How Reversible are 'Reversible Dementias'?

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Abstract

Reversible dementias comprise different groups of disorders of variable aetiologies, such as structural brain lesions or metabolic, infectious, toxic, autoimmune, paraneoplastic and psychiatric disorders. When patients present with cognitive symptoms, especially in the younger age groups, the first thought of the attending neurologist should be to try to identify an underlying treatable cause. The incidence of degenerative dementia rises with older age and its symptoms progressively become more evident and typical; in such cases, a differential diagnosis is limited and the chance of uncovering a treatable disorder is minimal. However, although uncommon, treatable dementias or dementia-like symptoms do exist. Future studies with better design and methodology, as well as longer observation periods and larger patient populations, are needed to clarify the controversial issues concerning the epidemiology and accurate diagnosis of, and treatment possibilities for, reversible dementias.

Keywords

Reversible dementia, classification, differential diagnosis, treatment, review

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Dementia is a syndrome that can have multiple causes and is characterised by deterioration in different domains of cognition, especially memory, language, praxis, visual perception and executive function.[1] It is estimated that the number of people with dementia will increase dramatically over the next few decades,[2] presenting a tremendous burden for patients, spouses and other family carers, and society. Consideration of the differential diagnosis of dementia is a complex process, and accurate diagnosis is challenging. Primary degenerative dementias result from irreversible aetiologies, such as beta-amyloid deposition, inclusion of Lewy bodies, taupathies or other dysfunctional proteins, whereas reversible dementias are secondary to other treatable conditions. When patients present with cognitive symptoms, especially in the younger age groups, the first thought of the attending neurologist should be to try to to identify an underlying treatable cause. Reversible dementias comprise different groups of variable aetiologies, such as structural brain lesions or metabolic, infectious, toxic, autoimmune, paraneoplastic and psychiatric disorders.[3] The aim of this article is first to define these treatable conditions and second to explore how reversible they really are according to data from the literature.[4,5]

Traditional and New Approach to Reversibility

Between the 1980s and early 1990s, most studies estimated the prevalence of reversible dementias to be almost 20 %, introducing aetiologies such as normal pressure hydrocephalus (NPH), structural brain abnormalities, depression, hypothyroidism and vitamin B12 deficiency.[6,7] However, many of these studies were lacking strict criteria, adequate follow-up and solid methodology.[8]

In recent years, neurologists have taken a new approach to reversibility. It seems that good history evaluation, clinical examination accompanied by certain psychometric tests and appropriate laboratory work-up should be considered for every patient with cognitive symptoms.[9] The incidence of degenerative dementia rises with older age and its symptoms progressively become more evident and typical; in such cases, the differential diagnosis is limited and the chance of uncovering a treatable disorder is minimal.[10] However, in patients with younger onset dementia, the process is different. The possibility of revealing a reversible cause is higher and the differential diagnosis and work-up are broadened.[11]

Different possible causes of reversible dementias or dementia-like symptoms are summarised in *Table 1* and detailed below.

Traditional Causes of Reversible Dementias

Structural Brain Lesions

NPH presents with the classical triad of gait disturbance, memory complaints and urinary incontinence. However, not all patients with NPH show improvement after cerebrospinal fluid drainage. Depending on the time of shunting, urinary incontinence and gait apraxia may resolve and memory may improve.[12] In the long term, full reversibility is unlikely if there is a parallel degenerative illness or a concomitant true dementia.[13]

Patients with subdural haematomas and brain tumours are likely to see a resolution of their cognitive symptoms after surgical treatment.

Alcoholic Dementia

Deterioration in cognition, behavioural changes and personality changes are well known to result from chronic alcohol abuse. The role of alcohol in the dementia process is still debated. It is not clear whether there is a direct toxic effect or a secondary cognitive decline due to other factors related to alcohol consumption. Abstinence may improve cognition, but true reversibility is uncertain.[14]

Nutritional Disorders

The role of vitamin B12 deficiency in neurological disorders has been known for many years. Vitamin B12 deficiency may cause subacute combined degeneration, psychiatric symptoms, multiple-sclerosis-like syndrome, delirium and dementia or cognitive impairment.[15] It was thought that, after B12 supplementation in patients with low serum cobalamin, dementia would resolve. However, most studies lack evidence of this.[16,17] Vitamin B12 deficiency may be an epiphenomenon of dementia rather than a cause of cognitive deterioration.[18]

Wernicke's encephalopathy and Korsakoff's syndrome are potentially treatable after alcohol withdrawal and nutritional supplementation. Wernicke's encephalopathy is characterised by the triad of opthalmoparesis, ataxia and confusion, and is a consequence of thiamine deficiency. Brain magnetic resonance imaging (MRI) shows atrophy of mammillary bodies and insult of the median thalamus.[19]

Endocrine Disorders

Thyroid disturbances, such as hypothyroidism and hyperthyroidism, can potentially cause depression and memory dysfunction. With the stabilisation of thyroid function, mood and memory may return to normal.[20] However, many people with dementia present with abnormal thyroid tests in their blood tests or history.

Idiopathic hypoparathyroidism is a rare disorder that causes cerebral calcification or Fahr's disease. As the disease progresses, dementia appears, together with other neurological complications such as epilepsy, Parkinsonism and raised intracranial pressure. Treatment is mainly symptomatic and dementia symptoms partially resolve.[21]

Metabolic Disorders

Electrolyte disturbances and hepatic, renal or pulmonary insufficiency may present as transient cognitive impairment that can mimic dementia. Cognition may be restored after treatment of the underlying disorder.

Wilson's disease is an autosomal recessive disorder of copper metabolism. Manifestations include psychiatric and movement abnormalities resulting from copper accumulation and toxicity. Treatment is through chelation with trientine and zinc supplementation. Cognitive symptoms are also present and improve with therapy.[22]

Toxic Conditions

Exposure to toxic agents may occur in some professions and cause neurocognitive impairment. For example, lead exposure causes lead encephalopathy in industrial workers. Heavy metals such as mercury, bismuth, aluminium, manganese and arsenic have also been implicated in dementia symptoms. Carbon monoxide intoxication can present with confusion and altered memory. Most of these symptoms are often not reversible; however, sequestration of the offending agent may prevent further clinical decline.[23]

Psychiatric Disorders

Depression in older people was initially thought to cause dementia-like symptoms. However, depression may actually be the first symptom of a dementia illness.[24] Older people who were treated for depression showed improvement in cognition without absolute reversibility of dementia, indicating a possible overlap between the two conditions in older patients.[25] However, the question still is: does pseudodementia really exist or are we dealing with pseudo pseudodementia?

Table 1: Summary of Different Possible Causes (Traditional and New) of Reversible Dementias or Dementia-like Symptoms

Groups	Diseases/Causative Agents	Diagnostic Tests
Structural brain lesions	NPH Subdural haematomas Brain tumours	Brain CT, MRI
Alcoholic dementia		
Nutritional disorders	Vitamin B12 deficiency	Serum B12
	Wernicke's encephalopathy	Thiamine
Endocrine disorders	Hypothyroidism Hyperthyroidism	Serum T3, T4, TSH
	Hypoparathyroidism	Parathormone
Metabolic disorders	Electrolyte disturbances	K^+, Na^+, Ca^{2+}
	Hepatic and renal insufficiency	Hepatic enzymes, creatinine
	Wilson's disease	Copper, ceruroplasmin
	Obstructive sleep apnoea	Polysomnography
Toxic conditions	Poisoning with CO, bismuth, aluminium, manganese, arsenic, mercury	History, serum levels
Psychiatric disorders	Depression	Psychometric tests
Epileptic disorders	Transient epileptic amnesia	History, EEG
Autoimmune encephalopathies	Hashimoto's encephalopathy	Anti-TPO, anti-TG
	Paraneoplastic encephalopathies	Anti-Yo, anti-Ri, anti-Hu, anti-NMDAR
	Non-paraneoplastic encephalopathies	VGKC
Inflammatory vasculopathies	Primary CNS angiitis	Angiography, biopsy
	Sjögren syndrome	Anti-Ro, anti-La
	SLE	Anti-dsDNA, ANA
	Behçet's disease	Oral, genital ulcers
	CNS sarcoidosis	ACE
	Antiphospholipid syndrome	Lupus anticoagulant, cardiolipines
Vascular causative factors	Dural arteriovenous fistulae	MRV
Infections	Cryptococcal meningitis	PCR for *Cryptococcus*
	Whipple's disease	PCR for *Tropheryma whippelii*
	Lyme disease	Serum and CSF antibodies for *borellia*
	Syphilis	CSF for VDRL
	HIV dementia	Serology for HIV
Medications	Benzodiazepines, antiepileptics, antipsychotics, tricyclic antidepressants	History, serum levels

ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; CNS = central nervous system; CO = carbon monoxide; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging; MRV = magnetic resonance venography; NMDAR = N-methyl-d-aspartate receptor; NPH = normal pressure hydrocephalus; PCR = polymerase chain reaction; SLE = systemic lupus erythematosus; TG = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; VDRL = venereal disease research laboratory test; VGKC = voltage-gated potassium channel.

Miscellaneous Causes

Many other heterogeneous conditions have been shown to be involved in the reversible dementia pathogenesis. For example, dementia cases due to radiation or dialysis have been reported to reverse after appropriate treatment.[26] The identification of such conditions is easier when patients' previous history is considered.

New Causes of Reversible Dementias

Epileptic Disorders

Transient epileptic amnesia is a syndrome characterised by recurrent, brief attacks of memory loss in middle-aged or older people, usually after sleep, associated with symptoms of temporal lobe epilepsy (automatisms, electroencephalogram findings, etc.). It is a benign syndrome that is responsive to antiepileptic medication, but complete resolution of cognitive symptoms is unusual.[27] It has been suggested that a degenerative process exists in parallel with the epileptic disorder.[28]

Autoimmune Encephalopathies

Autoimmune encephalopathies (or autoimmune dementias) is a newly proposed term for dementias underlying an autoimmune process. They constitute a heterogeneous group of disorders that may present with cognitive decline.[29] With the discovery of antibodies such as anti-Yo, anti-Hu and anti-Ri, which are related to paraneoplastic disorders, the spectrum of potentially treatable dementias has been broadened. Also, a specific search for other antibodies – such as voltage-gated potassium channel antibodies in non-paraneoplastic encephalopathies and anti-N-methyl-d-aspartate receptor antibodies in paraneoplastic encephalopathies[30,31] – has demonstrated that reversible dementias are not a myth. A favourable prognosis is achieved with resection of the underlying tumour and/or immunosuppression in paraneoplastic cases, and with appropriate management using immunosuppression in non-paraneoplastic cases.

Hashimoto's encephalopathy is another potentially treatable disorder that presents as rapidly progressive dementia accompanied by myoclonus, epileptic seizures and altered level of consciousness. Brain computed tomography or MRI may be normal but thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) can be found in high titres. Steroid initiation is the treatment of choice, with immediate improvement (steroid-responsive encephalopathy).[32]

Obstructive Sleep Apnoea

Some patients referred to memory clinics are suffering from obstructive sleep apnoea. These patients are often younger and may represent around 5 % of patients under 65 years attending these clinics.[33] Due to the bad quality of sleep and the excessive daytime sleepiness, memory problems may be the first symptoms these patients experience. Improvement in memory is evident after treatment.

Inflammatory Vasculopathies

Other inflammatory or autoimmune diseases may present with central nervous system (CNS) involvement. Systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, antiphospholipid syndrome and sarcoidosis can affect CNS vasculature.[34] Isolated CNS angiitis is another condition that may initially present with cognitive symptoms.[35] The diagnosis of these disorders is usually difficult and requires a high degree of suspicion.

Primary CNS angiitis is a rare autoimmune disease that typically presents in middle-aged people with headache, cognitive symptoms, stroke and seizures. Angiitis of the CNS may have a fluctuating course or a stepwise rapid deterioration that could be misleading. The diagnosis is confirmed by conventional angiography or brain biopsy and the recommended treatment is a combination of corticosteroids and immunosuppression. Relapses are not unusual.

CNS sarcoidosis may also present with dementia symptoms. It is a multisystem granulomatous disease that commonly affects the lungs, eyes and skin. The condition is difficult to diagnose but is responsive to steroids. With early treatment, reversal of symptoms may occur.[36]

Vascular Causative Factors

Dural arteriovenous fistulae (DAVF) have been associated with progressive cognitive dysfunction. These lesions often occur with focal neurological symptoms or signs, but cognitive impairment may be the sole manifestation.[37] The prognosis after selective embolisation is very good, with complete resolution of the symptoms. Magnetic resonance angiography and catheter angiography show venous flow reversal and decreased perfusion of the cerebral parenchyma. Diagnosis is difficult, but DAVF should be in the differential diagnosis of atypical cases with subacute cognitive decline. It is hypothesised that the symptoms and imaging findings result from venous hypertension.

Infections

Infections of the CNS such as cryptococcal meningitis, Lyme disease, Whipple's disease, syphilis and HIV could induce dementia symptoms. Early management of these infections may result in reversibility of the cognitive impairment. However, permanent damage and irreversibility of the cognitive symptoms is not an unusual scenario in untreated or undetected cases.

Whipple's disease is very rare. The incidence is about 5–10 cases in one million every year. It can affect the CNS and present as dementia without gut involvement. It is difficult to diagnose, but treatable if managed when symptoms first start.[38] Lyme disease is another treatable infection that can affect the CNS and present as dementia.[39]

Cognitive symptoms are a late complication of neurosyphilis. Diagnosis is easy and based on the evaluation of serology for *Treponema pallidum*. Syphilis is a common complication in immunocompromised patients.[40] Serological tests for *Treponema* should be available in everyday clinical practice, as the incidence of the disease has risen in recent years due to people migrating from underdeveloped countries.

HIV dementia is irreversible, but HIV-related neurocognitive impairment may be reversed by highly active antiretroviral therapy. Treatment response is strongly related to the neurocognitive status of the patient prior to initiation of treatment.[41]

Medications

There are several reports of drugs that have provoked cognitive impairment, especially in older people who are susceptible to polypharmacy and drug–drug interactions.[42,43] Benzodiazepines, antipsychotics, antiepileptics and tricyclic antidepressants have been accused of worsening memory and executive functioning. Newer and older antiepileptic drugs, such as topiramate and sodium valproate, have been implicated in worsening cognition.[44,45] Cognitive symptoms may be reversed after withdrawal of the responsible drug. Steroid psychosis is a well known adverse event of chronic steroid treatment. In

contrast, steroid dementia is still debated. There are well documented reports showing that cognitive problems have resolved after steroid discontinuation.[46] In experimental rat models, the use of corticosteroids affects the hippocampus and induces dysfunction in cognition.[47]

Discussion

As we have shown, reversible dementias comprise a group of diseases with different aetiologies. With a detailed history, a thorough clinical examination and sometimes extensive laboratory investigations, a treatable cause of dementia is often difficult to be reached but can alter the patient's progress. Traditional treatable dementias, such as those arising from NPH, brain tumours, B12 deficiency, endocrine disorders and depression, are partially reversible.[48] Reversibility depends on the time of diagnosis and concomitant medical problems. In vitamin B12 deficiency, for example, if supplementation can be started early, stabilisation of memory complaints and improvement may be seen – however, many people with dementia present with low serum B12 concentrations.[49] The same may happen with NPH after shunting. Some of the symptoms may improve and stabilise, but the condition is not fully reversed.

For autoimmune dementias, with an accurate diagnosis and early treatment, the chance of reversibility is higher.[50] However, other issues arise in these patients. How long should they receive treatment, and which medication would be the safest to use? In Hashimoto's encephalopathy, the condition may relapse after steroid tapering or discontinuation.[51]

In dementias with an infectious cause, such as HIV, early drug intervention is crucial as they are reversible, at least in the first stages.

In younger patients with atypical presentation or a rapidly progressive disease course, a brain biopsy, although invasive, should be the final investigation to rule out or confirm an inflammatory or autoimmune process,[52] especially if other investigations have failed to reveal a cause. However, in a number of such patients, a biopsy may only show non-specific findings and it will not be possible to reach a firm conclusion, even after such an invasive procedure.

In recent years, as neurologists have approached reversibility from a different angle, the prevalence of reversible dementias has decreased.[53] The traditionally quoted figure of a 20 % prevalence has been mostly abandoned.[54] A new look at an old problem shows that true reversibility is rare (1 %)[55] and uncommon in older patients with cognitive decline who fulfil the proposed criteria for primary degenerative dementia. In contrast, in younger patients, especially those experiencing a rapid deterioration of their cognitive abilities, further diagnostic work-up with newly recognised antibodies and specific serological tests is highly warranted.

In conclusion, although uncommon, treatable dementias or dementia-like symptoms do exist,[56] but their actual prevalence is not known. Future studies with better design and methodology, as well as longer observation periods and larger patient populations, are needed to clarify the controversial issues concerning the epidemiology and accurate diagnostic of, and treatment possibilities for, reversible dementias. ■

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