity

Even in patients diagnosed with Alzheimer's disease or another progressive dementing disorder, the search for a potentially reversible disorder should not stop. These patients may develop depression or other treatable complications of their disease. Some may have hypothyroidism and other treatable comorbid conditions, which may worsen their cognitive impairment if left unidentified and so untreated. The prevalence of potentially-treatable comorbid conditions may be as high as 20%–25% in patients referred for dementia (Hejl et al. 2001).

## Summary

Reversible dementias do exist. Potentially-reversible conditions are frequently encountered in patients with cognitive impairment or dementia, in some they are the cause of the dementia, in others they are a comorbidity to a progressive dementing disorder. Numerous potentially reversible conditions may be associated with or even present with cognitive impairment. Some are very rare, yet treatable (e.g. Wilson's disease). Other conditions are more common, but may only occasionally present with dementia in the absence of other neurological symptoms (e.g. space-occupying lesions). Finally, some are very common (e.g. depression, vitamin deficiency). In some of the treatable conditions, reversibility of the cognitive symptoms has not been well-documented in the literature and is based on case reports, clinical belief, or common sense. Although more research is needed, it is essential that patients with cognitive impairment are evaluated for possible reversible conditions. Such conditions will be encountered most often in patients with mild symptoms, more rarely in patients meeting all the present criteria for dementia. Most reversible conditions are easily identified by a careful history, physical examination, psychiatric evaluation, brain CT or MRI, and routine laboratory tests. With more patients presenting for early assessment of cognitive impairment, the neurologist should be very aware of reversible conditions.

## Acknowledgements

I would like to thank the '1991 Pharmacy Foundation' and the 'Health Insurance Foundation' for their financial support for research and development in the Memory Disorders Research Unit at the Copenhagen University Hospital.

## Conflict of interest

This paper has not been published elsewhere. I have no conflicts of interest that are relevant to this paper, but I do serve as a speaker and consultant for several pharmaceutical companies (Pfizer, Janssen-Cilag, Lundbeck and Novartis).

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